Life Sciences Regulators in Brazil: Overview

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A Practice Note providing an overview of regulatory authorities with jurisdiction over pharmaceuticals and medical devices in Brazil, including requirements enforced by the National Sanitary Surveillance Agency (ANVISA) under Brazilian law.

Countries around the world, including Brazil, regulate pharmaceuticals and medical devices and require approval from a regulatory authority before a new product can be legally marketed. Countries often also require continued monitoring, reporting, and inspections by a regulatory authority to ensure that pharmaceuticals and medical devices remain safe and effective.

This Practice Note discusses:

- Legislation and regulations concerning pharmaceuticals and medical devices in Brazil.

- The regulatory authority (or authorities) responsible for enforcement.
- Key requirements and considerations for marketing pharmaceuticals and medical devices in Brazil.
- The consequences of failing to obtain regulatory approval.

Legislation and Regulatory Framework

The 1988 Brazilian Federal Constitution (*Constituição da República Federativa do Brasil*) provides general principles and rules for many social rights, especially health care. Article 196 of the Constitution provides for a citizen's right to health and the government's duty to implement health policies to reduce illness and other risks. Article 197 sets out the government's obligation to regulate health services and products, and justifies the mandates of regulatory authorities in those industries and sectors.

The main statutes related to the manufacturing, authorization, and commercialization of pharmaceuticals and medical devices are:

- Federal Law No. 6,360/76 regulates the manufacturing, commercialization, advertising, labelling, inspection, quality control, penalties, importation, and marketing approval of medicines, drugs, active ingredients, and medical devices. Federal Decree No. 8,077/13, which implements Law No. 6,360/76, also regulates these topics.
- Federal Law No. 5,991/73 establishes sanitary control of commerce and trade in drugs, medicines, active pharmaceutical ingredients, and medical devices.
- Federal Law No. 6,437/77 sets out the penalties for infringing federal sanitary statutes and corresponding regulations, including criminal sanctions.
- Federal Law No. 9,294/96 imposes restrictions on the use and advertising of medicines and therapies, including smoking products, alcoholic beverages, and agrochemicals. Federal Decree No. 2,018/96, which implements Law No. 9,294/96, also regulates these topics.
- Federal Law No. 9,782/99 creates the National Sanitary Surveillance Agency (ANVISA), an autonomous regulatory agency administratively linked to the Ministry of Health. ANVISA regulates the production and marketing authorization of pharmaceuticals, food, household products, cosmetics, medical devices, smoking products, and related new technologies.

ANVISA's regulatory framework applies these laws. The key ANVISA regulations are:

- Collegiate Board Resolution (*Resolução da Diretoria Colegiada*) (RDC) No. 753/22 provides the criteria for granting marketing authorization of medicines for human use with synthetic and semi-synthetic active ingredients, which are classified as new, innovative, generic, and branded generic.
- RDC No. 55/10 (amended by RDC No. 406/20) provides for marketing authorization of new biological products.

- RDC No. 205/17 (amended by RDC Nos. 763/20 and 406/20) establishes a procedure for approval of clinical trials, certification of good manufacturing practices, and marketing authorization of new drugs for the treatment, diagnosis, or prevention of rare diseases.
- RDC No. 505/21 establishes general conditions for the approval of marketing authorization of advanced therapy products.
- RDC No. 96/08 regulates the advertising and promotional practices of prescription and over-the-counter drugs.
- RDC No. 751/22 sets out risk classification, reporting, notification, and registration regimes and labelling requirements and instructions for the use of medical devices.

No supranational legislation is applicable in Brazil. However, ANVISA incorporates some rules of the Southern Common Market (Mercosul in Brazil and in Portuguese, also known as Mercosur) and also follows some of the standards of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and International Medical Devices Regulators Forum (IMDRF).

Regulatory Authority and Responsibility

ANVISA regulates the manufacturing and marketing authorization of pharmaceuticals, food, household products, cosmetics, medical devices, agrochemicals, smoking products, and related new technologies.

