Comparative study between global pharmaceutical company and public institution of production and innovation in health

Estudo comparativo entre empresa farmacêutica global e instituição pública de produção e inovação em saúde

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ABSTRACT The technological scenario in the field of health is an alarming fact, especially in the context caused by COVID-19. In this context, the Oswaldo Cruz Foundation, through the Bio-Manguinhos Unit, and the Butantan Institute were protagonists for universal access, dialoguing with international strategies. In the strategic discussion for Public Institutions of Production and Innovation in Health (IPPIS), the use of guidelines of the Technological Assessment in Health stands out as a way of paradigmatic change for the introduction of technologies in the Unified Health System (SUS) in line with the vision of future innovation in health in accordance with national demands. This article, methodologically developed through qualitative descriptive research, bibliographical, documentary and field work, sought to trace symmetries and asymmetries based on the experiences collected in a global pharmaceutical company and a public national reference institution in the field of technological incorporation in health. As a result, key points are explained for the technical and political strengthening of the Health Economic-Industrial Complex, through the organizational review of the IPPIS regarding innovation and management aspects, culminating in the promotion of improvements in the science, technology and innovation policy in response to the challenge of sustainability, effectiveness and access in the SUS.

KEYWORDS Access to essential medicines and health technologies. Technology assessment, biomedical. Unified Health System. Health Economic-Industrial Complex.

RESUMO *O cenário tecnológico no campo da saúde é um fato alarmante, mormente no contexto provocado pela Covid-19. Nessa conjuntura, a Fundação Oswaldo Cruz, por meio da Unidade de Bio-Manguinhos, e o Butantan foram protagonistas para o acesso universal, dialogando com estratégicas internacionais. No adensamento da discussão estratégica para Instituições Públicas de Produção e Inovação em Saúde (Ippis), o uso de diretrizes da Avaliação de Tecnologias em Saúde destaca-se como via de mudança paradigmática para a introdução de tecnologias no Sistema Único de Saúde (SUS) alinhada à visão de inovação de futuro em saúde consonante às demandas nacionais. Este artigo, desenvolvido metodologicamente mediante pesquisas descritiva qualitativa, bibliográfica, documental e trabalho de campo, buscou traçar simetrias e assimetrias baseado nas experiências coletadas em empresa farmacêutica global e instituição de referência nacional pública do campo de incorporação tecnológica em saúde. Como resultados, são explicitados pontos-chave para o fortalecimento técnico e político do Complexo Econômico-Industrial da Saúde, por meio da revisão organizacional das Ippis quanto a aspectos de inovação e de gestão, culminado na promoção de melhorias na Política de ciência, tecnologia e inovação em resposta ao desafio da sustentabilidade, efetividade e acesso no SUS.*

PALAVRAS-CHAVE *Acesso a medicamentos essenciais e tecnologias em saúde. Avaliação da tecnologia biomédica. Sistema Único de Saúde. Complexo Econômico-Industrial da Saúde.*

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Introduction

The health area is clearly perceived as an area of great dynamism and absorption of knowledge and a balance between economic development and social well-being, with the Unified Health System (SUS) as one of the largest consumers of innovation. Therefore, it is assumed as the critical link that subordinates industrial policy, innovation, and health management. Thus, in the essential role of the State, the Health Economic-Industrial Complex (CEIS) acts as an articulator of essential factors (technological knowledge, industry, products and services, and technological incorporation in the SUS) in its subsystems, in favor of universal access to health in Brazil, strengthening the industry and technology, as a counterpoint to the capitalist logic that permeates the dynamics of the national health system[1,2].

On the other hand, the expansion of access in the health system by introducing new technologies establishes a progressive increase in public spending on health, especially in the chemical and biotechnological base of the CEIS, fueled by the demand for new medicines. Thus, the incorporation of technology and sustainability becomes a central topic in countries that have adopted ways to universalize the health system, such as Brazil and the United Kingdom. To the detriment of the sustainability of this system, the increase in public spending, enhanced by the judicialization of health, the perspective of accountability and the recent systematization of the flow of incorporation of health technology in Brazil impose pressure on managers of the health sector[3-5].

