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Incorporation of drugs for rare diseases in Brazil: is it possible to have full access to these patients?

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Abstract *This study aims to describe the profile for the requested incorporation of rare disease drugs submitted to CONITEC and its recommendations, comparing the incorporation criteria employed by other HTA agencies globally. To this end, requests for the treatment of rare diseases submitted to CONITEC from July 2012 to June 2019 and its recommendations to the Brazilian Unified Health System (SUS) were included in this study. Subsequently, we compared the criteria used by CONITEC and other HTA agencies to incorporate these drugs. Sixty medicine incorporation requests to treat thirty rare diseases were submitted to CONITEC. Pharmaceutical companies made the most requests (66%). Budget impact analyses were presented in 85% of the requests and HT economic analyses in 68%. A total of 52% of the requests were incorporated into the SUS. CONITEC's justifications for the non-incorporation were the lack of quality clinical evidence, non-cost-effective technologies, and modest clinical benefits that do not justify the high prices. International HTA agencies (CAN, UK, FR, AUS) use different criteria for rare diseases assessments. The data indicate that most of the evaluated drugs were incorporated into the SUS, and adopting different criteria to assess the incorporation of rare diseases medicines will possibly strengthen decision-making.*

Key words *Rare diseases, Health technology assessment, Unified Health System*

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Introduction

In Brazilian public health, Law N° 8080 was created in 1990. It established the Unified Health System (SUS) based on Universality, Comprehensiveness, and Equity[1], in obeyance to Art. 196 of the 1988 Constitution *health is a right for all and a duty of the State*[2]. Universality calls for access to health for all citizens. Equity would allow the lack of unfair, avoidable, or remediable differences in the health of populations or groups defined with social, economic, demographic, or geographic criteria[3]. Comprehensiveness, more specifically, is the need to understand individuals as biopsychosocial beings in their essence, traversing the possibility of access to all system levels, which leads us to its more concrete practice to provide materiality to the life of services[4]. Thus, Carnut[4] defined comprehensiveness as a guiding principle of the SUS. It is a principle that adopts the philosophical explanation of human beings and a guideline for having become something concrete, which guides the work process.

In this context, specific access to medicines is ensured by two public health policies, the National Medicines Policy[5] and the National Pharmaceutical Care Policy[6]. However, the SUS sustainability and funding have endured some challenges in recent years. Scientific health research has produced a significant increase in alternatives for detecting, preventing, and treating diseases, but budget constraints do not allow health care systems to provide patients with all interventions[7].

Health technology assessments (HTA) and the growing demand for efficient allocation of health resources have led to the need to establish a committee to assist the Ministry of Health in decision-making, called the National Committee for the Incorporation of Technologies (CONITEC), which was created on April 28, 2011, the date on which Law No. 12.401 was enacted, defining criteria and deadlines for the incorporation of technologies in the SUS[8].

The daunting challenge for HTAs is ensuring that analyses, registrations, and availability of medicines for rare diseases (RD) are also realized[9]. The group term – rare diseases – is used to include a very heterogeneous group of disorders that can affect any system in the body. They are also called "orphan" diseases because, usually, little is known about their causes and effective therapies are still limited[10]. Most of these diseases are genetic. They are often disabling and substantially affect life expectancy. They also impair physical and mental abilities, reducing the individual quality of life. These diseases are a significant public health issue and have been neglected for many years by health systems and pharmaceutical industries[11].

In 2012, the World Health Organization mapped between 5,000 and 8,000 rare diseases. The concept of rare diseases adopted by this group involves disease characteristics and epidemiological factors, with low prevalence determination[12]. Noteworthy is that the epidemiological definition varies between different countries. In Brazil, for example, in 2014, the Ministry of Health established that a rare disease is one with a prevalence below 65 per 100,000 people[13]. The actual prevalence of these diseases is difficult to estimate, as the literature has not provided us with reliable data, showing low consistency among the information sources and low methodological quality of epidemiological studies[14].

Following extensive discussion with government agents, researchers, doctors, and patient associations, the National Policy for the Comprehensive Care of People with Rare Diseases in the SUS[13] was promulgated in 2014, which seeks more dignified, humane, and inclusive care for those with rare diseases. One of the guiding principles of this policy is the incorporation of medicines for rare diseases and indicated within the SUS, which should result from the recommendations by government agencies from CONITEC's assessment and approval. Based on this principle and to ensure the effectiveness of the objectives of this Policy, the first action by the Ministry of Health was a panel of experts who prioritized twelve clinical protocols for comprehensive care for people with rare diseases[15].