ANVISA is a self-governing agency managed by a board of directors (board) under the regime set out in Law No. 9,782/99.

The main activities of the ANVISA board include:

- Reviewing and approving the regulatory agenda.
- Approving, monitoring, and evaluating compliance with the agency's Strategic Plan and Annual Management Plan.
- Evaluating the performance of the agency's organizational units.
- Complying with and ensuring compliance with regulatory acts relating to health surveillance.
- Deciding on the agency's strategic administration.
- Carrying out the procedures necessary to select persons to fill positions at the agency.
- Issuing normative acts on matters within the agency's jurisdiction.
- Preparing and disseminating periodic reports on the agency's activities.

- Preparing, approving, and enacting the agency's by-laws and defining the scope of action of the organizational units and the executive structure of the agency.
- Establishing and defining strategic projects regarding the representatives, deadlines, and products to be presented to the board.
- Ruling on administrative appeals filed against the agency's decisions as the last level of administrative review.
- Proposing government policies and guidelines intended to enable the agency to fulfill its objectives to the Ministry of Health.
- Expressing its opinion, consistent with the Regulatory Impact Analysis (*Análise de Impacto Regulatório*) (AIR) report, on the adequacy of proposed new rules to meet intended objectives, indicating whether the estimated impacts justify recommending adoption of the rules, and, when applicable, determining which additional rules should be enacted.

Each of the five board members leads an area at ANVISA:

- The Director-President's Office (known as DIRE 1) is responsible for:
  - co-ordinating corporate risk management, internal control, transparency, and integrity programs;
  - defining practices for improving the quality of organizational processes;
  - proposing alignments between governance and management practices; and
  - promoting communication and institutional relations with governmental and non-governmental bodies to strengthen social participation in ANVISA's regulatory activities.
- The second board member's office (known as DIRE 2) leads the medicines and food offices, which are primarily responsible for marketing authorization assessments and approvals.
- The third board member's office (known as DIRE 3) is responsible for the medical devices office.
- The fourth board member leads the inspections team, which has a broad scope that includes good manufacturing practices (GMP) inspections and enforcement actions.
- The fifth board member leads activities connected to ports and airports.

Other authorities with roles in regulating the marketplace of pharmaceuticals and medical devices are:

- The Pharmaceutical Market Regulation Chamber (*Câmara de Regulação do Mercado de Medicamentos*) (CMED), created by Federal Law No. 10,742/03, is responsible for defining a price cap for most new medicines after ANVISA grants marketing authorization.

- The National Committee for Technologies Incorporation (*Comissão Nacional de Incorporação de Tecnologias no Sistema Único de Saúde*) (CONITEC), created by Federal Law No. 12,401/11, is responsible for Health Technology Assessments (HTA), which includes making recommendations for whether the Brazilian public health care system, known as the Unified Health System (*Sistema Único de Saúde*) (SUS), should adopt health technologies.

- The National Supplementary Health Agency (*Agência Nacional de Saúde Suplementar*) (ANS), a federal agency related to the Ministry of Health created by Federal Law No. 9,961/00, establishes the rules and coverage of private health care systems (for example, HMOs) and the mandatory minimum coverage of health insurance plans.

- Local sanitary authorities at the state, county, or municipality levels, which are responsible for monitoring and enforcing sanitary laws and rules in a decentralized manner, including the granting of sanitary licenses, which are required for companies to perform activities (for example, manufacturing, distribution, and commercialization) involving regulated products.

- The National Institute of Metrology, Quality, and Technology (*Instituto Nacional de Metrologia, Qualidade, e Tecnologia*) (INMETRO) and the Brazilian Association of Norms Techniques (*Associação Brasileira de Normas Técnicas*) (ABNT), which certify specific devices.

- The National Health Council (*Conselho Nacional de Saúde*) (CNS), a joint committee established by Federal Law No. 8,142/90, has broad mandates, including regulating clinical trials in Brazil, especially under Resolution Nos. 251/97 and 466/12.

