



HEALTH SCIENCES

Brazilian national production of active pharmaceutical ingredients: regulatory and strategic framework

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Abstract: Active Pharmaceutical Ingredient (API) is any component of the final pharmaceutical product that serves as the active ingredient. The goal of the API Manufacturing is to produce APIs that are competitively priced and meet the quality standards with the least possible impact on the environment. The global API market is expected to experience massive growth in the coming years reaching the size of USD 355.94 billion. The global Pharmaceutical Industry is facing a new scenario in 2023 after responding to the COVID-19 pandemic. In this new panorama, rethinking the pharmaceutical production and market is necessary. Despite Brazil's prominence in terms of worldwide pharmaceutical spending, only 5% of the APIs required by local pharmaceutical companies are produced domestically. Therefore, Brazil is an untapped field for APIs' manufacturing and faces a scenario of health vulnerability associated with the reliance on foreign API imports to ensure the viability of national Pharmaceutical Production and Services. Huge investments are required to boost the growth of the API Manufacturing sector. Herein is presented a critical analysis of the current regulatory and strategic status of Brazilian national production and/or acquisition of APIs, which represent the key starting materials for the Pharmaceutical Industry.

Key words: Active pharmaceutical ingredient, API, Anvisa, Brazilian API market, Pharmaceutical market, Pharma industry.

INTRODUCTION

Pharmaceutical Manufacturing includes a series of processing steps, aiming to generate effective and safe pharmaceutical products (Lachman et al. 2001). Regarding to the Active Pharmaceutical Ingredient (API), the Brazilian Health Surveillance Agency, Anvisa (from Portuguese: *Agência Nacional de Vigilância Sanitária*), defines, through its 2020 Resolution of the Collegiate Board of Directors (from Portuguese: *Resolução da Diretoria Colegiada*), RDC N°. 359, API as any substance used in a finished pharmaceutical product that, when used in human beings, acts as active ingredient. Such substances are

intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease or to affect the structure and function of the body (Anvisa 2020a). Such definition is based on the International Council for Harmonisation (ICH) guidelines published by the European Medicines Agency (EMA 2000, ICH Q7).

Ensured access to high quality APIs should be considered a public policy priority given that low quality APIs can compromise the safety and efficacy of the final pharmaceutical product. In this context, in-depth and adequate scientific knowledge about APIs, proper registration of this

knowledge and careful attention to regulatory aspects that control their use in the manufacture of medicines are extremely important for a safe guarded pharmaceutical market (Anvisa 2020a, b, 2022a, b).

The API Manufacturing, a branch of the chemical industry responsible for the production of APIs, has the mission of preparing APIs that meet the quality and purity requirements specified by current legislation, in a competitive manner and ensuring the minimum environmental impact. The main product of this manufacturing sector, the API, represents the key starting material to be applied in the Pharmaceutical Industry, responsible for manufacturing the final pharmaceutical product, based on this API and the respective pharmaceutical excipients. Operations and processes carried out within the scope of the APIs Manufacturing and Pharmaceutical Industries must be submitted for approval by the respective regulatory agencies for registration granting, in order to ensure consistent quality of pharmaceutical products (Bezerra & Rodrigues 2017).

The International Council on Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) is an initiative that brings together regulatory agencies from different countries and experts in the industrial field, being led by American (Food and Drug Administration – FDA), European (European Medicines Agency – EMA) and Japanese (Japan Pharmaceuticals and Medical Devices Agency – Japan PDMA) agencies for the purpose of establishing unified protocols for the development and registration of pharmaceutical and medical products around the world. It is worth mentioning that Brazilian regulatory agency Anvisa has participated as a collaborator of the ICH since 2016, becoming part of ICH Management Committee in 2019 (Bermudez et al. 2020).

The ICH's core premise is to guarantee uniformity and raise the quality criteria associated with APIs and pharmaceutical products marketed worldwide, through the production of technical documents for standardization, the so-called ICH Guidelines. Furthermore, ICH seeks to foster a new concept in the production of medicines based not only on quality tests to be carried out on the final product, but on the application of the principles of Quality by Design (QbD), a systematic approach to be applied in pharmaceutical development, emphasizing the understanding and knowledge about the product, the process and its quality control, based on science and risk management. The QbD paradigm proposes that, through the adequate construction of knowledge about the production process, several variables relevant to the final quality of the product can then be properly identified, allowing the development of more efficient control strategies and optimized processes (Bezerra & Rodrigues 2017).

This initiative is extremely important, since APIs and finished pharmaceutical products are often imported or exported. Particularly with regard to the production of APIs, Asian countries such as India and China have grown significantly in the API Manufacturing market, exporting APIs to several countries around the globe at extremely competitive prices (Bansal 2020, Nikkei Asia 2022).

