RABELO MAURER advocacia

## BRAZILIAN LIFE SCIENCES SECTOR

# Drug and Medical Devices Regulation Guide Book


주 브라질 대한민국 대사관
Embaixada da
República da Coreia

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# Introduction

The **Embassy of the Republic of Korea in Brazil** with **Rabelo Maurer Advocacia** prepared this Guidebook for foreign investors interested or doing business in the Brazilian life sciences sector, specifically in the drug and medical device areas.

The current global situation has significantly highlighted the importance of the life sciences practice, namely due to the unprecedented transformations brought by COVID-19. Governments worldwide have been pressured to act fast and effectively tackle this pandemic. In Brazil, the Brazilian Health Regulatory Agency (ANVISA) has been the protagonist of this pandemic, especially for the regularization of immunizers and implementation of several new regulations on health safety and protection, and emergency use of drugs. The vertiginous increase in demand for drugs and medical services, materials, and devices also forced the life sciences and healthcare markets to quickly adjust and readapt for greater industrial production and healthcare capacity.

Such intense environment of transformation in the life sciences and healthcare sectors have reinforced the importance of rigorous sanitary controls not only to ensure the safety of population, but also to increase efficacy of drugs and medical devices.

This Guidebook covers a wide range of themes, including an overview on the Brazilian Unified Health System, regulations on drugs and medical device activities, clinical trial regulations, drug pricing and reimbursement system, and among all, the most relevant COVID regulations.

All subjects of this Guidebook were carefully drafted after an intensive research and analysis of applicable laws and policies of Brazil, with emphasis on explaining the functions of responsible technical organizations, internal procedures, and relevant procedures for granting of product and company authorizations.

November, 2021

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# 1. Legal and Regulatory Framework

## Brazilian Federal Constitution and Right to Health

According to the Brazilian Federal Constitution[1], government actions and services related to the protection of human health are performed through a public health system, financed with the resources from the social security funds from the Federal Government, States, Federal District and Municipalities[2], for the performance of actions and delivery of services following the main principles of universality and equality of healthcare [3], via a regionalized public healthcare system organized following the guidelines of decentralization, full access and community participation[4].

Whilst the Federal Government, the States, and the Federal District have a joint lawmaking power with regards to the protection of human health[5], Municipalities are responsible for delivering healthcare services to the population with the technical and financial cooperation of the State and Federal governments[6], and may enact legislation on local public health matters, respecting the general rules established by the Federal and State governments.[7]

## Unified Health System – SUS

On September 19, 1990, the Brazilian Congress passed Law n. 8,080/1990, creating the Unified Health System ("SUS") following the principles of universality and equality as provided under the Brazilian Federal Constitution. According to the Law, the SUS is comprised by the health actions and services performed by public federal, state, and municipal institutions[8] for the promotion, protection, and recovery of health in the Brazilian territory, delivering health care and performing preventive actions[9]. Therefore, the idea of creating a politically and administratively decentralized system, with separate leaderships in the Federal, State and Municipal spheres, was to ensure that the implementation of actions for physical, mental, and social well-being of the Brazilian population throughout the country.

[1]Brazilian Federal Constitution enacted on October 5, 1988
[2]Brazilian Federal Constitution, 1988, art. 195 and 198, §1
[3]Brazilian Federal Constitution, 1988, art. 196
[4]Brazilian Federal Constitution, 1988, art. 198, I to III.
[5]Brazilian Federal Constitution, 1988, art. 24, XII.
[6]Brazilian Federal Constitution, 1988, art. 30, VII
[7]Brazilian Federal Constitution, 1988, art. 30, I and II
[8]Law n. 8,080/1990, art. 4
[9]Law n. 8,080/1990, art. 5, I to III

The Law provides for a wide range of activities which are within the scope of the SUS, such as: the performance of health and epidemiological surveillance; therapeutic and pharmaceutical care [10] ; formulation of public policies on drugs, equipment, immunobiological substances, and other raw materials, besides the control of services, products, and substances of interest to public health.[11]

The health surveillance activities included within the scope of the SUS are defined as the set of actions intended for eliminating, mitigating, or preventing human health risks to, and intervening in health issues resulting from the environment, production and circulation of consumer goods, and health services[12].

Law n. 8,080/1990 also sets out the powers of each sphere of government regarding health issues. Even though State and Municipal authorities are competent to supervise and authorize health-related activities, only the federal government has the authority to create and coordinate the health surveillance system; control and conduct the health supervision in harbors, airports and borders; establish criteria, parameters and methods for quality control of human use and consumption products, substances, and services; control and inspect procedures, products and substances of interest to public health, among others.[13]

## National Health Surveillance System, and Brazilian Health Regulatory Agency ("ANVISA")

On January 26, 1999, the Brazilian Congress passed Law n. 9,782/1999, defining the structure of the National Health Surveillance System and the functions of the Federal Government, States, Federal District and Municipalities with regards to the regulation, control and inspection in the area of health surveillance[14].

Law n. 9,782/1999 also created the Brazilian Health Regulatory Agency ("ANVISA"), as an independent administrative agency linked to the Ministry of Health ("MoH"), with nationwide powers and authority[15].

The MoH, ANVISA and certain executive branches of the Federal Government share the responsibility for the fulfillment of the Federal Government's responsibilities within the National Health Surveillance System[16].

[10] Law n. 8,080/1990, art. 6, I
[11] Law n. 8,080/1990, art. 6, VI and VII
[12]Law n. 8,080/1990, art. 6, §1
[13] Law n. 8,080/1990, art. 16, III(d), VII, VIII, and XII.
[14] Law n. 9,782/1999, art. 1
[15] Law n. 9,782/1999, art. 3
[16] Law n. 9,782/1999, art. 2, §1

ANVISA´s responsibilities include[17]: controlling and supervising products, substances and health-related services; supervising harbors, airports and borders in health-related issues; enacting regulations and standards on product labeling and advertising, contaminant limits, waste disposal, sanitizing products, heavy metals, and other substances which may be of concern to health; authorizing the activities of companies engaged in the manufacture, distribution, importation[18], and marketing of drugs and other products subject to health control; granting of marketing authorizations and Good Manufacturing Practices Certificates; approving the importation of products subject to health control; and applying penalties in cases of violation of health laws.

The list of products under ANVISA´s control is comprehensive[19]: drugs for human use; pharmaceutical raw materials; foods and beverages, including bottled water, food packaging materials; cosmetics, perfumes, and personal hygiene products; sanitizing products; cigars and other tobacco-based products; medical and dental equipment; radioisotopes for *in vivo* diagnostic, radiopharmaceuticals and any radioactive product used for diagnosis and therapy, and any other products or processes that may pose any risk to human health.

ANVISA is also responsible for the control and supervision of outpatient and inpatient care services, emergency rooms, therapeutic or diagnostic services, as well as for the inspection of health facilities, equipment, technologies, manufacturing, and waste disposal processes[20].

## Supervision of Health-Related Activities by States and Municipalities

The supervision of activities subject to health control, except for harbors, airports, and borders[21], is usually conducted by State and Municipal authorities, which have the power to supervise the compliance with Federal, State and Municipal health laws, perform inspections, issue notices of violations and impose penalties in case of violation of the law. Inspections carried out by local health authorities usually include facilities, equipment, technologies, and vehicles used for the transportation of products subject to health control.

## Health Legislation Violations

[17] Law n. 9,782/1999, art. 7
[18]Law n. 6,360/1976, art. 10
[19] Law n. 9,782/1999, art. 8
[20] Law n. 9,782/1999, art. 8, §§ 2 and 3
[21] Law n. 9,782/1999, art. 8, §8

Penalties for health law violations are provided for under Law n. 6,437/1977 and include: (i) warning; (ii) fines ranging from BRL 2,000 to BRL 1,500,000; (iii) seizure of products; (iv) suspension of activities; (v) cancellation of the operating authorization or marketing authorization; (vi) partial or total closure of the establishment; and (vii) prohibition or suspension of the advertisement of the product or service.

All penalties may be applied cumulatively or alternatively, and the fines may vary according to the seriousness of the violation. Penalties are applied through an administrative proceeding that usually starts with an inspection by the health authority and is followed by a notice of violation. Penalties are calculated taking into consideration (i) the attenuating and aggravating circumstances, (ii) the seriousness of the fact and its consequences for public health; and (iii) the previous standing of the violator in relation to the health legislation.

# 2. Company and Product Regularization

## Operating Licenses

According to the Law[22], companies engaged in activities related to extracting, producing, manufacturing, transforming, synthesizing, purifying, fractioning, packaging, repackaging, importing, exporting, storing or shipping of drugs, pharmaceutical raw materials, medical devices and equipment, personal hygiene products, cosmetics, perfumes, sanitizing products, among others, must obtain: (i) a Federal Operating Authorization ("Autorização de Funcionamento de Empresa" – AFE) with ANVISA, and (ii) a Local Health Permit issued by the health authority of their respective location ("Alvará Sanitário").

The Federal Operating Authorization – AFE will be valid throughout the national territory for an indefinite term[23], except for companies and establishments carrying out activities involving substances subject to special control or the bottling of medical gas, for which the license must be renewed annually[24]. Likewise, Local Health Permits are also renewed annually, following the local health regulations and procedures.

Additionally, establishments where activities involving substances or drugs subject to special control are carried out must also have a Special Authorization ("AE") issued by ANVISA[25], which is subject to an annual renewal procedure[26].

[22] Law 6,360/1976, arts. 1 and 2
[23] Law 6,360/1976, art. 50, sole paragraph, and ANVISA RDC n. 16/2014, art. 19, sole paragraph
[24] ANVISA RDC n. 16/2014, art. 19
[25] PRT SVS/MS 344/1998, Chapter 2
[26] ANVISA RDC n. 16/2014, art. 19

Companies are allowed to perform only the activities detailed in the AFE, Health Permit, and AE.