As a means of organizing and maturing the process of technological incorporation in Brazil, the institutionalization of the National Policy on Technological Management in Health (PNGTS), in 2009, aimed at the systematization of the Health Technology Assessment (HTA) as an element of strategic subsidy. Under the responsibility of the National Commission for the Incorporation of Technology in the Unified Health System (CONITEC), inserted organizationally within the Ministry of Health, a strict look at economic issues is widened for a multidisciplinary view regarding the assessment of innovations for health, because, by including territorial, epidemiological, cultural aspects, living conditions, and health needs of the population, they impute a cost-effectiveness relationship to the incorporation of technology[4].

The methodological guidelines of HTA help the systematization and give methodological rigor in the identification of relevant alternatives, providing an environment to reduce uncertainties. Thus, in addition to subsidizing studies and responses to control bodies, they may minimize the questioning of whether new technologies are part of the problem, part of the solution, or both[6].

Thus, assessing means establishing a flow of analysis and monitoring, in order to promote feedback and influence the entire system and actors involved. The search for cost-effective solutions, mainly by strategic institutions of CEIS, may reflect in the reduction of asymmetries before the international market, in public spending on the acquisition of imported inputs and products, and in the strengthening of the national industry[7,8].

Despite the advances observed in the field of HTA, developing countries face all kinds of challenges regarding resource limitation, diversity in the pattern of morbidity, cultural diversity, political system, health system structure, low availability of information and data, and insufficient technological and productive capacity[9]. Therefore, there is a scenario in which the main actors in technological learning have been the large economic groups capable of internalizing skills to select technologies acquired abroad, for their efficient use and adaptation, intensifying the process of crystallization of technological asymmetries and the time gap between innovators and imitators[10,11].

The emergence of the assessment between the technological dynamics and the

increase in health costs is reaffirmed by the perspective of the technological imperative of those who value the new launches, the increase in intensity, as well as the indication and expansion of the use of technology-based products, as factors that generate the leverage of competitiveness in the health market[12]. This scenario makes technological assessment a responsibility of institutions to participate in the construction and improvement of the SUS, in technological learning, and social control, implying the establishment of a flow of analysis and monitoring, feeding back and influencing the entire system and its stakeholders[8].

Because the technological competitiveness strategy is supported by the production of innovations due to the dependence on scientific advancement, and because technological discoveries confer sectoral specificities in the health sector, the asymmetries before the international market and its impacts on the national industry led by the Public Institutions of Production and Innovation in Health (IPPIS) that act directly in the supply and maintenance of the SUS are clearly observed.

Methodology

Immersed in this context of Science, Technology, and Innovation in Health (STI&H), the methodology of this work was determined using descriptive qualitative documentary research (Ministry of Health, National Health Surveillance Agency – ANVISA and the Institute of Immunobiological Technology of the Oswaldo Cruz Foundation – Bio-Manguinhos/FIOCRUZ) and bibliographic research. We searched for the descriptors "Health Technological Assessment" AND "Technological Incorporation" AND "Unified Health System" OR "Universal Health System" OR "SUS" AND "Health Economic Industrial Complex"; on scientific bases (Scopus, SciELO, Virtual Health Library at the Ministry of Health – VHL, Virtual Health Library – VHL), with the collection period comprising the last ten years (period linked to the creation of CONITEC in 2011), for understanding the technological incorporation and assessment in the SUS.

In addition, fieldwork was carried out, through benchmarking, in order to observe and compare the strategic perspectives and organizational structure between Bio-Manguinhos/FIOCRUZ, the largest IPPIS in Latin America, and a leading global pharmaceutical company in the market, patents, and investment in Research and Development (R&D) with direct impact on the Brazilian market, given the number of Productive Development Partnerships (PDP) and product submissions to CONITEC.

The comparative analysis aims to promote elements that establish a dialogue between the strategies and challenges of a national agenda to enable access through local production, considering the specificities of the SUS, with the IPPIS having a unique role as an agent of change and capillarization of knowledge within the SUS and CEIS.

The research was duly evaluated and approved by the Research Ethics Committee of the National School of Public Health Sergio Arouca (ENSP), according to opinion number 4.230.033.

Health Technology Assessment

HTA emerged in the international context, becoming an important instrument in helping the decision-making of the entire health ecosystem, as well as in the judicial system[13]. Originating from national health systems and the dynamics of health technologies, HTA is an applied discipline methodologically guided in epidemiology and, conceptually, in Evidence-Based Medicine (EBM)[14].