GLOBAL API MARKET

The market for Active Pharmaceutical Ingredients (APIs) is anticipated to increase at a compound annual growth rate (CAGR) of 7.1% from 2022 to 2030, reaching a value of USD 355.94 billion from USD 203.8 billion in 2022 (Precedence Research 2023).

The development in the production of APIs as well as the increased incidence of chronic

diseases including cancer and cardiovascular conditions are both responsible for the expansion (Grand View Research 2021). Highly potent APIs (HPAIP) make up an increasing share of the market, which is largely due to the development of numerous innovative oncology treatments (Cortellis 2019).

The expansion of the worldwide API market is also correlated with the expansion of the bio/pharmaceutical sector as a whole, which saw some changes in demand patterns as a result of the COVID-19 pandemic (DCAT Value Chain Insights 2022).

As the pharmaceutical sector was in the forefront of treating COVID-19 symptoms, such as high fever, cough, and cold, the Pharmaceutical Industry's increased output during the pandemic led to APIs market growth as well (Grand View Research 2021).

The worldwide API industry is dominated by synthetic APIs, which are pharmaceutical fine chemicals (APIs and intermediates), accounting for more than 80% of the market (DCAT Value Chain Insights 2022).

There are over 3,000 companies operating worldwide in the API Manufacturing Industry, with China accounting for 48.0% and India for 19%. Manufacturing of API is increasingly moving away from highly regulated markets (US, EU) and toward low-cost Asian nations, mainly China and India. This trend has been well-documented and has been going on for decades. According to the Chemical Pharmaceutical Association (CPA), South Korea, which makes up 3% of all API manufacturers, is the third-largest producer of API in Asia after China and India and the fifth-largest producer overall. With only 1% of all API companies in the world, Taiwan is among other Asian nations developing as a "second wave" of API suppliers. Western Europe makes up about 11% of all API makers worldwide, the US makes up nearly 6%, and Japan makes up 5% (Chemical

Pharmaceutical Association 2021, DCAT Value Chain Insights 2022).

Some factors are relevant to ensure China and India dominance in the global API market. For instance, government support, technology and automation, scale of operation, lower labor and utility costs represent pertinent factors to be mentioned (Cherian et al. 2021). However, the low-cost and efficient manufacture of APIs as a result of their extensive manufacturing could be highlighted as a major factor for their central role in API international supply (Technavio Research 2021).

Moreover, Chinese regulators have brought their regulatory framework to comply with international standards while also implementing policy measures that lowered the costs of domestic production, enabling the Chinese manufacturers to take a great part in the global API market (Graham 2023).

A substantial part of China's leadership in the global API supply chain can be additionally attributed to the availability of chemical intermediates. China produces over 80% of the intermediates utilized globally for the production of APIs. For instance, China is the largest supplier of intermediates to India, contributing with something around 70% to 80% of India's need for intermediates required to manufacture APIs in the country, as well as a key supplier of intermediates to developed markets, such as the US and Europe (see Table I) (DCAT Value Chain Insights 2022).

WuXi AppTec (WuXi STA), Asymchem Laboratories, Reyoung Pharmaceutical, Zhejiang NHU Co., Ltd., CSPC Pharmaceutical Group Limited (Shijiazhuang Pharmaceutical Group Co., Ltd) are some of the major companies operating in China API market. They are putting a lot of effort into growing their businesses through partnerships, facility expansion, and medicinal approvals (Mordor Intelligence 2023b).

Table I. China's position in the global API supply chain (DCAT Value Chain Insights 2022).

Intermediates
80% of intermediates used worldwide for APIs manufacturing are produced in China (mostly chemical APIs and generic APIs, bulk size, low value APIs).
US and China
Only 20,4% of APIs and intermediates are directly imported into the US from China.
But the majority of APIs imported into the US by other countries (Europe, India) are made with intermediates produced in China.
Europe, China and India
Europe relies on India and China for ~ 46-47% of its finished APIs.
Most APIs imported from India (and other countries overseas) are manufactured with intermediates produced in China.
India and China
~ 70 up to 85% of intermediates used to make APIs in India are from China.

The majority of APIs imported into the US from other locations (Europe, Asia) are made with intermediates produced in China, while only 20% of APIs and intermediates are directly imported from China into the US. 26% of the API manufacturers that supply the United States market are based in Europe, but China provides the majority of the intermediates needed by EU-based companies for the production of their APIs (DCAT Value Chain Insights 2022).

North America is one of the largest global active API markets, accounting for over 41% share in 2022 (Arizton - Advisor & Intelligence 2023), and the US represents most of this market (Mordor Intelligence 2023a). However, less than 5% of large-scale API sites, globally, are located in the US (DCAT Value Chain Insights 2023). The following are the major players in the country: Eli Lilly and Company, Pfizer, ABBVIE, Bristol-Myers Squibb, Ashland Specialty Ingredients, Parchem - Fine & Specialty Chemicals, SAFC Pharma, BoroPharm Inc. (Fortunachem 2022).