In addition to these authorizations and permits, Companies performing activities subject to ANVISA´s control must have legally capable professionals in charge of the technical activities performed in each of the Company's establishment. Also, the establishments themselves must also be enrolled with the relevant Professional Regional Council and obtain the Technical Responsibility Annotation Certificate ("Certificado de Anotação de Responsabilidade Técnica")[27].

## Product Marketing Authorization

### Main Requirements

Once the company and establishments' licensing processes above are concluded, companies may start the product marketing authorization (product registration, enrolment or notification, depending on the product category) procedures, which is the regulatory step to be conducted prior to the marketing of any product subject to ANVISA´s control[28]. There are different procedures and requirements for obtaining a product marketing authorization, depending on the category in which the product falls within, but all of them are intended for quality, efficiency, and safety controls, varying according to the level of risk a product may pose to consumer health.

The marketing authorization of the products provided for under Law n. 6,360/1977, art. 1 (i.e. drugs, pharmaceutical raw materials, medical devices and equipment, personal hygiene products, cosmetics, perfumes, sanitizing products, and products for aesthetic correction) will be valid for 5 years, and can be renewed for the same period, keeping the same registration number[29]. The marketing authorization renewal application must be filed with ANVISA from 12 to 6 months before its expiry, otherwise it will be considered forfeited. [30]

In 2015, an amendment to the Law introduced a simplified procedure for the renewal of drug marketing authorizations held for over 10 years, and which have not been reported to the authorities as ineffective or causing major adverse events, and which comply with the regulatory requirements in force.[31]

As for the procedures for obtaining a product marketing authorization, ANVISA has a far-reaching list of resolutions for each and all categories of product it is responsible for. The procedures a Company must follow for obtaining a marketing authorization will vary

[27] Law 6,360/1976, arts. 53 to 56, and Decree n. 8,077/2013, art. 5
[28] Law 6,360/1976, arts. 12, and Decree n. 8,077/2013, art. 7
[29] Decree n. 8,077/2013, art. 8, §1
[30] Decree n. 8,077/2013, art. 8, §2
[31] Law 6,360/1976, arts. 24-A, as amended by Law 13,097/2015.

greatly depending on the product type and classification defined by the applicable legislation. In the following chapter, we will highlight the main requirements for companies to obtain marketing authorizations for new, similar, and generic drugs, as well as for medical devices, and we will also provide a summary of the main resolutions (RDCs) which must be observed when applying for or renewing a new drug marketing registration.

## New Drugs

According to ANVISA[32], the term new drug ("medicamento novo") refers to new drugs with associated or non-associated synthetic or semi-synthetic active ingredients, and not to biological drugs, herbal, homeopathic, specific drugs ("medicamentos específicos"), drugs exempt from registration, neither to generic nor similar drugs, all of which have specific regulations.

New drugs for experimental use, under medical control, are exempt from marketing authorization, and may be imported upon authorization from the Ministry of Health. Such exemption will be valid for the period of up to 3 (three) years, and upon its expiry, the company must follow the applicable regulation and pursue the regular marketing authorization procedures. Otherwise, the products in the market may be subject to seizure.[33]

On the other hand, ANVISA also defines new or innovative drugs as those that have at least one active ingredient as a molecule not registered in the country, or new salts, isomers or mix of isomers, esters, complexes or derived from a registered molecule[34]. The application for obtaining a marketing authorization for a new drug must follow the electronic procedures made available by ANVISA, and must be submitted on an individualized basis, per pharmaceutical form[35].

Furthermore, ANVISA determines that all clinical studies conducted in the country have to follow the applicable legislation, including the ethical approvals, otherwise they will not be considered valid for the purposes of the marketing authorization process.[36]

Below you find a list of the main resolutions and rulings which must be observed when applying for or renewing a new drug marketing authorization. For more and detailed information, companies should go to ANVISA´s website and access "Biblioteca de

[32] Information available on 11/16/2021 at: https://www.gov.br/anvisa/pt-br/acessoainformacao/perguntasfrequentes/medicamentos/conceitos-e-definicoes/conceitos-e-definicoes
[33] Law 6,360/1976, art. 24 and sole paragraph.
[34] ANVISA RDC n. 20/2013, art. 1, sole paragraph, and ANVISA RDC n. 200/2017, art. 4, XXVIII and XXIX
[35] ANVISA RDC n. 20/2013, art. 2 and §1, and ANVISA RDC n. 200/2017, art. 21
[36] ANVISA RDC n. 200/2017, arts. 15 and 17

Medicamentos"[37] ("Library of Drugs"), where all links to the full content of the regulation below are available:

| Resolution/Ruling # | Subject Matter |
|---|---|
| ANVISA RDC n. 200/2017 | Marketing authorization granting and renewal procedures for drugs with synthetic and semi-synthetic active ingredients, classified as new, generic, and similar |
| ANVISA RDC n. 20/2013 | Marketing authorization application electronic procedures for new drugs |
| ANVISA RDC n. 222/2006 | Anisa's general petition and tax collection electronic system ("TFVS") |
| ANVISA RDC n. 73/2016 | Post-market changes, marketing authorization cancellation procedures for drugs with synthetic and semi-synthetic active ingredients |
| ANVISA Normative Ruling (IN) 2/2009 | Drug pilot batch production guide |
| ANVISA RDC n. 35/2012 | Criteria for drug indication, inclusion, and exclusion in the Reference Drugs List |
| ANVISA RDC n. 205/2017 | Establishes a special procedure for clinical studies approval, good manufacturing practices certificate, and new drug marketing authorization for the treatment, diagnostic or prevention of rare diseases |
| ANVISA RDC n. 1/2013<br>ANVISA RDC n. 46/2012 | Reference chemical substances batches of the Brazilian Pharmacopoeia |
| ANVISA RDC n. 55/2010 | Marketing authorization procedures for new biological and biological products |
| ANVISA Normative Ruling (IN) 65/2020 | Regulation on the classification of post-market changes, and technical documents required for post-market changes and cancellation of biological product marketing authorizations |
| ANVISA RDC n. 413/2020 | Post-market changes and marketing authorization cancellation procedures for biological products |
| ANVISA RDC n. 412/2020 | Establishes the requirements and conditions for the conduction of stability studies for purposes of the marketing authorization and post-market changes for biological products |
| ANVISA RDC n. 323/2003 | Technical regulation for marketing authorizations, post-market changes and renewal for probiotic drugs |
| ANVISA RDC n. 301/2019 | General guideline for good manufacturing practices for drugs |
| ANVISA RDC n. 24/2011 | Marketing authorization procedures for specific drugs ("medicamentos específicos") |
| ANVISA RDC n. 76/2016 | Post-market changes and marketing authorization cancelation procedures for specific drugs ("medicamentos específicos") |

[37] "Biblioteca de Medicamentos", updated on 09/21/2021, available on 11/16/2021 at: https://www.gov.br/anvisa/pt-br/assuntos/regulamentacao/legislacao/bibliotecas-tematicas/arquivos/medicamentos

| | |
|---|---|
| ANVISA RDC n. 235/2018 | Provides for amendments, quality control inclusions in the marketing authorization of dynamized, herbal, and specific drugs, as well as biological products |
| ANVISA RDC n. 238/2018 | Marketing authorization, renewal and post-market changes, and notification of industrialized dynamized drugs |
| ANVISA RDC n. 70/2008 | Medical gas notification procedures |
| ANVISA RDC n. 26/2014 | Marketing authorization for herbal drugs and traditional herbal products, and notification procedures for traditional herbal products |
| ANVISA RDC n. 38/2014 | Post-market changes for herbal drugs and traditional herbal products |
| ANVISA RDC n. 47/2009 | Guidelines for drug package inserts |
| ANVISA RDC n. 71/2009 | Guidelines for drug labeling |

## Generic and Similar Drugs

Generic and similar drugs were introduced in the Brazilian regulatory system in 1999, when the National Congress passed Law n. 9,787/1999 to amend Law 6,360/1976 and introduce the concepts of generic, similar, and reference drugs.

According to the Law, a generic drug is similar to a reference or innovative product, interchangeable with it, generally produced after the expiry or waiver of patent or other exclusivity rights, whose efficacy, safety, and quality have been proven, and designated per the Brazilian Nonproprietary Names (in Portuguese, DCB – Denominação Comum Brasileira) or, in its absence, as per the International Nonproprietary Names (in Portuguese, DCI – Denominação Comum Internacional)[38].

The Law also defines as a reference drug the innovative product registered and marketed in the country, whose efficacy, safety, and quality have been scientifically proven to obtain the marketing authorization[39].

A similar drug is defined as a medicine which contains the same active ingredients, concentration, pharmaceutical form, administration route, posology, and therapeutic indication of an equivalent drug registered in Brazil, from which it must only differ in terms of size, product form, expiry date, packing, labeling, excipients, and vehicles. Like generic drugs, a similar drug must have its efficacy, safety, and quality demonstrated.[40].