The scope and increase in the intensity of the advancement of technologies applied to health, from the 20th century, are conditioned

by changes in the epidemiological profile and the challenges observed in public management, and the articulation between the sectors responsible for the production, incorporation, and use of technologies in health systems[13]. Thus, HTA as a methodological and management tool gained strength due to its multidisciplinary characteristic, contributing to equity and access to health services, efficiency in the allocation of resources, effectiveness and quality of services and financial sustainability of the health system.

Systematized as a strategic factor in countries with a universal health system, such as the United Kingdom, within the scope of public administration, it represented a significant transformation in the form of governance and formulation of management policies, through the coordination of technical activities, to mitigate the interference of political vicissitudes[15]. In Brazil, the institutionalization of PNGTS in 2009 and the creation of CONITEC in 2011 marked the institutionalization and the path of knowledge development in HTA. However, the low participation of strategic institutions in the CEIS regarding the flow of technological incorporation in the SUS, as well as their use of CONITEC products, requires a broader look at the assessments carried out by these institutions[16].

Benchmarking: comparative analysis

The fast and competitive market model of the pharmaceutical industry requires large investments from the companies in the sector with concentration in multinationals. Given this scenario, benchmarking and comparative analysis, considering the specificities of the legal models, focused on information about the internal organization and how inherent knowledge is provided to the flow of incorporation and HTA, an objective considered sensitive and strategic by the company consulted. Subject to secrecy, the answers provided made it possible to draw strategic and organizational parallels and relations with the respective health systems and HTA agencies. The industry selected for research is one of the largest research pharmaceutical companies and patent leaders in the world (*table 1*). This multinational company has an immunobiological division that positions it among the largest researchers and vaccine manufacturers worldwide. Globally, in 2019, this industry invested £4.6 billion in R&D, with 6 studies underway, 3 in multiple myeloma, 2 in head and neck cancer and 1 in lung cancer, involving 59 research centers and 144 participants.

Table 1. Ranking of the main economic groups in the pharmaceutical sector (R$)

Ranking	Economic Group	Classification
1	Grupo Sanofi/Medley/Genzyeme	> = 3 billion
2	Grupo E.M.S	> = 3 billion
3	Grupo Sandoz/Novartis	> = 3 billion
4	Grupo Aché/Biosintética	> = 3 billion
5	Grupo Eurofarma/Momenta	> = 3 billion
6	Grupo Hypera	> = 3 billion
7	Grupo Johnson & Johnson	Between 2 billion and 3 billion
8	Grupo Pfizer/Wyeth	Between 2 billion and 3 billion
9	Grupo MSD/Schering Plough	Between 2 billion and 3 billion
10	Grupo Glaxo/Stiefel	Between 2 billion and 3 billion

Table 1. Ranking of the main economic groups in the pharmaceutical sector (R$)

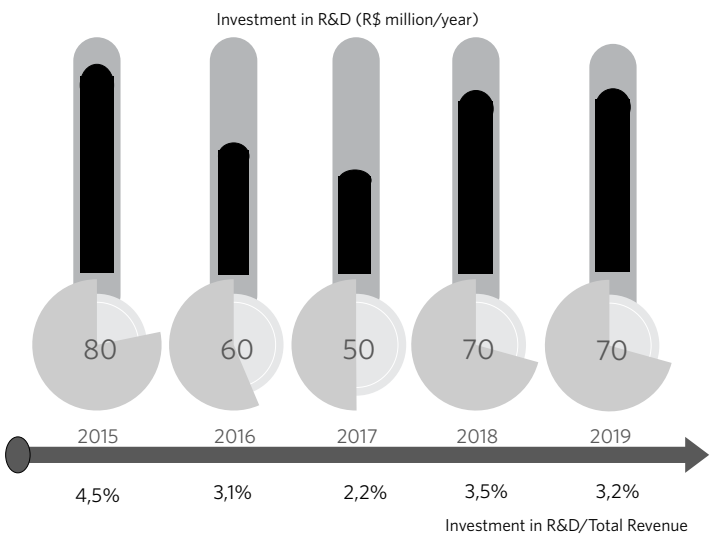
Ranking	Economic Group	Classification
11	Grupo Bayer/Schering do Brasil	Between 2 billion and 3 billion
12	Grupo Takeda/Multilab	Between 2 billion and 3 billion
13	Grupo Cristália	Between 2 billion and 3 billion

Source: Adapted from the ANVISA Statistical Yearbook 2019[17].