Despite the important local US API Manufacturing, in terms of values (Avalere

2022), there is no US-based manufacturing source for more than 80% of APIs used in key therapeutic areas and for essential medicines (DCAT Value Chain Insights 2023). Only 28% of the APIs manufacturers for the US market are local-based. In contrast, the remaining 72% of API manufacturers supplying the US market are located abroad, especially in China, India and in European Union (FDA 2019).

India is one of the biggest API exporters accounting for about 20% of global generic drug demand by volume, but it imports about 70% of the intermediates and key starting materials (KSMS) from China, according to the European Commission (Fischer et al. 2023). This is explained by the fact that, although India has strong API capabilities in certain segments, Chinese players have developed an advantage due to scale and favorable regulatory policies. Furthermore, one reason India is struggling to produce cheaper APIs, compared to China, is that fewer Indian manufacturers produce raw materials such as KSMS and intermediates. Many Indian API manufacturers therefore rely on

imports, mainly from China (Bogaert et al. 2015, Guerin et al. 2020, Cherian et al. 2021, EFPIA 2022, Nikkei Asia 2022, Fischer et al. 2023).

Some of the major players in India include the following companies: Cipla Limited, Aurobindo Limited, Sun Pharmaceutical Industries Limited, Lupin Limited, Teva API India Limited, Granules India Limited, Ipca Laboratories Limited. They are largely engaged in manufacturing APIs for asthma, cardiovascular diseases, diabetes, weight control, depression, vaccines, biopharmaceuticals and many more (Kandhwe 2022).

European manufacturers account for 30% of the world’s API production, making them important players in the market (Badwy 2021). Some of the main API producers in Europe are Germany, UK, France, Italy and Spain (Grand View Research 2023). Around 60.5% of the APIs used in Europe are domestically produced. Key factors that are driving the European API market growth include expansion in the biopharmaceutical industry, the establishment of new advanced manufacturing facilities that support the production of complex products, and advancements in developing API. The synthetic segment dominated the European

API market in 2022 with a share of 70.4%, and Germany had the highest market share of 18.24% in this same year, been considered a leader in European API production (Grand View Research 2023). Nevertheless, European countries are still greatly dependent on Asiatic API and intermediates production (Badwy 2021).

The key players in the European API market include the following companies: Cipla Inc., Merck & Co. Inc., Boehringer Ingelheim International GmbH, Sun Pharmaceutical Industries Ltd., AbbVie Inc., Bristol-Myers Squibb Company, Teva Pharmaceutical Industries Ltd., Albemarle Corporation, Aurobindo Pharma, Viatris Inc. (Grand View Research 2023).

The companies operating globally are categorized in Figure 1 based on their objective and demonstrable regulatory and market experience. According to data provided by Cortellis™ report, 1,792 corporations, or 55% of the industry, are made up of “Local” producers who can only service unregulated countries and their own home market. On the other end of the scale, only 6% of the sector is made up of “Established” producers who have years of expertise selling huge quantities of APIs to highly regulated markets like Europe, North

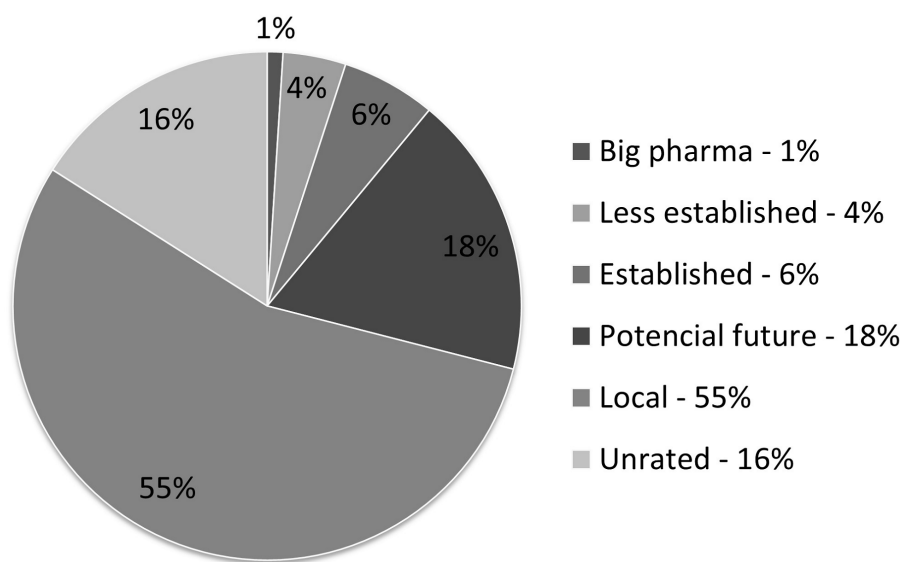


Figure 1. Among global API manufacturers, sorted by experience as “Established”, “Less established”, “Potential future”, “Local” or “Big Pharma”, those classified as “Local” manufacturers represent more than half (adapted from Cortellis 2019).