[38] Law 6,360/1976, art. 3, XXI
[39] Law 6,360/1976, art. 3, XXII
[40] Law 6,360/1976, art. 3, XX

Before proceeding with the generic or similar drug marketing authorization application, companies must consult the list of reference drugs available at Anvisa's website[41], to verify whether there are eligible reference drugs with concentration and pharmaceutical form equivalent to the one the company intends to apply for, and in case there is no eligible reference drug in the list, the company must follow the procedures and apply for ANVISA to elect it.[42]

Biological, immunotherapeutic, plasma and human blood derived products; herbal, specific, dynamized drugs; radiopharmaceuticals; and medical gases are examples of products which cannot be subject to a generic or similar drug marketing authorization application.[43]

Below you find a list of the main resolutions and rulings which must be observed when applying for or renewing a generic or similar drug marketing authorization. For more and detailed information, companies should go to ANVISA´s website and access "Biblioteca de Medicamentos"[44] ("Drug Library"), where all links to the full content of the regulation below are provided:

| **Resolution/Ruling #** | **Subject Matter** |
|---|---|
| ANVISA RDC n. 16/2007 | Technical regulation for generic drugs' marketing authorization |
| ANVISA RDC n. 17/2007 | Technical regulation for similar drugs' marketing authorization |
| ANVISA RDC n. 47/2001 | Labeling requirements for generic drugs |
| ANVISA RDC n. 36/2001 | Forbids the marketing of similar drugs with generic denomination |
| ANVISA RDC n. 92/2000 | Guidelines for drug package inserts, labeling and promotional materials |
| ANVISA RDC n. 222/2006 | Anisa's general petition and tax collection electronic system ("TFVS") |
| ANVISA RDC n. 58/2014 | Measures for the interchangeability between similar drugs and reference drugs |
| ANVISA RDC n. 200/2017 | Marketing authorization granting and renewal procedures for drugs with synthetic and semi-synthetic active ingredients, classified as new, generic, and similar |

[41] Available on 11/16/2021, at: https://www.gov.br/anvisa/pt-br/setorregulado/regularizacao/medicamentos/medicamentos-de-referencia/lista-de-medicamentos-de-referencia
[42] ANVISA RDC n. 200/2017, art. 19
[43] ANVISA RDC n. 200/2017, art. 20
[44] "Biblioteca de Medicamentos", updated on 09/21/2021, available on 11/16/2021 at: https://www.gov.br/anvisa/pt-br/assuntos/regulamentacao/legislacao/bibliotecas-tematicas/arquivos/medicamentos

## Health Products

According to the Brazilian health legislation, health products are the medical, dental or laboratory equipment, devices, materials, items or systems, intended for prevention, diagnosis, treatment, rehabilitation, or birth-control and that do not use pharmacological, immunological, or metabolic means to accomplish their respective functions in humans, although they may have their functions assisted by such means.[45]

## Classification According to Risk Category

The health product area embraces the vastest range of regulated products within the Brazilian National Health Surveillance System, including products with various complexity and risk levels, ranging from infrared lamps to magnetic resonance imaging equipment.

The manufacturing, transformation, importation, exportation, storage, shipping, and commercialization of health products, among other activities, depend on their prior registration, enrollment with, or notification to ANVISA.[46]

The current regulation defines the following products and devices as health products[47]:

1. Active Medical device: any medical device relying for its functioning on a source of electrical energy or source of power other than that generated by the human body or gravity and which acts by converting this energy. Medical devices used to transmit energy, substances or other elements between an active medical device and the patient, without any significant change, shall not be deemed to be active medical devices.

2. Active Medical Devices for Diagnosis: any active medical device, used alone or in combination with other medical devices, intended to supply information for the purpose of detecting, diagnosing, and monitoring purposes, as well as for treating health or physiological conditions, diseases, or congenital deformities.

3. Active Medical Device for Therapy: any active medical device, used alone or in combination with other medical devices, intended to support, modify, replace, or restore biological functions or structures for the purpose of treating or alleviating an illness, injury or handicap.

[45]ANVISA RDC n. 185/2001, Annex I
[46] Law 6,360/1976, art. 11
[47]ANVISA RDC n. 185/2001, Annex I

4. Single-Use Medical device: any medical device intended for the prevention, diagnosis, treatment, rehabilitation, or birth-control that can be used only once according to the manufacturer's instructions.

5. Implantable Medical device: any medical device which is intended to be totally or partially introduced in the human body or to replace an epithelial or ocular surface, through surgical procedure, and intended to remain in the human body, permanently or for a considerable time.

6. Invasive Medical device: any medical device intended to penetrate the human body through the skin or a body orifice.

7. Surgical Invasive Medical device: any medical device intended to penetrate the human body through the skin or any orifice in a surgical procedure.

In addition, health products are classified into four different categories according to the intrinsic risk they may pose to the health of consumers, patients, operators, or third parties involved, as follows: class I (low risk), class II (medium risk), class III (high risk), class IV (maximum risk). There are several criteria to determine the risk degree of a health product[48]. Please find below a few examples of health product classification according to RDC 185/01:

| | | |
|---|---|---|
| Invasive Medical Device | For bodily orifices and not connected with an active medical device | Class I |
| Invasive Medical Device | For surgical use | Class II |
| Active Medical Device | For emitting ionizing radiation for radio diagnosis or radio therapeutic purposes | Class III |
| Invasive Medical Device | For surgical use in the diagnosis, monitoring, or correction of cardiac function with direct contact with such body parts | Class IV |

## Notification and Registration Requirements

Health products are subject to notification (generally, Risk Class I and II) or registration ("registro") procedures, depending on the product's risk classification, as described above.

[48] ANVISA RDC n. 185/2001, Technical Regulation Annex, Part 2, and Annex II

All medical products must be duly registered with or notified to the Ministry of Health, as the case may be, no matter its risk class[49], except for cases expressly provided in the regulation, such as health products undergoing clinical research[50].

The regulation clearly establishes the cases in which a product will be subject to a notification or registration procedure, providing that:

Notification is the communication a company makes to ANVISA of its intention to market a medical product, to have the manufacturing or importing rights granted in relation to a product pertaining to Risk Class I or II[51]; and

Registration is one of ANVISA's proprietary functions, granted upon satisfactory conclusion of the product dossier review, which serves as a proof of the manufacturing or import rights in relation to such product.[52]

Below you find a list of the main resolutions and rulings which shall be observed for product notification or when applying for a health product registration. For more and detailed information, companies should go to ANVISA´s website and access "Biblioteca de Produtos para Saúde"[53] ("Library of Health Products"), where all links to the full content of the regulation below are provided:

| **Resolution/Ruling #** | **Subject Matter** |
|---|---|
| ANVISA RDC n. 185/2001 | Technical regulation for registration, amendments, revalidation, and cancellation of the medical product registration before ANVISA |
| ANVISA RDC n. 36/2015 | Provides for the risk classification, notification control system, and labeling and instructions for use requirements, for in vitro diagnostic products, including their instruments |
| ANVISA RDC n. 40/2015 | Defines the requirements for notification of medical products |
| ANVISA RDC n. 211/2018 | Expiration date for medical product registration |
| ANVISA RDC n. 15/2014 | Provides for Good Manufacturing Practices requirements for health products registration |
| ANVISA RDC n. 222/2006 | Anvisa´s general petition and tax collection electronic system ("TFVS") |
| ANVISA RDC n. 539/2021 | Minimal identity and quality requirements for single-use transfusion equipment, gravitational infusion, and infusion pumps |

[49] ANVISA RDC n. 185/2001, Technical Regulation Annex, Part 3, item 1
[50] Law n. 6,360/1976, art. 25, §1; ANVISA RDC n. 185/2001, Technical Regulation Annex, Part 3, items 2 and 3
[51] ANVISA RDC n. 40/2015, art. 3, III, as amended by ANVISA RDC n. 423/2020
[52] ANVISA RDC n. 36/2015, art. 3, XXXI
[53] "Biblioteca de Produtos para Saúde", updated on 09/09/2021, available on 11/16/2021 at: https://www.gov.br/anvisa/pt-br/assuntos/regulamentacao/legislacao/bibliotecas-tematicas/arquivos/produtos

| | |
|---|---|
| ANVISA RDC n. 540/2021 | Minimal identity and quality requirements for hypodermic needles and gun needles |
| ANVISA RDC n. 541/2021 | Minimal identity and quality requirements for single-use sterile hypodermic syringes |
| ANVISA RDC n. 542/2021 | Definition of "group products" for the purposes of item 5.3, Annex II of Law 9,782/1999 (direct importation by individuals for services provided to third parties) |
| ANVISA RDC n. 543/2021 | Authorizes the medical devices notification procedures for textile yarn with thermal properties, indicated for the composition of clothing with therapeutic effects, beautification, or aesthetics correction |
| ANVISA RDC n. 544/2021 | Provides for the requirements for human blood collection, storage, and transfer plastic bags, and its components |
| ANVISA RDC n. 545/2021 | Electronic filing application for the issuance of health product certificates (subject to notification or registration procedures), and Foreign Government Certificate for exportation purposes |
| ANVISA RDC n. 546/2021 | Safety and efficiency requirements for health products |
| ANVISA RDC n. 548/2021 | Regulation on the performance of clinical studies with medical devices in Brazil |
| ANVISA RDC n. 549/2021 | Mandatory certification procedures for medical equipment |
| ANVISA RDC n. 550/2021 | Minimal identity and quality requirements for breast implants and product certification for compliance with the Brazilian Compliance Assessment System ("Sistema Brasileiro de Avaliação da Conformidade"- SBAC). |
| ANVISA RDC n. 551/2021 | Mandatory execution and notification of field actions by health products registration holders. |
| ANVISA RDC n. 552/2021 | Registration, manufacturing, quality control, marketing, and use of Intrauterine devices (IUD) containing copper. |
| ANVISA RDC n. 553/2021 | Registration of products used in artificial permanent skin pigmentation |
| ANVISA RDC n. 556/2021 | Requirements for the grouping of health products, and traceability labels for implantable products |

## Good Manufacturing Practices

The Good Manufacturing Practices (GMP) certificate is a document issued by ANVISA per manufacturing unit, certifying that the facility complies with certain standards and criteria for good manufacturing practices. Such certification is applicable to companies that manufacture drugs and medical devices, located either on national territory or abroad.[54]

[54] ANVISA RDC n. 497/2021, art. 2

GMP as a mandatory requirement, for its different purposes, will be provided for under ANVISA´s specific regulations.[55]

ANVISA RDC n. 497/2021 provides for the administrative procedures for obtaining the certificate[56].

## Drug GMP

The GMP certification for drug manufacturers will be granted to each establishment, per production line, and per pharmaceutical form[57].