It has offices in more than 115 countries, and major research centers in the United Kingdom, the United States of America, Spain, Belgium and China, as well as an extensive production network, in around 70 locations worldwide. It has been present in Brazil for more than 100 years, engaging in large projects with the Brazilian government through partnerships with strategic State and CEIS institutions (FIOCRUZ since 1985 and Bio-Manguinhos since 1998).

Comparatively, in the dimension aspect, Bio-Manguinhos has the Technological Vaccine Complex (CTV), one of the largest production centers in Latin America, installed in the FIOCRUZ campus in Manguinhos and expected to expand with the Research, Development, and Industrial Production unit, in Eusébio/CE, and the Industrial Biotechnological Health Complex (CIBS), in Santa Cruz/RJ (an area of 580,000 square meters). Its worldwide coverage is highlighted on the international scene by the export of the surplus of its production to more than 70 countries in partnership with the Pan American Health Organization (PAHO) and the United Nations Children's Fund (UNICEF). Since 2001, it has been active in the supply of the yellow fever vaccine as a pre-qualified institute in the World Health Organization (WHO) and, since 2008, in the distribution of the meningococcal AC vaccine to United Nations' agencies. Despite its scope, the efforts made in Research, Development, and Innovation (RD&I) add up to an investment of 3.2% of the Institute's total revenue between 2015 and 2019, as shown in *figure 1*, and are still insufficient to meet the numerous demands of society[18].

Figure 1. Evolution of investment in Bio-Manguinhos R&D



Source: Adapted from Bio-Manguinhos, Activity Report 2020[18].

In the governmental aspect, the company under research has a consolidated relationship with the health system where it is headquartered, through joint projects supported by the belief that the strong relationship with its government may lead to a better understanding of the health system, providing a better quality of longevity in its country. According to them, such efforts are extendable to Brazil to promote technological efficiency and reduce costs in the SUS through partnerships with the Brazilian government. Such partnerships are periodically reviewed by a Steering Committee in order to maintain alignment with the original scope and alerts to any needs.

In the case of Bio-Manguinhos, its relationship with the SUS is expressed in its mission and values, contributing to the improvement of Brazilian public health standards through innovation, technological development, production of immunobiologicals, and provision of services to primarily meet the country's health demands, as observed in its portfolio (*figure 2*) and PDP (*table 2*). To monitor these partnerships, Bio-Manguinhos has decision-making bodies and areas to monitor the evolution of partnerships, such as the Technological Transfer Coordination (COTEC) – although still in the process of consolidating institutional roles and processes –, the Project Management area (GEPRO), and the Planning and Organization Advisory (ASSPO), responsible for strategic and budgetary monitoring.

Figure 2. Bio-Manguinhos Portfolio

Vaccines

- Diphtheria, tetanus, pertussis and Haemophilus influenzae d (conjugate) (DTP and HIB) – 5 doses;
- Covid-19;
- Yellow Fever – 5, 10 and 50 doses;
- Meningococcal AC (polysaccharide) – 10 doses;
- Inactivated Poliomyelitis (IPV) – 10 doses;
- Oral Poliomyelitis (OPV) – 25 doses;
- Measles, mumps, rubella (triple viral – TVV) – 10 doses;
- Measles, mumps, rubella, and varicella (MMRV) – 10 doses;
- Human rotavirus – 1 dose;
- Pneumococcal 10-valent – 1 and 4 doses.

Kit - Diagnosis

- Rapid immunoblot DPP HIV-1/2;
- TR DPP Canine visceral leishmaniasis;
- Indirect immunofluorescence (IFI) Chagas disease;
- Canine visceral leishmaniasis enzyme-linked immunosorbent assay (ELISA);
- TR DPP Leptospirosis;
- TR DPP Schistosomiasis;
- NAT Plus Kit (HIV/HCV/HBV/Malaria);
- NAT Plus Kit (HIV/HCV/HBV);
- TR DPP Sars-CoV;
- TR DPP ZDC (Zika, Dengue, Chikungunya) IgM/IgG;
- Yellow Fever Molecular Kit.

Biopharmaceuticals

- Alfataliglicerase (200 UI);
- Infliximabe (100mg);
- Betainterferona 1ª (22 mcg e 44 mcg);
- Etanercepte (50mg);
- Rituximabe (100 e 500 mg);
- Trastuzumabe (150 mg);
- Golimumabe (50 mg);
- Somatropina (4 e 12 UI).

Source: Adapted from Bio-Manguinhos, 2019[19].