America and Japan. Just 345 manufacturers worldwide (those ranked “Established” and “Less Established”), or 10% of all manufacturers, have extensive experience catering to highly regulated markets. 16% of the sector, or approximately 538 companies, lack information or have insufficient information to base a ranking. 582 companies are rated “Potential Future,” indicating that they have limited regulated market experience over a brief period. These are the companies that will be expected to keep growing their capacities and move up to the “Less Established” classification in a few years.

Moreover, Figure 2 indicates that more than half of the experienced companies, those with “Established” and “Less Established” ratings, are headquartered in the United States, China, India and Japan (Cortellis 2019).

There is a significant concentration of API manufacture in these nations, and over the years, there hasn’t been much evidence that production is shifting to other emerging nations as some observers had previously projected. In fact, only South Korea, Taiwan, Brazil and Argentina have any significant API industries. Many of these industries have grown recently as a result of governmental incentives designed

to lessen reliance on foreign API imports and to promote local innovation and capacity in API development and production (Cortellis 2019).

OVERVIEW OF THE BRAZILIAN API MARKET

Brazil is the largest country in South America and the fifth largest globally, with the world’s sixth largest population. The overwhelming majority of people experience unstable economic conditions in their daily lives. Seven out of ten Brazilian workers had an income up to two minimum wages (R\$2,600.00 ~ US\$496 monthly¹) and 62.5 million people live below the poverty line, according data released by the Brazilian Institute of Geography and Statistics (IBGE 2023). Thus, large part of the population relies on the public health system. Brazil has the largest publicly funded healthcare system in the world in terms of beneficiaries, known as SUS (Unified Healthcare System, from Portuguese: *Sistema Único de Saúde*). SUS is a healthcare system which provides full, free and universal access to healthcare for the country’s entire population (over 215 million people) (IBGE 2023,

¹ exchange rate for the first quarter of 2023.

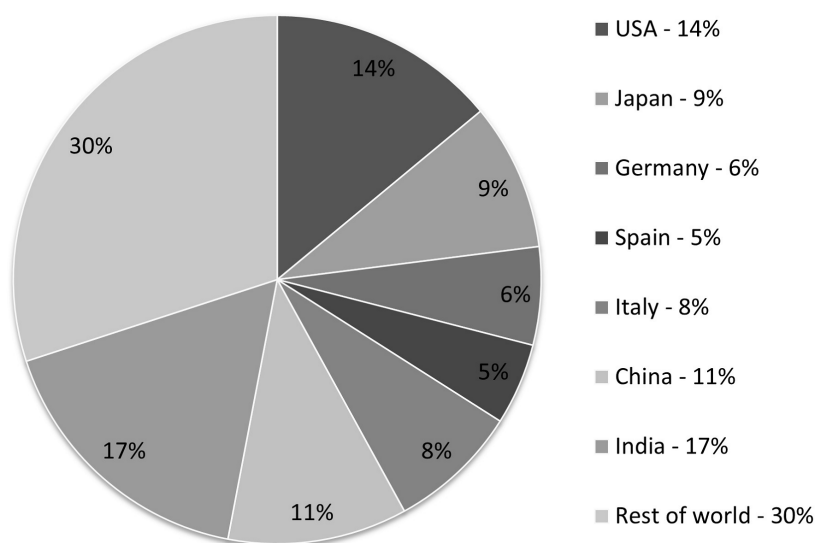


Figure 2. Geographic location distribution of “Experienced” API Manufacturing corporate groups (adapted from Cortellis 2019).

Ministério da Saúde 2023). 75% of Brazilians completely rely on the SUS to have access to health treatments (Interfarma 2022). Therefore, the national pharmaceutical production is crucial to improve the population's access to pharmaceuticals.

A limited number of international pharma companies operate manufacturing sites in the country. FDA and EMA-approved sites are only present in Brazil's eastern states, most of which are in São Paulo (see Figure 3) (Pharmaceutical Technology 2022).

Brazil has the largest pharma market in Central/Southern America (GlobalData 2022), and stands out in the global pharmaceutical landscape, currently bouncing between the 8th and 10th position on pharmaceuticals spending (IQVIA 2022, Interfarma 2022).

However, Brazil is heavily dependent on the foreign market for APIs acquisition, as indicated by the US\$ 2 billion deficit in 2017 (Bermudez et al. 2020). The internal production of APIs is tiny and decreasing, with approximately 90-95% of the sector's needs currently being supplied by imports, according to data from the Brazilian Association of Pharmochemical Industry and Pharmaceutical Ingredients (ABIQUIFI, from Portuguese: *Associação Brasileira da Indústria Farmoquímica e de Insumos Farmacêuticos*) (Rodrigues et al. 2018, Anvisa 2020c, Abiquifi 2022).