ANVISA RDC n. 301/2019 establishes the general guidelines for Drugs GMP, including the requirements for quality control, technical responsibility, and quality risk management. GMP applies to all stages of the product life cycle, from the manufacture of investigational drugs, technology transfer, commercial manufacturing, to product discontinuation.[58]

The GMP adherence shall be ensured by the company's quality management to ensure that products are consistently produced and controlled according to quality standards, as well as the intended and required use planned by the sanitary license, clinical trial authorization, or product specifications. [59] Lastly, a GMP certificate is required in public tenders for drugs[60] for purposes of evidencing product identity and quality.

## Medical Devices GMP

According to the category of a medical device, the GMP certificate will be granted to each establishment, per production line, describing for each production line the respective product risk category [61].

ANVISA RDC n. 16/2013 approves the technical regulation of good manufacturing practices for medical devices, which addresses issues such as the general requirements for the quality system, production controls, and responsibility for product safety and effectiveness.

[55] ANVISA RDC n. 497/2021, art. 2, sole paragraph
[56] ANVISA RDC n. 497/2021, art. 8
[57] ANVISA RDC n. 497/2021, art. 13
[58] ANVISA RDC n. 301/2019, art. 6
[59] ANVISA RDC n. 301/2019, art. 12
[60] MoH Ordinance n. 2,184/1998, art. 5
[61] ANVISA RDC n. 497/2021, art.17, § 1

Medical devices classified under risk categories I and II are not eligible for GMP certification.[62] Notwithstanding, such products are subject to the notification system for sanitary control,[63]which requires from the manufacturer or importer the knowledge and compliance with the GMP practices established in the ANVISA RDC n. 16/2013.[64]

As for in vitro diagnostic products, classified under risk categories III or IV, the GMP application or GMP certificate issued by ANVISA is a required document for product notification, registration, or revalidation purposes.[65]

Below you find a list of the main resolutions and rulings which shall be observed for both, Drugs and Medical Devices GMP:

| Resolution/Ruling # | Subject Matter |
|---|---|
| ANVISA RDC n. 497/2021 | Administrative procedures for granting of GMP Certification |
| ANVISA RDC n. 301/2019 | General guidelines for Drug GMP |
| ANVISA RDC n. 16/2013 | General guidelines for Medical Devices GMP |
| ANVISA RDC n. 36/2015 | Risk classification, control regimes for notification and registration, and the requirements for labeling and instructions for use for in vitro diagnostic |
| ANVISA RDC n. 17/2017 | Administrative procedures applicable for granting GMP Certification for Medical Devices´ manufacturers (Risk Classes III and IV) located outside the Brazilian territory and outside Mercosur countries |

# 3. Drug Pricing and Reimbursement

## Drug Market Regulation Chamber (CMED)

### Drug Price Control System

The Drug Market Regulation Chamber (CMED) was created in 2003[66]as the Governmental body, under the structure of the Ministry of Health, responsible for the adoption,

[62] ANVISA RDC n. 497/2021, art.17, § 2
[63] ANVISA RDC n. 40/2015, art. 2
[64] ANVISA RDC n. 40/2015, art. 4, IV, d, and art. 10, § 1
[65] ANVISA RDC n. 36/2015, art. 19, VI, art. 24, IV, art. 19, § 2
[66] Law 10,742/2003, art. 5

implementation, and coordination of activities related to the economic regulation of the Brazilian drug market.

The powers granted to CMED include[67]:

(i) Issuing economic regulation for the drug market;
(ii) Establishing criteria for drug pricing and adjustments, in relation to new drugs and new drug presentations; and
(iii) Deciding on exemptions of groups, classes, or subclasses of drugs and pharmaceutical products from price control mechanisms

The rules for submitting a drug price approval application vary depending on the category in which the product falls under. CMED Resolution n. 2/2004 provides for the following[68]:

| Category | Description | Requirements |
|---|---|---|
| Category I | New product with a molecule patented in the country that brings gain to the treatment in relation to the drugs already used for the same therapeutic indication, with the confirmation of one of the following requirements: | a) Greater efficacy in relation to the existing drugs for the same therapeutic indication;<br>b) Same efficacy with a significant decrease in the adverse effects; or<br>c) Same efficacy with a significant reduction in the global cost of treatment |
| Category II | New products that do not fit the definition provided for in the last item | |
| Category III | New pharmaceutical presentation of a drug already marketed by the same company, in the same pharmaceutical form | |
| Category IV | New drug presentation that fall under one of the following situations: a) drug considered new on the list of the ones marketed by the company, except the cases provided for in item III of this article;<br>b) drug already marketed by the company, in a new pharmaceutical form | |
| Category V | Drug that fall under one of the following situations:<br>a) new pharmaceutical form in the country; b) new association of active | |

[67] Law 10,742/2003, art. 6
[68] CMED Resolution n. 2/2004, English version available on 11/16/2021 at: https://www.gov.br/anvisa/pt-br/assuntos/medicamentos/cmed/legislacao/arquivos/arquivos-resolucoes/6325json-file-1

| | | |
|---|---|---|
| | ingredients already existing in the country | |
| Category VI | Drug classified as generic, in accordance with Law n. 9,787/1999, related to item XXI of article 3 of Law n. 6,360/1976 | |
| | | |

Drug manufacturers that intend to market new products and new presentations should file an Informative Document at CMED's headquarters, informing the category they understand the product should be classified into. The Informative Document shall contain the following information:

| **Required Information**[69] | **C. I** | **C. II** | **C. III** | **C. IV** | **C. V** | **C. VI** |
|---|---|---|---|---|---|---|
| I. Brand name of the drug in Brazil and the other brand names for the same drug, used in the countries mentioned in item VII of this paragraph and in the manufacturer's country of origin | **X** | **X** | **X** | **X** | **X** | **X** |
| II. Drug approval number and EAN code, both comprised of thirteen digits | **X** | **X** | **X** | **X** | **X** | **X** |
| III. Substances from which the drug is formulated | **X** | **X** | **X** | **X** | **X** | **X** |
| IV. Copy of package insert | **X** | **X** | **X** | **X** | **X** | **X** |
| V. Presentation form in which the drug will be marketed | **X** | **X** | **X** | **X** | **X** | **X** |
| VI. Price at which the company intends to market each presentation, with the discrimination of taxes and sales margins | **X** | **X** | **X** | **X** | **X** | **X** |
| VII. Manufacturer's price, accompanied by the due proof of origin, practiced in Australia, Canada, Spain, United States of America, France, Greece, Italy, New Zealand, Portugal, and the manufacturer's price in the product's country of origin, excluding taxes | **X** | **X** | | | **X** | |
| VIII. Manufacturer's name and the manufacturing site of the active ingredient and the finished drug | **X** | **X** | | | **X** | |
| IX. Potential number of patients to be treated with the drug, with the indication of the corresponding period | **X** | | | | | |
| X. Cost-efficacy comparative analysis between the drug and the existing therapeutic alternatives | **X** | | | | | |

[69] CMED Resolution n. 2/2004, art. 4, §2

| | | | | | | |
|---|---|---|---|---|---|---|
| XI. Submittal of the following information on the product's patent: a) Number of the first international patent application, application date, and the country where it was filed; b) Number of patent application at INPI; c) Innovation presented by the product which the patent application was based on | **X** | | | | | |
| XII. When available, submittal of economic assessment studies published | **X** | | | | | |
| XIII. Phase III clinical trials conducted, which are relevant for the comparison between the new drug and those existing in the country for the same therapeutic indication, if any; and | **X** | **X** | | | **X** | |
| XIV. New therapeutic indications for the same drug – in trial, in approval phase, or approved in other countries, if any | **X** | **X** | | | **X** | |
| XV. List of all presentations of the drug in the market[70] | | | **X** | | | |

CMED shall inform the drug manufacturer of its decision within up to 90 days as regards to products classified under Categories I and II, and up to 60 days for products classified under Categories IV, V, and Category III[71], otherwise, the products may be marketed at the price proposed by the drug manufacturer[72]. Once approved by CMED, the drug price will be adjusted annually based on the indexes determined by CMED.[73]

## Incorporation of Technologies in Unified Health System – SUS

### CONITEC and Reimbursement System

CONITEC is the National Commission for Technology Incorporation at SUS, created in 2011 by Law n.12.401/2011, which addresses the therapeutic care and the incorporation of health technology in the scope of the Unified Health System (SUS). According to the Law, the Commission's main responsibility is to assist the Ministry of Health in the incorporation, change, or exclusion of health technologies provided by SUS, as well as in the elaboration or amendment of clinical protocols and therapeutic guidelines.[74]

[70] CMED Resolution n. 2/2004, art. 4, §5
[71] CMED Resolution n. 2/2004, art. 15
[72] CMED Resolution n. 2/2004, art. 15, §1
[73] Law 10,742/2003, art. 4 and §§
[74] Law n 8,080/1990, art. 19-Q, as amended by Law n. 12,401/2011; Decree 7,646/2011, art. 4

Once the drug price is approved by CMED, if the company intends to include the drug in the SUS, it must follow the procedures provided under the applicable legislation and file a tender with CONITEC – National Commission for Technology Incorporation at SUS, to initiate an administrative proceeding. Such tender shall provide the following information[75]:

(i) Standard form with all information required by CONITEC;
(ii) Marketing authorization number and expiry date, as provided by ANVISA;
(iii) Technical report with scientific evidence relating to efficacy, accuracy, effectiveness, and safety, compared with other drugs already included in the SUS;
(iv) Economic impact studies relating to the drug and corresponding comparison thereof with drugs already included in the SUS;
(v) Product samples, when applicable; and
(vi) Price approved by CMED, in case of drugs

Once CONITEC decides on the inclusion of the drug in the SUS, it will recommend its inclusion to the Ministry of Health and to the National Agency of Supplementary Health (ANS), in case the drug is also to be included in the private healthcare system.