Table 2. Current PDP

			PHASES				
General Framework		**OUTPUTS**	**I**	**II**	**III**	**IV**	**Total**
Current PDP	62	Biotechnological	1	6	7		14
Biotechnological	14	Blood products			1		1
Blood products	1	Synthetic	6	14	10	14	44
Synthetic	44	Vaccines			3		3
Vaccines	3	Total	7	20	21	14	62
Bio-Manguinhos	9						
Farmanguinhos	9						
Butantan	8						

Source: Adapted from the current PDPs of the Ministry of Health[20].

In the axis related to the organizational structure and focused on prospecting, including the Brazilian scenario with submission to CONITEC, the research collected in the multinational company studied the existence of a Pharmacoeconomics area responsible for conducting the HTA proposals positioned within the medical department. Discussions on this topic take place jointly with the access departments, focused on technological incorporation in health systems and the area of government relations and marketing. As a result of this structure, there is an expansion in the Brazilian market, such as its performance in the area of onco-hematology with a portfolio of 15 therapeutic options in clinical development, in addition to investment in several fronts, including immuno-oncology, epigenetics, synthetic lethality, and gene therapy. This initiative is based on the vast Brazilian market whose advancement in cancer incidence in emerging countries has the prospect of an increase of up to 78%, reaching approximately 998,000 new cases per year in the country by 2040[21].

Its structure, directly linked to R&D, considers smaller groups, more agile and with greater decision-making power in the search for compounds of a given disease, which enables an environment for the creation of molecules or biopharmaceuticals that will become new medicines in the future.

Here, the differences between the two institutions regarding institutional consolidation in the use of HTA methodologies as a tool to support prospecting and strategic guidelines for investment in R&D becomes more prominent. Bio-Manguinhos has in its formal structure the Center for Economic and Financial Analysis (Nafe), within the Administrative Department (DEPAD), responsible for Economic Feasibility Studies (EVE) for new products; and the New Business Division (DINNE), in the Market Relations Department (DEREM), responsible for capturing and evaluating partnership opportunities and technology transfers.

Added to this structure is the prospecting activity, still under development, with recent action in the case of success for selection and agreement of the technology order contract signed with AstraZeneca for the production of the COVID-19 vaccine, and the activity using the MBE inserted in the clinical advisory. Although the activities are established, there is little coordination between the organizational flows with a reflection on the formal structure, making it impossible for the Institute to strategically enjoy the knowledge and benefits of HTA methodologies, such as the global pharmaceutical company surveyed.

Finally, regarding the company's relationship with the country's HTA agency, the company that was consulted claims to make use of the products/studies published by the agency in its strategic planning and acts as a consultant participating in the national flow of technological assessments and incorporation. They also state that they recognize the increasing existence of the connection between the main regulatory agencies in the world, such as the National Institute for Health and Care Excellence (NICE), the global benchmark of HTA guidelines.

At this point, there is, again, a relevant difference between the two organizations of the pharmaceutical industry. When presenting its processes, Bio-Manguinhos demonstrates incipient use of the studies published by CONITEC and recent performance in the institutional flow of technological assessment and incorporation in the National Commission, by involving, to date, itself in public calls and making submissions to expand the use of Rituximab and Interferon beta products. It acts in the national flow of technological assessment and incorporation as a producer responsible for supplying the SUS from the disclosure of the list of strategic products advertised by CONITEC.

To make it clear, *table 3* shows the general aspects of the axes of the comparative analysis between the global pharmaceutical company and IPPIS.

Table 3. Comparative analysis between a global pharmaceutical company and an IPPIS