For comparison purposes, in terms of value in dollars, 53% of US expend on APIs' acquisition for production of domestically consumed medicines are directed to the local API Manufacturing sector, once the US facilities are producing more innovative and costly APIs.

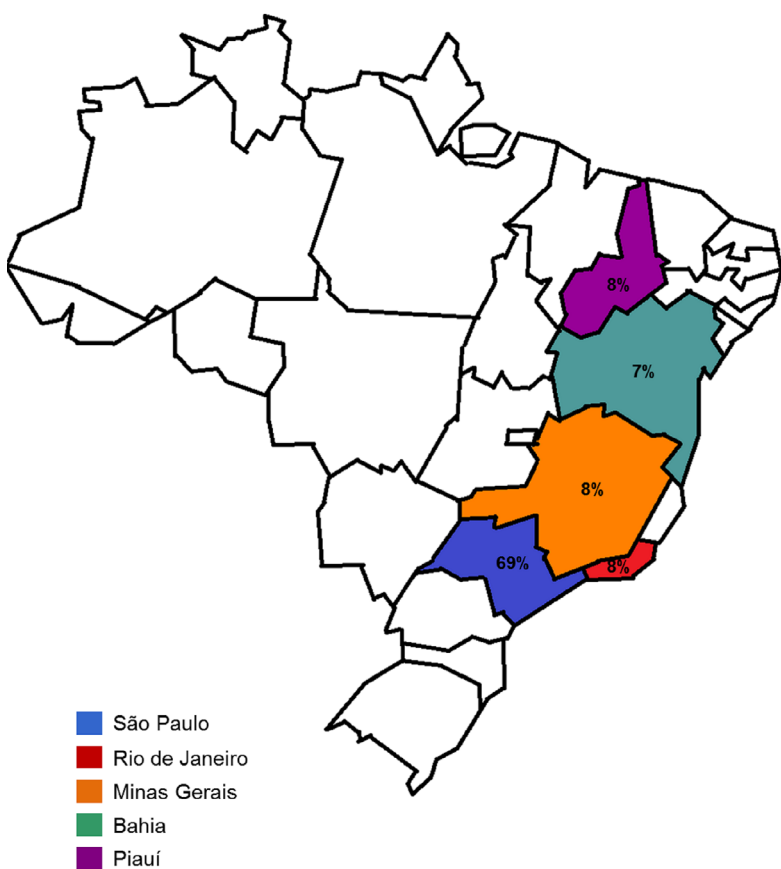


Figure 3. Map of Brazilian's FDA and EMA-Approved Contract Manufacturing Sites and their distribution around the States of the Country (adapted from Pharmaceutical Technology 2022).

However, as previously highlighted, despite the important local US API Manufacturing, in terms of values, more than 80% of APIs used in essential therapeutic areas lack US-based manufacturing sources (DCAT Value Chain Insights 2023). In Europe, 81% of pharmaceutical imports come from Europe itself. China accounts for 23% of all non-EU imports of APIs in terms of volume, representing the highest level of European dependency on APIs foreign supply, according to the European Centre for International Political Economy (ECIPE) (Guinea & Espés 2021).

According to information from Anvisa, 78% of production facilities abroad that export APIs to Brazil are located in China and India. Furthermore, for the majority of domestically produced APIs, the raw material consumed by the APIs manufacturing companies is in great part imported from these same countries (Anvisa 2020c).

Due to this growing dependence on imports, the country is currently in a situation of serious sanitary vulnerability, dealing with the constant imminence of a shortage of one or more essential medicines (Rodrigues et al. 2018, 2022). This problem became even more evident for authorities, health professionals and for the population in general in the context of the COVID-19 pandemic that affected the country and the world in 2020. The increased demand for certain APIs and other products relevant to the health sector, such as personal protective equipment and medical equipment used in Intensive Care Units (ICUs), has disclosed the sanitary vulnerability the country is exposed to once Brazil has no autonomy in the production of strategic items to guarantee the population health (Rodrigues et al. 2022). To worsen the increased demand issue, there was a simultaneous reduction in the supply of these same products on the international market during COVID-19 pandemic, due to the

forced interruption of entire manufacturing units around the world because of to the need to implement social distancing measures in order to contain the spread of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Chaves et al. 2020).

The circumstances mentioned above resulted in the scarcity of several drugs on the national and international market, such as those used in intubation procedures for patients affected by the severe form of COVID-19. This situation even costed lives of some patients, due to the impossibility of offering the best therapeutic approach for clinical management.