- Professional councils (like those for medicine, nursing, and pharmacy) may impact the relationship with those health care professionals.

Key Requirements to Market a New Medical Product in Brazil

Pharmaceuticals

ANVISA does not accept applications for any regulatory approvals from foreign companies. It only accepts submissions by companies with the required licenses and permits as either:

- A manufacturer, for domestic products.

- An importer, for products brought from abroad.

To obtain an operating permit, the manufacturer must:

- Specify its industrial activities and the kind of products it wants to manufacture.

- Prove its technical, scientific, and operational capability.

- Obtain a sanitary license from the local authority and a permit from ANVISA to carry out its activities.
- Satisfy other requirements set out in ANVISA rules.

(Articles 2, 50, 51, and 52, Law No. 6,360/76, as amended by Federal Law No. 13,097/15.)

To carry out its activities, the manufacturer must also obtain a GMP certificate from ANVISA, which requires an inspection of the manufacturer's plant by ANVISA.

To import pharmaceuticals and market them in Brazil, a foreign manufacturer needs to:

- Have a local subsidiary or commercial representative with an operating permit and sanitary license and marketing authorization for each imported product.
- Obtain a GMP certificate from ANVISA. ANVISA can use the inspection report of a foreign regulatory authority as a basis for granting the GMP certificate.

For a medicine to be registered, it must both:

- Be proven, by scientific and analytical evidence, to be safe and effective for its intended use.
- Have sufficiently high quality, efficacy, and purity for human use.

(Article 16, Law No. 6,360/76.)

Product Categories

ANVISA's resolutions set out specific product categories and the corresponding technical requirements for obtaining marketing approvals. The main types are:

- New medicines with small molecule active pharmaceutical ingredients (APIs) (RDC No. 753/22).
- Generic and branded generic drugs (similar medicines), which can benefit from an abbreviated marketing approval procedure (RDC No. 753/22).
- Biological products (RDC No. 55/10, as amended by RDC No. 406/20). RDC No. 55/10 defines a biological product as a product with biological origin. The regulation specifically lists as biological products vaccines, hyperimmune sera, blood products, biomedicines (medicines obtained from biological fluids or animal tissues or from biotechnological procedures), monoclonal antibodies, medicines containing live, attenuated, or dead microorganisms, probiotics, and allergens.
- New medicines for rare diseases (RDC No. 205/17, as amended by RDC No. 293/19). The resolution provides steps to expedite the registration of medicines for rare diseases.

- Over-the-counter medicines (RDC No. 98/16).
- Advanced therapies, including cell therapies, gene therapy, and products from tissue engineering (RDC No. 505/21).

ANVISA provides specific regulations and guidance for other product categories, for example, homoeopathic and phototherapeutic products and medicinal gas.

Certain low-risk medicines can be marketed without ANVISA's review and approval if they comply with the requirements of RDC No. 576/21 and contain only permitted active low-risk ingredients, subject to the required procedure, indications, and instructions for their use and the GMP requirements for the products.

ANVISA also has issued specific regulations and guidelines regarding post-approval amendments, renewals, and cancellations for products in the categories in the list above.

Abbreviated or Accelerated Approval Procedures

In addition to the abbreviated pathway for the successful introduction and consolidation of generics in the Brazilian market (see Product Categories), ANVISA is gradually enhancing its procedures to streamline the approval of new drugs.

Federal Law No. 13,411/16, which amends Laws No. 6,360/76 and 9,782/99, imposes the following time limits for ANVISA:

- Ordinary review: 365 days for marketing authorization requests, 180 days for post-authorization requests.
- Priority review: 120 days for marketing authorization requests, 60 days for post-authorization requests.

RDC No. 204/17 lists the criteria for an applicant to request priority assessment of its submission. Among the possibilities, an applicant can request accelerated approval for promising therapies that treat an unmet need or a serious or life-threatening condition and provide benefit over available treatments.