As per the provisions of the Law, the whole process concerning the analysis for the inclusion of technologies (including medications) in the SUS shall take up to 180 days, renewable for another 90 days, depending on the circumstances.[76] However, the timeframe involved varies a lot, considering that the inclusion of technologies in the SUS will depend on what the Ministry of Health prioritizes from time to time.

Hence, the incorporation of certain technologies may be prioritized in case there is (i) a health policy which may benefit from the incorporation of such new technology, (ii) an epidemiologic situation, (iii) the need for review or elaboration of clinical protocols or therapeutic policy concerning certain diseases; (iv) a demand from the Government Attorney's Office; among other matters involving the public interest.

After the drug is included in the SUS, its supply to the relevant public entities in the Federal, State, and Municipal levels will follow certain technical and legal criteria established by the legislation concerning the supply of products to public authorities, which can be achieved through public bidding or direct purchase procedures, depending on the circumstances provided for in the applicable law.

[75] Decree 7,646/2011, art. 15
[76] Law n 8,080/1990, art. 19-R, as amended by Law n. 12,401/2011

## Reimbursement of Health Services Provided by Private Institutions to Patients in Public Health System

The topic of reimbursement of health services provided by the private sector to patients in the Unified Health System - SUS is based on the provisions of article 199[77] of the Brazilian Federal Constitution, which establishes two modalities for the provision of health services by private institutions: complementary and supplementary.

In this sense, complementary health care designates the actions and services provided by private institutions that participate in a complementary way in the SUS, through an agreement with the Government. Supplementary health care, on the other hand, covers activities performed by health professionals, clinics, private hospitals and health care plan operators that do not have a business relationship with the Government.

Law n. 8,080/1990[78], which provides for the conditions for the promotion, protection and recovery of health, establishes in its article 26 that the criteria for remuneration of services provided by the complementary health care activity will be established by the national administration of the SUS, whose values are provided for in the SUS Table.

Conversely, in a recent judgment of the [79]Federal Supreme Court, it was decided that companies operating in the supplementary healthcare system - companies that do not have an agreement with the Government, and that are required to provide care to SUS patients due to a court decision, have the right to demand that reimbursement of these services be made based on the National Agency of Supplementary Health (ANS) table and not the SUS Table.

The decision considers that the SUS table is applicable to spontaneous contracts, entered into between the Government and the private sector – complementary healthcare system.

With this, the decision establishes that the form of reimbursement of services provided by companies operating in the supplementary system must follow the same criteria of reimbursements made to SUS, for services provided to beneficiaries who have a health care plan.

# 4. Research Involving Humans

## Regulation and Role of National Health Council (CNS)

[77] Brazilian Federal Constitution, art. 199, § 1
[78] Law 8,080/1090, art. 24
[79] RE 666094/2019 – DF, available on 11/16/2021 at https://jurisprudencia.stf.jus.br/pages/search/repercussao-geral10902/false

The Brazilian National Counsel of Health ("CNS") was created in 1937[80] as a deliberative and permanent instance of the organizational structure of the Ministry of Health. It is formed by representatives of the government, service providers, health professionals and users, commonly known as social control in the health area. Its competences include[81]:

(i) Formulation of strategies and execution control for public health policies;
(ii) Establishing guidelines to be observed by health plans in its elaboration, according to the epidemiological characteristics and the organization of services;
(iii) Proposing criteria for the definition of standards and assistance parameters; and
(iv) Process tracking of scientific and technological development and its incorporation in the health area, aiming at the observance of ethical standards compatible with the sociocultural development of the country

Considering that the ultimate competence of the council is linked to scientific development process under the observance of ethical standards, the CNS was responsible for setting some of the first guidelines on clinical research. Although CNS Resolution n. 466/2012 does not hold the status of a law, it is deemed as one of the main regulations on the conduct of research involving humans in Brazil, and it has been issued in compliance with all relevant national and global standards, such as Universal Declaration on Human Genome and Human Rights, Declaration of Helsinki and the Universal Declaration on Bioethics and Human Rights.

Clinical research is an investigation involving humans. According to the definition given by the CNS, research involving humans is research that, individually or collectively, have humans as participants, in their totality or parts, and involve them directly or indirectly, including the handling of their data, information, or biological material.[82]

The guidelines and rules that regulate research involving humans must be considered within the scope of the individual and the collectivities, contemplating references from bioethics, such as autonomy, non-maleficence, beneficence, justice, and equity.[83] Given the constitutional principle of human dignity[84], every clinical research requires free and informed consent of the participants, individuals or groups, that themselves or through their legal representatives, express their consent to participate in the research. The formal validation of this consent happens through the signature of the Free and Informed Consent ("Termo de Consentimento Livre e Esclarecido")[85], which contains important information about the study as its justification and objectives, the possible discomforts, the expected risks and benefits, existing alternative methods, and the procedures that will be performed during the research.

It is worth highlighting the issue involving the risks and benefits from the clinical research given the chance of risks in various types and degrees. Thus, the risk analysis is an

[80] Law n. 378/1937, art. 67
[81] Decree n. 5,839/2006, art. 2
[82] CNS Resolution n. 466/2012, II.14
[83] CNS Resolution n. 466/2012, I
[84] Brazilian Federal Constitution, 1988, art. 1, III
[85] CNS Resolution n. 466/2012, IV.3

indispensable component of the ethical analysis, from which the monitoring plan that must be offered by the "National Research Ethics Committees/National Research Ethics Commission" ("CEP/CONEP") system in each specific case derives.[86] The precautions and protection offered by the CEP/CONEP system to participants should be parameterized according to the variability of evidence and severity of the risks to which participants are subjected.

## Ethics Committees in Local and National Levels

The CEP/CONEP system is directly linked to the CNS and the organizational structure of the Ministry of Health, addressing its main objective of protecting research participants in Brazil through an accreditation process, which occurs in a coordinated and decentralized method. All the research involving humans in Brazil must be submitted to the CEP/CONEP system, which, by analyzing and deciding it, becomes co-responsible for guaranteeing the protection of the participants.[87]

The CEP is an interdisciplinary and independent collegiate body of public relevance, with a consultative, deliberative, and educational purpose. A committee created to defend the interests of research participants in their integrity and dignity and contribute to the development of research within ethical standards. Considering its attributions, the following stands out:[88]

(i) Evaluate research protocols involving humans, prioritizing topics of public relevance and strategic interest to the SUS agenda. In order to achieve this, it uses epidemiological indicators as a basis to elaborate a formal opinion, duly justified, and guided by the principles of impersonality, transparency, reasonableness, proportionality, and efficiency

CONEP is an independent collegiate body of advisory, deliberative, normative and educational nature. Some of its duties includes:[89]

(i) Examine the ethical aspects of research involving humans, as well as the adequacy and updating of the related rules, being able to consult the society, whenever consider necessary;
(ii) Encourage society's participation in the initiatives of Social Control of Human Research, as well as the creation of institutional CEPs and other instances, whenever such creation may result the strengthening of the protection of research participants in Brazil;
(iii) Register and supervise the operation of the CEPs;
(iv) Evaluate research protocols involving humans to prepare a formal opinion, duly justified, and guided by the principles of impersonality, transparency, reasonableness, proportionality, and efficiency;

[86]CNS Resolution n. 466/2012, V
[87]CNS Resolution n. 466/2012, VII
[88]CNS Resolution n. 466/2012, VIII
[89]CNS Resolution n. 466/2012, IX

(v) Strengthen the involvement of CEPs through a continuous process of training, qualification and accreditation; and
(vi) Coordinate the accreditation process of CEPs, certifying them according to levels of competence that enable them to be delegated responsibilities originating with the CONEP

## Clinical Research Phases

CNS Resolution n. 251/1997 approves the guidelines for research involving human subjects for the areas of new drugs, drugs, vaccines, and diagnostic tests. According to its provisions, clinical research on human subjects is divided into four distinct phases:[90]

(i) Phase I - The first study in humans in small groups of volunteers, generally healthy of a new active ingredient, or new formulation. This research aims to establish a preliminary development of safety and pharmacokinetic profile, and when possible, a pharmacodynamic profile.
(ii) Phase II - Pilot Therapeutic Study aims to demonstrate the activity and establish the short-term safety of the active ingredient, in patients affected by a particular disease or pathological condition. The research is conducted on a limited number of people and is often followed by an administration study. It should also be possible to establish dose-response relationships, in order to obtain a solid background for the description of extended therapeutic studies (Phase III).
(iii) Phase III - A study conducted on a large and varied group of patients with the objective of determining the short- and long-term risk/benefit outcome of the active ingredient formulations, as well the relative therapeutic value. The type and profile of the most frequent adverse reactions, as well as special characteristics of the drug, are also explored in this phase.
(iv) Phase IV - These are post-marketing surveillance studies, to establish the therapeutic value, the emergence of new adverse reactions and/or confirmation of the frequency of emergence of already known ones, and treatment strategies.

## Role of ANVISA

ANVISA's competence to control and supervise products, substances and health-related services[91] implies that the agency is responsible for setting rules regarding clinical research involving the products under its surveillance. Besides, the ethical approvals for the studies are considered for purposes of the marketing authorization process[92].

[90] CNS Resolution n. 251/1997, II.1
[91] Law n. 9,782/1999, art. 8
[92] ANVISA RDC n. 200/2017, arts. 15 and 17

One of the many types of clinical research that exist is the clinical trial, which is a study conducted on humans with the aim of proving that a drug, vaccine, health product, cosmetic or food subject to sanitary control is safe and efficacy. Each type of product must follow its specific regulation[93], more specifically ANVISA RDC n. 09/2015 provides for the regulation for the conduction of clinical trials in Brazil with drugs and the ANVISA RDC n. 548/2021 with medical devices.