A survey carried out in early June 2020 by the National Council of Health Secretaries (Conass, from Portuguese: *Conselho Nacional de Secretários de Saúde*) with the 27 State Health Secretariats (SES, from Portuguese: *Secretarias Estaduais de Saúde*) in Brazil regarding the difficulties in supplying drugs used in the orotracheal intubation process for mechanical ventilation indicated the lack of several drugs in more than half of the 25 SES that sent a response to the Conass query (Table II) (Conass 2020).

The shortage of drugs used in orotracheal intubation was not exclusive to Brazil, although it has certainly been exacerbated by the history of low investments in the API Manufacturing sector and by drawbacks in logistics and management to combat the COVID-19 health crisis.

It should be also mentioned that the current existing national API Manufacturing companies exhibit adequate operating conditions for the manufacture of main essential drugs consumed in the country by SUS and that these companies fulfill the quality and regulatory standards established by Anvisa. In addition, Brazil is rich in specialized human resources with operational qualification for the various unit processes involved. The national companies have versatility and technical capacity for the

Table II. List of drugs required to intubate patients in the ICUs missing from more than half of the State Health Departments in Brazil, according to data collected by Conass on June 1, 2020 (Conass 2020).

	Drug:	SES that reported shortages:
1	Rocuroniumbromide (10 mg/mL)	24 (96%)
2	Fentanylcitrate (0.05 mg/mL)	20 (80%)
3	Midazolam (5 mg/mL)	19 (76%)
4	Atracuriumbesylate (10mg/mL)	19 (76%)
5	Cisatracuriumbesylate (2 mg/mL)	19 (76%)
6	Suxamethoniumchloride (100 mg)	16 (64%)
7	Atropinesulfate (0,25 mg/mL)	15 (60%)
8	Propofol (10 mg/mL)	14 (56%)
9	Morphine sulfate (10 mg/mL)	14 (56%)
10	Ketaminehydrochloride (50 mg/mL)	13 (52%)
11	Dextroketaaminehydrochloride (50 mg/mL)	13 (52%)

implementation and development of organic processes of low and medium complexity, whose peculiarities are suitable for their industrial plants. There is still little technological mastery in biotechnological processes, enantioselective synthesis and resolution of enantiomers, the latter being, however, increasingly present in the portfolios of national companies, as they give rise to higher added value APIs (Costa et al. 2014).

Regarding the drug therapeutic classes, the main APIs produced in the country include analgesics, anesthetics, anxiolytics/muscle relaxants, antidepressants/antimaniacs and antivirals. In a study carried out by Costa et al. (2014), the therapeutic classes with the greatest weaknesses and dependence on the foreign market were identified and included antineoplastics (oncological), antibiotics and APIs intended for treatment of neglected diseases, central nervous system diseases or cardiovascular diseases.

More specifically in the case of antibiotics, global supply chains are fragmented and present important bottlenecks at critical stages of the

process, with concentration of API producers in a few countries, mainly China and India. Several examples of the fragility in the supply chain of this therapeutic class can be cited, including the explosion of a Chinese factory in 2017, which caused the global shortage of the antibiotic combination of piperacillin and tazobactam, used to treat hospital infections, including urinary tract infections, pneumonia and sepsis. Benzathine benzylpenicillin (Benzetacil®) also had its supply threatened in Brazil. This API is produced by only 4 laboratories in the world, 3 of them located in China. Threats of shortages and problems related to the quality of the API, when available, have caused recurring disruptions to the supply in recent years. Even so, there is currently no initiative for prompting the national production of antibiotics and there is no prospect that this will happen considering the current scenario (Bermudez et al. 2020).

The World Health Organization (WHO), since the 1970s, encourages the promotion of policies that ensure access to medicines, recommending the adoption of national lists by its member countries. In 1975, through the publication Nº.

233 of the Brazilian Ministry of Social Security and Assistance, the Brazilian list was made official as the National List of Essential Medicines (Rename, from Portuguese, *Relação Nacional de Medicamentos Essenciais*) (DOU 1975, BVS 2022). The Rename undergoes permanent updates and is an important guiding for recognition of priority medicines and supplies for the SUS (Ministério da Saúde 2022).

Due to the low socioeconomic status of the vast majority of the Brazilian population that depends on the SUS's assistance, any future initiative in favor of the local API production must be focused on those requested to produce the essential medicines listed in Rename.

ACCELERATION APPROACHES FOR BRAZILIAN API SECTOR

Which are the best approaches to guarantee the development of the Brazilian APIs production considering the high financial investment necessary to meet the costs of an industry with expensive and complex technology, demand for highly qualified human resources and strict and growing regulatory requirements, taking into account, in addition, the fierce competition with Asian countries producing APIs for export? This is really not a trivial question and the answer is probably lying on the understanding from governmental leaders that this is a strategic sector for the country, which needs investment and promotion, in order to minimize the national health vulnerability (Rodrigues et al. 2022).