Medical Devices

ANVISA can provide regulatory approval for medical devices in Brazil through two different paths, notification or registration. RDC No. 751/22, which became effective 1 March 2023, is the ANVISA regulation regarding classification of medical devices based on risk and how companies can market the devices.

Only a domestic legal entity registered in Brazil can request and hold approval to market a medical device. Some international companies either do not want to establish a local Brazilian affiliate or do not have an affiliate that is fully approved by ANVISA. These companies typically have a local distributor which holds the regulatory approvals.

Under Article 5 of RDC No. 751/22, medical devices are classified according to the sanitary risk framework involved with their use:

- Low risk (class I).

- Medium risk (class II).
- High risk (class III).
- Maximum risk (class IV).

Medical devices in classes I and II can be marketed through the notification process. Medical devices in classes III and IV must undergo a complete registration process. Each type of notification and registration has different requirements based on the risk involved in using the product.

Under RDC No. 751/22, ANVISA publishes notifications in the Official Gazette within 30 days. A published notification has no expiration date, and the holder does not need to renew approval granted by the notification.

Products subject to the registration process must are analyzed and examined by ANVISA according to their product category. The product categories are medical equipment, in vitro devices (IVD), materials, or implantable products. ANVISA can grant registration for ten years, and the holder must renew the registration.

A company can sell a medical device only after publication in the Official Gazette of either the notification or the grant of approval for the registration.

All of ANVISA's reviews are based on product safety, quality, and efficacy, using the evidence and proof produced by the company. The company must present a technical dossier that complies with standards provided by the IMDRF.

Additional rules applicable to medical devices include:

- Some medical devices have characteristics that require the device to have an INMETRO certification. This is true of, for example, all medical equipment and condoms.
- Applications to register products considered high and maximum risk (classes III and IV) must include the GMP certificate for the manufacturer's site.
- Imported products must have properly issued and apostilled free sales certificates and letters of authorization.
- All medical devices approved and sold in Brazil must have instructions for use, labelling, and packaging information in Portuguese.
- For new technologies, ANVISA requires clinical trials, a clinical evaluation, or both.

Key Post-Approval Requirements in Brazil

Pharmaceuticals

Manufacturers must seek approval from ANVISA for changes to critical aspects of products, for example, changes in the API manufacturing site and changes to the product formula. Depending on the change, manufacturers must either get prior ANVISA approval (for more substantial changes) or inform ANVISA before the change (for less substantial changes).

In addition, Law No. 6,360/76 (as regulated by RDC No. 406/20) sets out pharmacovigilance procedures, under which pharmaceutical companies must notify the authorities of any adverse reactions caused by medicines. RDC No. 406/20 consolidated rules and regulations and is consistent with the guidelines of the ICH.

RDC No. 406/20 came into force on 28 October 2020. It defines an adverse reaction as any undesirable medical occurrence in a patient to whom a medicine has been administered. There is no requirement for a cause-effect relationship between the reaction and the treatment. Rather, a company must report any unfavorable and unintentional sign, symptom, or disease temporarily associated with the use of the medicinal product. Companies must also:

- Create a risk management plan that sets out their pharmacovigilance actions and additional actions to minimize the risks of each drug.
- Report both:
    - serious and unexpected adverse effects from all sources (domestic and foreign); and
    - spontaneously reported adverse effects that occur domestically and that are serious and expected, non-serious and unexpected, and non-serious and expected.

Two other important post-approval notifications are:

- **Possible shortages.** RDC No. 18/14 requires marketing authorization holders to notify ANVISA of any interruption (either expected or unpredicted) in the manufacture/importation of products.
- **Recalls.** RDC No. 625/22 and Ministry of Justice Ordinance No. 618/19 require notice of recalls to both ANVISA and consumer protection authorities.

Medical Devices

Post-approval vigilance of medical devices (technovigilance) and field actions are regulated by RDC No. 67/09 (as amended by RDC No. 557/21) and RDC No. 551/21.