According to ANVISA RDC n. 09/2015, a clinical trial can be defined as research conducted in humans with the purpose of finding out or to confirm the clinical and/or pharmacological effects and/or any other pharmacodynamic effect of the experimental drug. In addition, it also verifies any adverse reaction to the experimental drug and study the absorption, distribution, metabolism and excretion of the experimental drug to verify its safety and efficacy.[94]

The beginning of the procedure, as well as the definition of the requirements for conducting clinical drug trials in Brazil, includes the submission of the "Drug Clinical Development File" ("DDCM") to be approved by Anvisa. DDCM is a compilation of documents used to evaluate the stages inherent to the development of an experimental drug, in order to obtain information to support the registration or post-registration changes of the product.[95] It also must ensure the safety and the rights of the participants in all phases of clinical development, the quality of the investigational medical product and of the data obtained in the clinical phases of development, to enable an evaluation of the efficacy and safety of the product.[96]

After receiving the DDCM, ANVISA will evaluate it within 90 days[97], and the following situations are possible:

(i) Issuance of a special notice indicating all studies that may be initiated in the country respecting the other ethical approvals[98];
(ii) If there is no manifestation from Anvisa within 90 days after the receipt of the DDCM, clinical development may be initiated after the relevant ethical approvals[99]. In the case of clinical development fits into at least one of the following situations: national development, clinical development of biological products - including vaccines - and phase I or phase II clinical development, the technical area will evaluate the DDCM within 180 days after receiving it and the clinical study may only begin after Anvisa's approval.[100]

ANVISA RDC n. 548/2021 introduces the concept of "Medical Device Clinical Investigation File" (MDICD) and its procedures and requirements for approval by ANVISA[101]. Clinical

[93] ANVISA RDC n. 09/2015, art. 4
[94] ANVISA RDC n. 09/2015, art. 6, XII
[95] ANVISA RDC n. 09/2015, art. 6, XIX
[96] ANVISA RDC n. 09/2015, art. 32, XIX
[97] ANVISA RDC n. 09/2015, art. 36
[98] ANVISA RDC n. 09/2015, art. 35
[99] ANVISA RDC n. 09/2015, art. 36, sole paragraph
[100] ANVISA RDC n. 09/2015, art. 36, § 3
[101] ANVISA RDC n. 548/2021, art. 1

trials with medical devices registered in Brazil may evaluate: (i) new indication for use; (ii) new intended use; (iii) relevant post-registration change. [102]

Clinical trials involving the medical devices under investigation that have the following characteristics are eligible for submission of a DICD[103]: (i) products of risk class III and IV; (ii) devices intended for diagnostic use, regardless of risk class, which meet the following criteria: (a) the device under investigation is invasive; (b) the device under investigation is intended to provide energy to the clinical trial participant; (c) the study uses the target device as the sole diagnostic procedure, using other devices or diagnostic procedures, duly recognized and approved, to confirm the diagnosis.

Regarding DICD evaluation by ANVISA, the process is very similar to clinical trials involving drugs. Therefore, it is possible to ANVISA release a special notice indicating all studies that may be initiated or in case of no manifestation from Anvisa within 90 days after the receipt of the DICD, clinical development may be initiated after the relevant ethical approvals.[104] It is worth mentioning that the notification system applies to clinical trials involving risk class I and II medical devices, observational clinical trials and post-marketing clinical trials regardless of risk class, without the need of submission of a DICD. [105]

Below you find a list of the main resolutions and rulings which shall be observed to consider apply for clinical research involving drugs or medical devices:

| **Resolution/Ruling #** | **Subject Matter** |
|---|---|
| CFM Resolution n. 1,098/1983 | Adopts the Helsinki Resolution as a guide for the medical profession regarding clinical research |
| MoH Resolution n. 251/1997 | Guidelines for research involving human subjects for the thematic area of new drugs, drugs, vaccines and diagnostic tests |
| CNS Resolution n. 466/2012 | Guidelines and regulations for research involving humans |
| ANVISA RDC n. 09/2015 | Regulation for clinical trials with drugs in Brazil |
| ANVISA RDC n. 172/2017 | Procedures for the importation and exportation of goods and products for scientific or technological research and studies involving humans |
| ANVISA Normative Ruling (IN) n. 20/2017 | Provides for inspection requirements in Good Clinical Practices for drugs clinical research |
| ANVISA Normative Ruling (IN) n. 21/2017 | Provides for inspection requirements in Good Clinical Practices for medical devices clinical research |
| ANVISA RDC n. 548/2021 | Regulation for clinical trials with medical devices in Brazil |

[102] ANVISA RDC n. 548/2021, art. 1, § 1
[103] ANVISA RDC n. 548/2021, art. 4
[104] ANVISA RDC n. 548/2021, arts. 10-11
[105] ANVISA RDC n. 548/2021, art. 5

# 5. PDP - Partnership for Productive Development

The Partnerships for Productive Development (PDP) are designed to promote access to drugs and medical devices considered strategic to SUS[106], for strengthening the country's industrial complex. The main purpose is to foster national development to reduce the cost of acquisition for products currently imported and that represent high costs for SUS. The PDPs may be made between two or more public institutions or between public institutions and private companies, seeking to promote national public production. According to the Law n. 8,666/1993 the PDP contracting process is exempt from public bidding procedures, including the acquisition of these products during the technological absorption stages. [107]

PDPs are also supported by the Brazilian Federal Constitution as a way to foster innovation in Brazilian companies and other entities, public or private.[108]Furthermore, the Brazilian Federal Constitution allows federative entities to execute PDPs for the implementation of research projects, scientific and technological development, and innovation, with financial or non-financial purposes.[109]

In general terms, the PDP's implementation stages consist of: (i) proposal submission; (ii) evaluation and decision; (iii) technology absorption and transfer; (iv) technology absorption and transfer with acquisition; and (v) technology internalization.

After the technology transfer period, the national public laboratory shall be able to start take over the product manufacturing to meet the national demand. With production taking place in the country, the public laboratories help reduce dependence on imports and produce quality drugs, increasing their competitiveness and technological capacity

For more and detailed information regarding the PDPs currently in progress, companies should go to MoH´s website and access "Produtos objeto de PDP"[110].

Below you find a list of the main legislation which shall be observed for PDPs:

| Resolution/ruling # | Subject Matter |
|---|---|
| Law n. 8,666/1993 | Establishes rules for bidding and contracts made by public administration |
| Law n. 8,080/1990 | Conditions for the promotion, protection and recovery of health, and the organization and operation of the corresponding services |

[106] Decree n. 9,245/2017, art. 7, I
[107] Law n. 8,666/1993, art. 24, XXXII
[108] Brazilian Federal Constitution, art. 219, sole paragraph
[109] Brazilian Federal Constitution, art. 219-A
[110] Available on 11/16/2021 at: https://www.gov.br/saude/pt-br/media/pdf/2021/setembro/28/pdp/medicamento-vacina-e-hemoderivados-parcerias-vigentes-parcerias-vigentes.pdf

| | |
|---|---|
| Law n. 10,973/2004 | Incentives for innovation and scientific and technological research in the productive environment |
| Inter- Ministerial Ordinance n. 128/2008 | Establishes guidelines for public contracting of drugs and pharmaceuticals by SUS |
| ANVISA RDC n. 50/2012 | ANVISA's procedures for registration of products in development process or technology transfer that are PDP object |
| Decree n. 9,245/2017 | Establishes the National Policy for Technological Innovation in Health |
| Decree n. 9,283/2018 | Establish incentive measures for innovation and scientific research in the productive environment, aiming at technological qualification, the achievement of technological autonomy, and the development of the national and regional productive system |
| Decree n. 9,307/2018 | Amends Decree n. 9,245/2017, which establishes the National Policy for Technological Innovation in Health |
| Decree n. 10,001/2019 | Deliberative Committee for PDP and the Technical Evaluation Committee for PDP |
| MOH/SCTIE Ordinance n. 45/2019 | Sets forth the Productive Development Partnerships Deliberative Committee and the Technical Evaluation Committee of the Productive Development Partnerships |

# 6. COVID Relevant Legislation

## Declaration of Public Health Emergency

On January 30, 2020, the World Health Organization ("WHO") declared the coronavirus outbreak (COVID-19) a Public Health Emergency of International Importance ("ESPII")[111], this is WHO's highest alert level as set forth in the Health International Regulations ("HIR")[112] - incorporated by Decree n. 10,212/2020. This decision seeks to improve and coordinate global cooperation and solidarity actions to combat the spread of the virus. In the terms of the IHR, the ESPII is defined as "an extraordinary event that may constitute a public health risk for other countries due to the international spread of disease; and potentially requires an immediate and coordinated international response.[113] On March 11, 2020, COVID-19 was characterized by WHO as a pandemic[114], this term referring to the geographical distribution of a disease with sustained person-to-person transmission.

[111] Available on 11/16/2021 at: https://www.paho.org/pt/covid19/historico-da-pandemia-covid-19
[112] Available on 11/16/2021 at: https://www.gov.br/anvisa/pt-br/assuntos/paf/regulamento-sanitario-internacional/arquivos/7181json-file-1
[113] Available on 11/16/2021 at: https://www.gov.br/anvisa/pt-br/assuntos/paf/regulamento-sanitario-internacional/arquivos/7181json-file-1
[114] Available on 11/16/2021 at: https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020

Currently, Brazil has about 21.5 million confirmed cases of the disease and almost 600,000 deaths[115]. Regarding vaccination, approximately 150 million people (70% of the population) have received at least one dose of the immunization and 95 million (45% of the population) are fully immunized. [116]

## ANVISA Regulation on Emergency Use

On February 3, 2020, the Ministry of Health decreed ESPII through MoH Ordinance n. 188/2020. Thereafter, Law n. 13,979/2020 was published, establishing measures for confronting the ESPII, which includes: [117](i) social isolation - separation of sick or contaminated people, or affected items, from others, in order to avoid the contamination or spread of the coronavirus; (ii) quarantine - restriction of activities and isolation of people suspected of contamination from those who are not sick; (iii) determination of compulsory performance of: medical examinations; laboratory tests; collection of clinical samples; vaccination and other prophylactic measures; and/or specific medical treatments; (iv) epidemiological study or investigation; (v) exceptional and temporary restriction of entry and exit from the country, as per ANVISA's technical and reasoned recommendation; (vi) exceptional and temporary authorization for the importation of products subject to sanitary surveillance without registration at ANVISA.