Alternatives to boost the growth of the sector include investment programs carried out through the National Bank for Economic and Social Development (BNDES, from Portuguese: *Banco Nacional de Desenvolvimento Econômico e Social*) and by innovation promotion agencies, such as the Financier of Studies and Projects (Finep, from Portuguese: *Financiadora de Estudos*

e Projetos). A study carried out by Oswaldo Cruz Foundation (Fiocruz, from Portuguese: *Fundação Oswaldo Cruz*) in the period from 2007 to 2013 identified, in fact, BNDES and Finep as the main funding bodies of API Manufacturing activity in the country (Bermudez et al. 2020).

A noteworthy initiative to be mentioned is the creation of the Support Program for the Development of the Pharmaceutical Productive Chain (Profarma, from Portuguese: *Programa de Apoio ao Desenvolvimento da Cadeia Produtiva Farmacêutica*) by BNDES in 2004, aiming to meet the following objectives: *i*) encourage the increase in the production of medicines and APIs for human use in the country; *ii*) improve drug quality standards and provide compliance with the requirements of the National Regulatory Agency - Anvisa; *iii*) reduce the trade deficit in the pharmaceutical production chain; *iv*) stimulate research, development and innovation projects; *v*) strengthen Brazil's economic, financial, commercial and technological position in the Pharmaceutical sector (Capanema et al. 2008).

The need for continued support to the Pharmaceutical sector, associated with a rapprochement between the BNDES sector responsible for Profarma and the Ministry of Health, resulted, in 2008, in the reformulation and expansion of Profarma's scope, being renamed the Support Program Development of the Health Industrial Complex. Thus, the program began to aim at reducing the vulnerability of the National Health Policy and promoting articulation between the industrial and public health sectors. For this, in addition to improving existing initiatives aimed at supporting production, innovation and restructuring of the national Pharmaceutical sector, new tools were created to encourage export activities by companies already installed in the country and also to provide financial support to public laboratories that produce drugs and immunobiologicals.

As a result, the BNDES bank signed, in 2009, a technical-scientific cooperation agreement with Fiocruz for the creation of a strategic partnership in the field of production and innovation in the Industrial Health Complex. The agreement involved important areas of the Foundation aimed at promoting the production of new drugs, vaccines and biotechnological medicines, using non-reimbursable resources from Funtec, the BNDES' Technological Fund.

NEW REGULATORY FRAMEWORK FOR APIS IN BRAZIL

Adopting international regulatory standards is also mandatory to ensure the supply of good quality APIs for the national Pharmaceutical sector. In the last years, Anvisa has taken a sequence of measures and actions in order to put Brazil in the context of international regulatory uniformity and provide a regulation up dated related to the manufacturing, imports and use of APIs for the production of medicines in Brazil.

In fact, for the last decades, Anvisa has been dedicating efforts to improve sanitary control over the APIs used in the national manufacture of medicines. This panorama is a consequence of the growing Brazil's reliance on the importation of APIs since 2000s (Costa et al. 2014). National API registry was initially established by RDC Nº 57/2009.

Afterwards, in 2014, the Registration Coordination of Active Pharmaceutical Ingredients (COIFA, from Portuguese: *Coordenação de Registro de Insumos Farmacêuticos Ativos*) was created. Since then, COIFA has been working systematically with the main objective of reducing the population's exposure to inherent risks related to low-quality APIs, by raising the level of APIs regulation in Brazil, consequently increasing the quality and safety of medicines.

Furthermore, COIFA had, over the last few years of work, the objective of providing an increase in the level of APIs regulation in Brazil (Anvisa 2019), culminating in the new regulatory framework for APIs established from 2020 on.

The implementation of these novel regulatory standards is extremely important to guarantee regulation equality between national and international manufacturers of APIs, since the Brazilian legislation for the national API Manufacturing sector was already following the strictest international standards of Good Manufacturing Practices recommended by the ICH. However, most of the APIs used in the manufacture of medicines in Brazil come from companies that did not have their factories audited by Anvisa or by the pharmaceutical laboratories themselves. Most of the time, imports were supported only by the analysis of the technical documentation sent. Thus, it is essential that external API manufacturing suppliers undergo the same sanitary rigor that Brazilian API manufacturing companies are subject to (Bermudez et al. 2020).

In this context, several novel Resolutions of the Collegiate Board of Directors from Anvisa (from Portuguese: *Resolução da Diretoria Colegiada - RDCs*) came into force in the last three years, aiming to regulating the sector.

The RDC Nº. 359/2020 establishes the Active Pharmaceutical Ingredient Dossier (Difa, from Portuguese: *Dossiê de Insumo Farmacêutico Ativo*), a set of administrative and technical documents of the API, which corresponds to the international Drug Master File (DMF); and the Suitability Letter of Active Pharmaceutical Ingredient Dossier (Cadifa, from Portuguese: *Carta de Adequação de Dossiê de Insumo Farmacêutico Ativo*), an administrative instrument that attests the adequacy of the submitted Difa to the corresponding Resolution (Anvisa 2020a).