These regulations require marketing authorization holders (including importers and manufacturers) to report certain device-related adverse events and product problems.

Marketing authorization holders must report when any device may have caused or contributed to a severe threat to public health, death, a technical complaint with the potential to cause death or a severe adverse event, a non-serious adverse event, or is counterfeit.

Importers and manufacturers are responsible for any regulatory, civil, and criminal issues regarding their products.

Through its affiliation with the IMDRF, ANVISA collects information about adverse events for medical devices and shares it with other international authorities.

Consequences for Failure to Comply

ANVISA and other Brazilian local authorities at the state and the municipal levels perform inspections and enforce compliance with drug and device laws and regulations. For inspections, regulators can access facilities and records, but this access cannot be broader than the inspector's responsibilities. For example, a sanitary inspector cannot request access to tax records.

Law No. 6,437/77 lists potential sanctions:

- A warning letter.
- A fine from BRL2,000 to BRL1.5 million.
- Product seizure.
- Product destruction.
- Product ban.
- Suspension of sales or product manufacturing or both.
- Cancellation of marketing authorization.
- A partial or total ban of the manufacturing site.
- An advertising ban.
- Cancellation of the company's operating permit.

Depending on the facts found during an inspection or an audit, ANVISA or a local authority may issue a breach notice, which reports the facts regarding the noncompliance and the infringed provisions of the law and regulations. The breach notice starts an administrative process that must observe the principle of due process of law. The company that received the breach notice can file an administrative defense showing, for example, that the facts found did not actually violate the law. ANVISA issues an administrative decision after the defense filing. The company can appeal an adverse decision to two administrative appeal instances. Because the proceeding takes place before ANVISA, the agency cannot appeal an adverse decision.

At any time, the company can take its case to court by filing a lawsuit against ANVISA to challenge the legality of the infraction notice. Preliminary injunctions are available in the Brazilian judicial system. Courts usually decide whether to grant a preliminary injunction within one to two weeks from the filing. A final court decision takes an average of four to five years.

In Brazil, regulatory authorities like ANVISA cannot impose civil and criminal penalties, but authorities with jurisdiction can prosecute civil and criminal actions in court, for example, in cases of counterfeit or adulterated pharmaceutical products or medical devices. In these cases, the authorities often consider potential harm to consumers.

Other Considerations

Foreign Marketing Authorizations

A company with a foreign marketing authorization for a medicine must still obtain a Brazilian marketing authorization from ANVISA before selling it in Brazil.

Due to COVID-19, under Federal Law No. 14,006/20 and implementing regulations, ANVISA had 72 hours to authorize the import and distribution of materials, medicines, equipment, and health-related ingredients registered with a foreign health authority and authorized for commercial distribution in that country. This legislation applied only during the pandemic period, but it triggered a process of ANVISA revising its regulatory strategy regarding reliance on registration decisions made by foreign authorities.

In 2022, ANVISA issued RDC No. 750/22, which established a streamlined procedure for reliance on analysis conducted by foreign authorities that ANVISA recognizes as its equivalents for registration and post-registration requests regarding pharmaceutical products, biological products, and ingredients or supplies. This is a temporary measure valid until 31 March 2024 while ANVISA analyzes the impact of relying on foreign authorities' decisions.

Authorization Validity and Renewals

ANVISA sets time limits for marketing authorization renewals under Law No. 6,360/76.

A marketing authorization can be renewed for up to a ten-year term, depending on the nature of the product and the health risk involved.

A company must request renewal of a marketing authorization no more than 12 months but at least six months before the expiration date (RDC No. 31/14). If the company does not request renewal within this period, ANVISA cancels the marketing authorization.

Marketing authorization is considered automatically renewed if ANVISA has not issued its decision on a renewal application before the expiration date.

If the company does not market a medicine within certain time limits, the company cannot renew the marketing authorization. Under Law No. 13,411/16, a renewal requires evidence that the company marketed the medicine for at least the last two-thirds of its marketing authorization period. In other words, the holder of a 60-month marketing authorization must provide evidence that its drug has been marketed for at least 40 months before it expires. ANVISA has not issued any guidelines regarding how it will enforce this requirement, and there is no case law regarding it.