Among ANVISA's competences, the exercise of health surveillance of ports, airports, and borders, combined with its necessary action in special circumstances of health risk, demand from the agency a leading position in countering the spread of the COVID-19 pandemic. As previously mentioned, restrictions on entering and leaving the country were necessary, as well as exceptional authorizations to be able to meet the high demand for services and products used because of the ESPII.

In early March 2020 and from a general perspective, ANVISA RDC n. 346/2020 was published, defining the extraordinary and temporary criteria and procedures for the certification of good manufacturing practices for the purposes of registration and post-registration changes of active pharmaceutical ingredients, drugs and health products due to the international public health emergency of the COVID-19. According to the rule, it permitted (i) the temporary and emergency use of information from foreign regulatory authorities to replace the health inspections carried out by ANVISA; (ii) use of remote inspection mechanisms; (iii) temporary certification.

Another general rule that deserves to be highlighted is the ANVISA RDC n. 483/2020, which sets forth, on an extraordinary and temporary basis, the requirements for the importation of new medical devices and drugs identified as priority for use in health services, by virtue of the ESPII. Annex I of the rule provides a list of drugs and medical

[115]Available on 11/16/2021 at: https://especiais.g1.globo.com/bemestar/coronavirus/estados-brasil-mortes-casos-media-movel/ - Consórcio de veículos de imprensa
[116] Available on 11/16/2021 at: https://especiais.g1.globo.com/bemestar/vacina/2021/mapa-brasil-vacina-covid/ - Consórcio de veículos de imprensa
[117] Law n. 13,979/2020

devices that can be imported on a special basis being exempt from sanitary regularization by ANVISA, or if regularized by authorization[118]. The products covered by the rule may be imported, since the importer guarantees its origin, quality, safety and effectiveness[119]. The public and private entities authorized to import such products must have AFE and AE for the case of drugs subject to special control, not requiring its submittal to the Ministry of Health, State Health Departments, Municipal Health Departments, and public and private hospitals.[120]

## Drugs

In the context of drugs, ANVISA has attempted to adapt the pertinent regulations by defining new criteria and extraordinary procedures capable of providing the best possible response to the pandemic. Among these adaptations, it is worth mentioning that measures were developed for aspects such as (i) specific labeling and package requirements[121] (ii) treatment of registration petitions and post-registration changes of drugs and biological products [122]; (iii) maximum quantities of drugs subject to special control[123]; (iv) requirements for submission of request for temporary authorization for emergency use (AUE) on an experimental basis [124]; (v) submission of request for exceptional and temporary authorization for importation and distribution of drugs[125].

## Medical Devices

Although products for the prevention, diagnosis, and treatment of COVID-19 do not form a specific regulatory category, they end up, for example, being regulated by the rules for drugs and medical devices. Indeed, the regulatory agency has demonstrated a lot of activity through the amount of publication of regulatory acts in order to help Brazil face the pandemic.

Therefore, some normative rules were enacted that, as in the case of drugs, established in an extraordinary and temporary manner on topics such as: i) the regime for the submission of clinical trials used for the validation of class III and IV medical device[126]; ii) requirements for importation, commercialization and donation of equipment used in

[118] ANVISA RDC n. 483/2020, art.1, §1
[119] ANVISA RDC n. 483/2020, art.1, §2
[120] ANVISA RDC n. 483/2020, art.1, §3 e §4
[121] ANVISA RDC n. 400/2020
[122] ANVISA RDC n. 415/2020
[123] ANVISA RDC n. 425/2020
[124] ANVISA RDC n. 475/2020
[125] ANVISA RDC n. 476/2020
[126] ANVISA RDC n. 365/2020

intensive care units[127]; iii) manufacturing, import and commercialization of individual personal protection equipment[128].

## Vaccines

From a health and sanitary perspective, there are currently four options for a COVID-19 immunizer to be made available for use in the country on a regular basis: (i) emergency use; (ii) exceptional importation; (iii) Covax Facility consortium (WHO); (iv) standard registration.

Provisional Measure n. 1,026/2021 was one of the first actions taken by the government to provide access to the vaccine in Brazil. This, in turn, was converted into Law n. 14,124/2021, which establishes exceptional measures for the acquisition of vaccines and the National Vaccine Operationalization Plan. According to the law, the direct and indirect public administration are authorized to enter into contracts for the acquisition of immunizers without requiring a bidding process, and even before sanitary registration or temporary authorization of emergency use. [129]

Subsequently, ANVISA RDC n. 475/2021 set the procedures and requirements for submitting an application for temporary authorization for emergency use (AUE), on an experimental basis, of vaccines to combat COVID-19. According to the rule, the AUE applies for vaccines with completed phase III clinical trials or with interim results from one or more phase III clinical trials. [130]The company applying for the AUE must commit to complete the vaccine's clinical development and submit its results to ANVISA, as well as apply for its sanitary registration with the agency.[131] ANVISA's opinion regarding the granting of the AUE will consider the registration approval report or authorization for emergency use issued by a foreign regulatory agency, such as the Food and Drug Administration (FDA - USA) and the European Drugs Agency (EMA - European Union), among others.[132] It is also worth mentioning that the applicant must submit the AUE application with the documents stipulated in ANVISA Guide n. 42/2020[133], which sets out the minimum requirements for the application.

In addition to the previous regulation, ANVISA released ANVISA RDC n. 476/2021 to establish the procedures and requirements for submitting an application for exceptional and temporary authorization to import and distribute drugs and vaccines for Covid-19. Among them are:[134] (i) import electronic petition; (ii) description of the products in the

[127] ANVISA RDC n. 378/2020
[128] ANVISA RDC n. 448/2020
[129]Law 14,124/2021, art. 1
[130] ANVISA RDC n. 475/2021, art.4
[131] ANVISA RDC n. 475/2021, art.5
[132] ANVISA RDC n. 475/2021, art.8
[133] Available on 11/16/2021 at: https://www.gov.br/anvisa/pt-br/centraisdeconteudo/publicacoes/medicamentos/publicacoes-sobre-medicamentos/guia-sobre-os-requisitos-minimos-para-submissao-de-solicitacao-de-autorizacao-temporaria-de-uso-emergencial-em-carater-experimental-de-vacinas-covid-19
[134]ANVISA RDC n. 476/2021, art. 11

import license, authorized under Law 14,124; (iii) submission of the proof of exceptional and temporary import authorization granted by Anvisa's Collegiate Board; (iv) batch release certificate; (v) import license (LI) registered in SISCOMEX; (vi) AFE when applicable.

Brazil's admission to the vaccine consortium promoted by the WHO called Covax Facility was signed on October 25, 2020 and is expected to provide about 42 million doses to the country. Thus, ANVISA RDC n. 465/2021 was issued, and establishes the exemption of registration and emergency use authorization and the procedures for import and monitoring of the vaccines acquired by the Ministry of Health, within the Covax Facility.[135]The rule provides that these vaccines must have their quality, safety, and efficacy proven through their approval in the global access instrument and must be destined exclusively for the National Immunization Program ("PNI").

ANVISA RDC n. 55/2010 provides for the registration of biological products, among them the vaccine, describing it as an immunobiological drug that contains one or more antigenic substances that, when inoculated, are capable of inducing active specific immunity in order to protect against, reduce the severity of, or combat the disease(s) caused by the agent(s) from which the antigen(s) originated.[136] The rule further provides that for its registration is necessary the presentation of: [137](i) AFE; (ii) sanitary license; (iii) certificate of technical responsibility; (iv) certificate of good manufacturing practices.

Under normal conditions, the development of a vaccine usually takes years due to the need to attend to high standards of demand, quality, safety and efficacy. Thus, the immunization development stages, in general terms, can be listed as:[138]

(i) Non-clinical trials: before human trials are conducted, laboratory and animal trials should be promoted to investigate the safety of the vaccine and its ability to generate antibodies;
(ii) Clinical trials: studies conducted in humans after significant data and information is obtained from the previous step;
    a. Phase I. Evaluates safety and possible undesirable reactions. During this phase, the ability to generate antibodies against the new virus can also be verified.
    b. Phase II. The safety analysis is maintained, but the dose, vaccination schedule, and ability to generate antibodies in the population to be vaccinated are also evaluated.
    c. Phase III. Tests performed in large populations to evaluate the safety and efficacy of the vaccine.
(iii) Registration: A registration application must be submitted to ANVISA following specific legislation[139], and after analysis and review of all technical documents by the agency, it will grant the registration and consequently the permission for the vaccine to be marketed.