The RDC N^o. 361/2020, in turn, modifies the previous RDCs N^o. 200/2017 and N^o. 73/2016 to establish the submission of the Difa in the registration and post-registration of medicines, respectively (Anvisa 2020b).

In turn, RDCN^o. 654/2022 deals with Good Manufacturing Practices for APIs (Anvisa 2022a) and RDCN^o. 672/2022 specifies the requirements for Good Manufacturing Practices certification and establishes the inspection program of multinational APIs Manufacturing facilities (Anvisa 2022b).

Finally, RDCN^o. 637/2022 provides for the obligation of all companies based in the country, which carry out the activities of manufacturing, importing, exporting, fractioning, storing, dispatching and distributing APIs, to register, with Anvisa, all the APIs they work with (Anvisa 2022c).

REGULATORY CHALLENGES FOR APIS QUALITY GUARANTEE

International regulation of APIs and pharmaceutical products marketed worldwide is a challenging sector which is constantly changing, evolving and updating. Considering that, collaborative initiatives such as the International Council on Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), bringing together the regulatory and industrial production sectors, are crucial to the effective and strategic decision-making process aimed at ensuring the safety and quality of pharmaceutical products available in the global market.

One emblematic and quite recent example was the unexpected identification of impurities from the so called *N*-nitrosamines class of compounds in different pharmaceutical products available on the market.

In 2018, regulatory agencies around the world suddenly became aware of the presence of the impurity *N*-nitrosodimethylamine (NDMA) in drugs from the “sartans” class. In 2019, the presence of NDMA was also reported in other drug classes, such as nizatidine, ranitidine and metformin (Anvisa 2022d, FDA 2021).

N-nitrosodimethylamine (NDMA) is included in the class of *N*-nitrosamines, which are characterized by the chemical bond between a nitroso group and an amine (R-N-N=O). Due to the mutagenic, genotoxic and carcinogenic potential of some compounds of the nitrosamine class, the formation of these impurities must be controlled at levels considered acceptable and safe, since exposure above acceptable levels and for a long period may increase the risk of cancer (Anvisa 2022d, FDA 2021).

N-nitrosamines can be formed by a reaction between amines and nitrosating agent (nitrous acid, nitrite salts), under specific conditions (Figure 4). Amines are common compounds in synthetic processes for the production of APIs and can appear as API degradation products, intermediate products, starting materials, catalysts, solvents, reagents, impurities or degradation products of solvents and reagents. All these amines can further react with nitrosating agents to generate nitrosamines (Anvisa 2022d).

Considering this, regulatory agencies were forced to take emergency measures to regulate the levels of these *N*-nitrosamine impurities in different medicines already available and widely used on the market (FDA 2021, Anvisa 2022d).

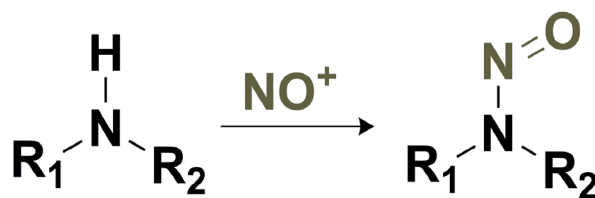


Figure 4. Nitrosamine formation.

These actions comprise the careful evaluation of the entire API and drug production process in order to assess whether there is a risk of nitrosamine formation at any stage of the process. In Brazil, the pharmaceutical industries must follow the rules described in the Resolution of the Collegiate Board (RDC) Nº 677, of April 28, 2022, to carry out the risk assessment and control of potentially carcinogenic nitrosamines in APIs and medicines for human use (Anvisa 2022e).

CONCLUSIONS

Brazil clearly faces a challenging scenario to ensure population's access to high quality and safe pharmaceutical products and to reduce the health vulnerability associated with the country's reliance on foreign API imports. There is no doubt that regulatory demands on APIs control will also continue to rise, as they have in the past, as manufacturers develop and expand their operations. Despite the relevance of a national pharmaceutical production to improve the availability of essential drugs, the local API production can be sometimes unfeasible due to the competitive low-cost of the Asian major API Manufacturing countries. Therefore, there is much work to be done in order to place Brazil in a significant position in the international APIs market. Its' local API industry growth depends on being economically viable in relation to the competitive cost of the international market. For sure, only by massive investments in infrastructure and research this ideal panorama could come into reality.

The government's goal should be to achieve at least partial self-sufficiency in API Manufacturing for production of essential medicines listed in Rename. In this regard, financial incentive policies and public investments are crucial to encourage not only

the state-controlled manufacturers, which should pay special attention to drugs used for endemic diseases' treatment, but also the private Brazil-based companies.

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