Cancellations

ANVISA can cancel the marketing authorization for a medicinal product if:

- The product or manufacturing process may present a risk.

- The manufacturer requests cancellation because:
  - it no longer wants to market the product; or
  - It wants to transfer the marketing authorization to another company (known as cancellation by transfer; see Marketing Authorization Transfers).

ANVISA can cancel a marketing authorization only after it conducts a review and issues an approval under specific rules.

Marketing Authorization Transfers

Before 2016, transfer of a marketing authorization was impossible outside of a merger or acquisition. Under RDC No. 102/16, issued on 25 August 2016, a company can request a marketing authorization transfer because of corporate operations like a merger, spin-off, incorporation, or succession, with or without changing the company's name, if the product's original technical specifications are unchanged. A marketing authorization transfer can also arise from ordinary commercial operations (for example, an asset sale) if the asset is clearly identified. RDC No. 102/16 lists the terms and conditions necessary for the transfer.

Combination Products

Generally, Brazilian regulations allow combinations of pharmaceutical products. When combinations involve a small molecule drug and a biologic product, one of ANVISA's areas responsible for complex cases is likely to conduct the analysis (for example, the area responsible for biologic products). A company can always request a pre-submission meeting with ANVISA to confirm the company's submission strategy and whether it should make any adjustments.

Medical devices can be combined with other substances. Special Rules in Rule 14 of RDC No. 751/22 apply to the categorization of these combinations. In general, combined products are treated as high (class III) or maximum (class IV) risk medical devices. Some examples of products within Rule 14 are pharmacological stents, intrauterine hormonal devices, and spermicide condoms.

Advanced therapy products like gene therapies are not health products because they are governed by specific legislation.

ANVISA created the Classification Committee of Products Subject to Sanitary Surveillance (*Comitê de Enquadramento de Produtos sujeitos à Vigilância Sanitária*) (COMEP), which is responsible for sanitary categorization of new technologies. COMEP refers to products that can be classified within more than one industry area as regulated by ANVISA as frontier products.

Software as a Medical Device

In March 2022, ANVISA published RDC No. 657/22, which sets out the requirements for registration of software as a medical device (SaMD). The resolution incorporates concepts from the IMDRF work group for SaMD. After the publication of RDC No. 751/22, the concepts and procedures for SaMD were incorporated into the general standards for software, bringing clarity to the sector.

RDC No. 657/22 defines SaMD as a system for medical, dental, or laboratory use, or applications intended for prevention, diagnosis, treatment, rehabilitation, or contraception. They must have no pharmacological, immunological, or metabolic effect on humans.

SaMD is defined as a medical device, including if linked to in vitro diagnosis, if it is intended for one or more of the above purposes and is not part of any medical device hardware. Software licensed under subscription or centrally hosted software (software as a service) also meets this definition.

However, the definition of SaMD does not include any software that is:

- For well-being (that is, software that encourages healthy activities or physical exercise that is not intended for prevention, diagnosis, treatment, rehabilitation, or contraception).
- Listed by ANVISA as a non-regulated product.
- Used solely for health service providers' administrative or financial management.
- Used to process demographic and epidemiological medical data, without any clinical, diagnostic, or therapeutic purpose.
- Linked to medical devices that are already registered.

RDC No. 657/22 requires that SaMD must be resubmitted for approval or updates if:

- The company adds new clinical features or the software includes different forms of clinical use.
- The company makes significant changes to the software's clinical features, safety, or efficacy.
- The software is intended for purposes other than those previously identified.
- There are changes to the software's visual identity that make it no longer recognizable from the images submitted to ANVISA.

Minor changes that do not alter the visual identity of the software do not require ANVISA's post-marketing authorization if they have no impact on the SaMD's indicated use, efficiency, or patient safety.