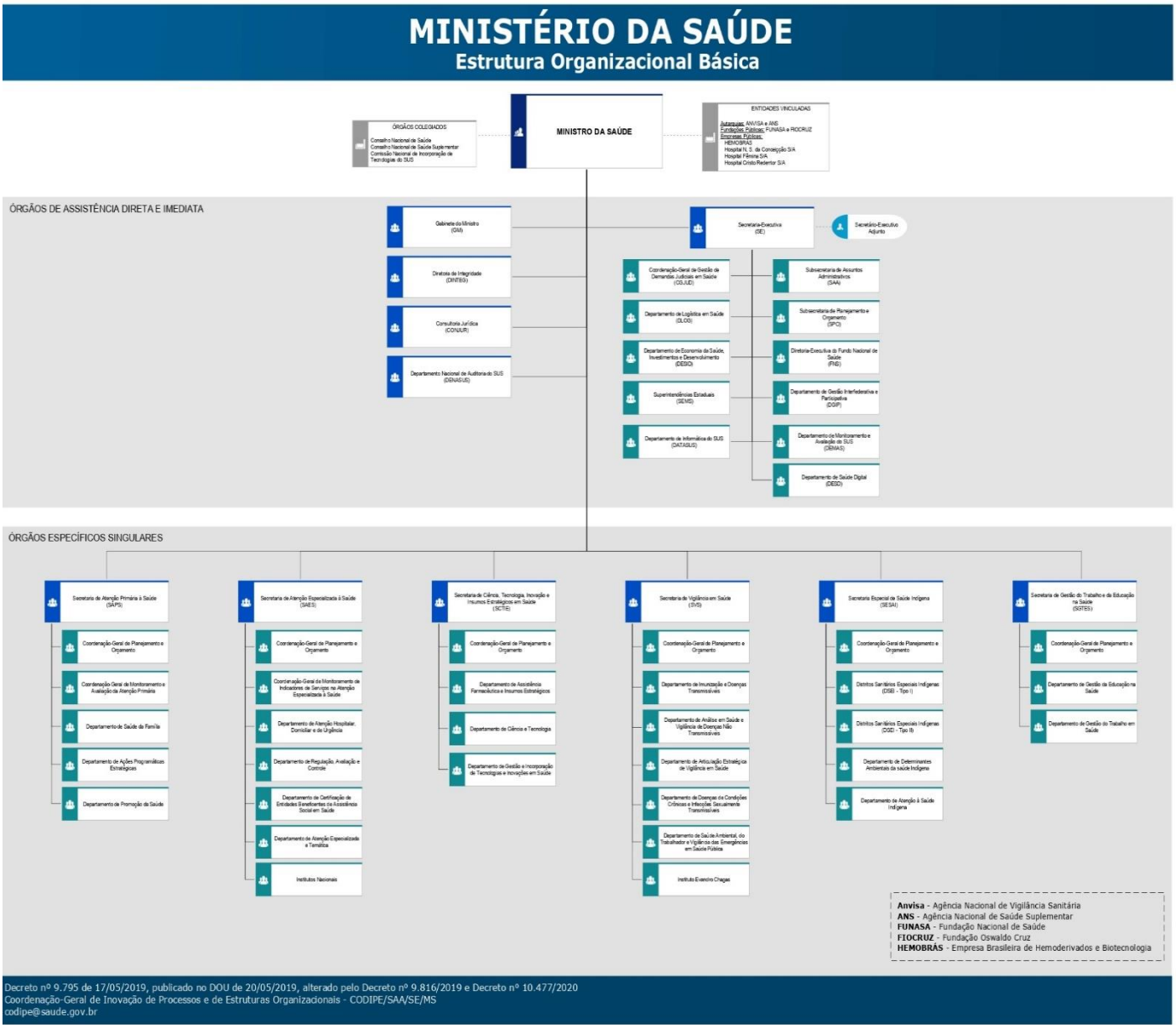
[135]ANVISA RDC n. 465/2021, art. 1
[136]ANVISA RDC n. 55/2010, art. 2, XXIV
[137]ANVISA RDC n. 55/2010, art. 30
[138] Available on 11/16/2021 at: https://www.gov.br/anvisa/pt-br/assuntos/noticias-anvisa/2020/vacina-contra-covid-19-dos-testes-iniciais-ao-registro
[139] ANVISA RDC n. 55/2010

Below you find a list of the main resolutions and rulings which shall be considered due to regulatory changes promoted by COVID-19:

| Resolution/Ruling # | Subject Matter |
|---|---|
| ANVISA RDC n. 346/2020 | Extraordinary and temporary procedures for certification of good manufacturing practices for registration and post-registration changes of active pharmaceutical ingredients, drugs and health products |
| ANVISA RDC n. 357/2020 | Temporarily extends the maximum quantities of drugs subject to special control |
| ANVISA RDC n. 375/2020 | Submission of clinical trials used for the validation of class III and class IV medical devices |
| ANVISA RDC n. 378/2020 | Requirements for the importation, commercialization and donation of used lung ventilators, vital sign monitors, infusion pumps, oximetry equipment and capnographs |
| ANVISA RDC n. 400/2020 | Specific requirements for drugs labeling and packaging |
| ANVISA RDC n. 415/2020 | Registration petitions and post-registration changes for drugs and biological products |
| ANVISA RDC n. 448/2020 | Requirements for the manufacture, importation and commercialization of individual personal protection equipment |
| ANVISA RDC n. 525/2021 | Appreciation and deliberation of administrative appeals, in the last instance, by means of a Deliberative Circuit |
| ANVISA RDC n. 465/2021 | Authorization for emergency use and the procedures for importing and monitoring Covid-19 vaccines purchased by the Ministry of Health (Covax Facility) |
| ANVISA RDC n. 475/2021 | Submission of application for temporary authorization for emergency use (AUE), on an experimental basis, of drugs and vaccines |
| ANVISA RDC n. 476/2021 | Submission of application for exceptional and temporary authorization for importation and distribution of drugs and vaccines |
| ANVISA RDC n. 483/2021 | Requirements for the importation of new medical devices and drugs |
| ANVISA RDC n. 484/2021 | Anesthetic drugs, sedatives, neuromuscular blockers, and other hospital drugs |
| ANVISA RDC n. 534/2021 | Continuous submission of clinical development dossiers for Covid-19 vaccines by Brazilian public universities or publicly funded institutions |

# 7. Organizational Charts and Contact Information

## Ministry of Health Organizational Chart[140]




[140] Ministry of Health's Basic Organizational Chart. Available on 09.29.2021, at: https://antigo.saude.gov.br/images/pdf/2020/October/15/-A3-Organograma-Basico-MS-Dec-9795-alterado-10.477.pdf

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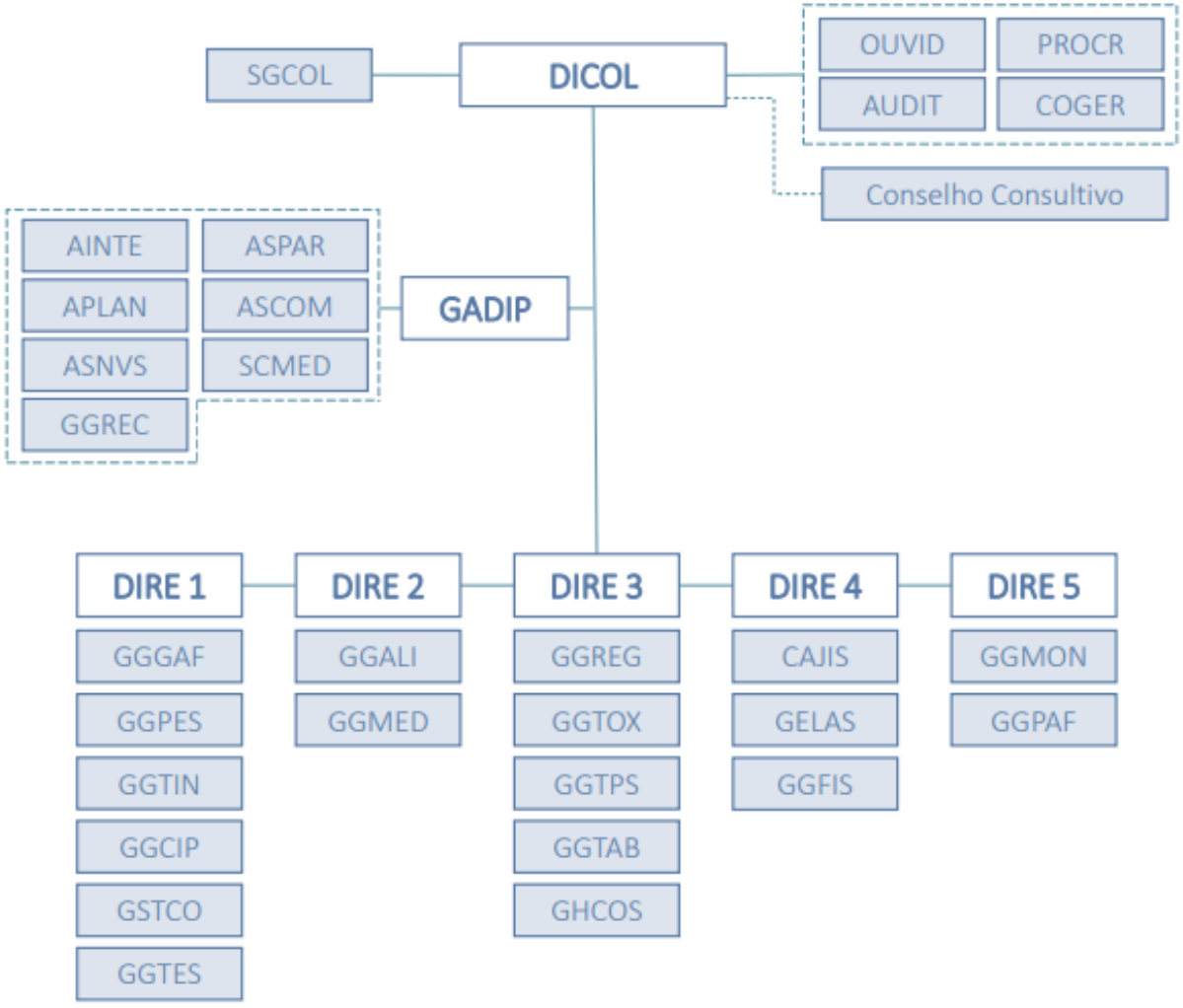
## ANVISA Organizational Chart[141]




[141] Anvisa's Annual Management Plan for 2021. Available on 11.16.2021, at: https://www.gov.br/anvisa/pt-br/assuntos/noticias-anvisa/2020/anvisa-divulga-plano-de-gestao-anual-para-2021/pga-2021-final.pdf

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