Ranking	Benchmarking	Bio-Manguinhos
Dimension	• It has offices in more than 115 countries, as well as major research centers; • Extensive production network in about 70 locations worldwide.	• It has CTV, one of the largest production centers in Latin America, and the pilot plant installed on FIOCRUZ's *campus* in Manguinhos. Forecast of new units in Santa Cruz and Eusébio; • Linked to the MH, since 1976, it meets the needs of the SUS, and has been a strategic agent of public health policies as one of the drivers of the National Immunization Program (PNI) and of export of products to more than 70 countries.
Management Model and Organizational Structure	• Smaller groups, more agile and with greater decision-making power.	• Large groups, verticalized decision flow, with traditional and divided structure;
R&D	• Investment of £4.6 billion in 2019; • There are 6 studies currently planned in Brazil, 3 in multiple myeloma, two in head and neck cancer, and one in lung cancer, involving 59 research centers and 144 participants.	• Investment of R$70 million (3.2% of total revenue), in 2019; • 14 ongoing technological development projects and 13 current PDP; • 16 initiatives in the InovaBio Notice and participation in the Inova Labs FIOCRUZ and Inova FIOCRUZ programs
Partnerships	• Partnership with FIOCRUZ since 1985 and with Bio-Manguinhos since 1998; • Partnership with another public agency in the Onco-Hematology market in Brazil constituting a portfolio with more than 15 therapeutic options in clinical development on several fronts, including Immuno-Oncology, Epigenetics, Synthetic Lethality and Gene Therapy (prospective basis of the Brazilian scenario in 2040).	• Twelve technology transfer projects managed in 2019, four of which are viral vaccines (triple viral, quadrivalent viral, rotavirus, and inactivated polio); one of bacterial vaccine (pneumococcal 10-valent); six of biopharmaceuticals (epoetin alpha, interferon alpha, infliximab, interferon beta 1a, alfataliglycerase and etanercept); and one of diagnostic kit on DPPs® and DDPPs® platforms.
HTA	• Use of HTA methodologies in its processes and in the organizational structure; • It uses the studies produced by a Country's HTA agency; • Consulted for contribution inserted in the set of actors of the Country's flow of technological incorporation assessment in health.	• It has institutionalized the economic and financial analysis center, responsible for the EVE activity of products and has Evidence-Based Medicine activities in Clinical Advisory and Prospecting activity directly linked to the Board; • The Unit makes incipient use of the studies advertised by CONITEC; • Occasional performance in a public call and in the submission to evaluate the expansion of the use of a medicine.

Source: Prepared by the authors.

Conclusions

The use of HTA knowledge in management models supporting strategies makes increasingly evident the difference among the countries with leading and peripheral technology. The strategic role of innovation is highlighted as the core of contemporary industrial policies and as an endogenous factor of economic dynamics in the capitalist mode of production. Such policies create actions and open spaces for the sustainability and effectiveness of the SUS, as well as the consolidation of CEIS.

The formalization and instrumentalization of the methodological knowledge of HTA aim to promote learning, growth, and dialogue

with the instances inherent to the flow of incorporation and HTA, which will translate into independence and construction of new networks of knowledge and performance. Therefore, the invitation to discuss the topic is of great relevance for CEIS and its strategic institutions and spurring innovation.

Undeniably, the creation of CONITEC is the result of the development of the institutionalization of HTA in the Brazilian health system, representing a central aspect in the complex decision-making process that governs the financing and access to pharmaceutical products in the SUS.

However, the lack of policy and clarity in the IPPIS performance model in the flow of incorporation and HTA, the national industrial and technological vulnerability, with a predominance of large economic conglomerates, the low investment in R&D and the need for better qualification and appropriate use of HTA methodologies, have a direct impact on the performance strategy of the institutions that make up CEIS. Such impacts are related to monitoring the external technological, political-governmental environment, installed capacity, innovation-oriented learning and collaborative structure, which are important coordinating factors that can lead to the success of sustainable innovations.

Compared to IPPIS, Bio-Manguinhos, despite many advances, still seeks to consolidate a better organizational structure and institutional model that allows leveraging the technological incorporation and development, as well as the dissemination of HTA knowledge, linking it to production to expand universal access. As market leaders, like the benchmarking carried out, it has an agile and flexible management model consistent with the needs imposed by innovation, a notorious focus on R&D, and a mature knowledge and performance in HTA, as management tool, providing the opportunity to fill technological gaps in other countries, as in Brazil.

This research shows the institutionalization of the perspective of incorporation based on HTA methodologies to meet the State strategy for the SUS as a clear differential. Used as a management tool, it provides a breadth of knowledge implying the internalization of a conception that does not restrict the development of new products but encourages partners to present more advantageous technological paths for the country and for the CEIS, with the relevant role of the IPPIS, in meeting social needs, reducing the vulnerability of the SUS, and guaranteeing the structural sustainability of universal access to health.

Collaborators

Rocha KCR (0000-0002-7002-8741)* contributed to the design, planning, data collection, interpretation of results, and writing of the work. Gadelha CAG (0000-0002-9148-8819)* contributed to the supervision of the study, analysis, and critical review of the manuscript.■

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