Despite advances in recent years, compliance with the principles of universality, equity, and comprehensiveness in the SUS is still a challenge in light of the National Policy for the Comprehensive Care of People with Rare Diseases[16]. The lack of adequate scientific evidence and the high cost of treatments hamper the inclusion of these therapies, and individuals often resort to the Judiciary to rule on the access to health products[17,18]. Given this setting, rare diseases have demanded the attention of researchers and decision-makers to verify whether they should gain different assessment criteria than other diseases within the HTA[9]. Knowing that patients suffering from a rare disease is an essential part of the population, it is vital to understand the results of incorporating the technologies made available to them, compared to countries that also have consolidated HTA agencies.

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This study aims to describe the profile of requests for incorporating medicines for rare diseases submitted to CONITEC and its recommendations, comparing the criteria used for including medicines for rare diseases with other globally recognized HTA agencies.

Methods

Profile of requests for incorporating medicines for rare diseases in Brazil

This is a descriptive and exploratory study carried out through surveys and quantitative analyses of requests for including medicines submitted to CONITEC and their recommendations to the SUS, from July 2012 – month and year of the onset of publications of the assessments on the website (http://conitec.gov.br/) – to June 2019 for the treatment of rare diseases.

Data regarding CONITEC's submissions and recommendations were collected from documents made available on its website (http://conitec.gov.br/), considering the criteria established by Ordinance N° 199, of January 30, 2014, called National Policy for the Comprehensive Care of People with Rare Diseases, which considers a rare disease one that affects up to 65 people in every 100,000 individuals[13].

The quantitative analysis of positive or negative recommendations was performed after selecting all requests that met the definition of rare disease mentioned above. Then, the requests were presented regarding the indications of the drugs, active ingredients, applicant, year, type of study for clinical evidence, type of economic assessment, initial recommendation, recommendation after public consultation, and the result of the required inclusion. The collected data were stored and analyzed in a pre-formatted Microsoft Office Excel®365 ProPlus spreadsheet. Descriptive statistics were used, and the results were expressed as absolute or relative frequency.

Criteria used by other HTA agencies to incorporate medicines for rare diseases

We performed a comparative analysis of the criteria used by CONITEC for the incorporation of medicines for rare diseases in Brazil and by international HTA agencies. The HTA agencies of interest were chosen due to their pioneering spirit in the field and because they belong to countries whose health system is similar to the Brazilian one. They are the Pharmaceutical Benefits Advisory Committee (PBAC) of Australia, the Canadian Agency for Drugs and Technologies in Health (CADTH) of Canada, The National Institute for Health and Care Excellence (NICE) of the United Kingdom, and *Haute Autorité de Santé* (HAS) of France. We proceeded with a bibliographic search in the PubMed and SciELO databases, considering the search period until June 2019 and the websites of the HTA agencies mentioned above.

Results

General analysis of incorporation requests

Sixty requests for incorporating medicines to treat 30 rare diseases to CONITEC were identified from July 2012 to June 2019 (Charts 1 and 2). It is noteworthy that in 2018, an applicant submitted an incorporation request for the treatment of uveitis. However, during its assessment, CONITEC decided on two subgroups of the disease, Active Uveitis, and Inactive Uveitis. Thus, we will analyze the 60 requests and 61 recommendations.

Most incorporation requests submitted to CONITEC were from the pharmaceutical industry (40; 66%), followed by the Ministry of Health's Science, Technology, and Strategic Inputs – SCTIE/MS (11; 18%), and the Health Care Secretariat of the Ministry of Health – SAS/MS (6; 10%). Only a negligible portion was requested by state governments (2; 3%), the Judiciary (1; 2%), and both industry and doctor together (1; 2%). Requests were based on varying levels of clinical evidence, from case reports to systematic reviews with metanalyses. Systematic reviews became part of the dossiers more frequently from 2017 onwards.

Budget impact analyses were found in about 85% (51) of the 60 requests sent to CONITEC, while economic analyses of health technologies, such as cost-minimization, cost-effectiveness, and cost-utility, were found in 68% (41) of them. As shown in Figure 1a, eight out of the nine requests that did not present a budget impact analysis had the SAS/MS, SCTIE/MS, or state governments as applicants. Regarding the lack of economic analyses of health technologies, 17 of the 19 requests that did not show any such analysis also came from the same applicants mentioned above (Figure 1b).

Chart 1. Requests for medicines for rare diseases incorporated in the Unified Health System.

Year	Medicine	Indication	Applicant	Study types	Budget Impact Analysis	Health Technology Economic Analysis	Initial recommendation	Was there a Public Consultation?	Incorporated?
2012	Lanreotide Acetate	Acromegaly	Industry	Phase II e III	Yes	Cost minimization	Recommended	Yes	Yes
2012	Biotin	Biotinidase Deficiency	SAS/MS	Case Reports	Yes	No	Recommended	Yes (no contributions)	Yes
2012	Naproxen	Ankylosing Spondylitis	SAS/MS	SR and observational	No	No	Recommended	No	Yes
2012	Sildenafil	Raynaud Syndrome in Systemic Sclerosis	SAS/MS	Phase II	No	No	Recommended	No	Yes
2012	Tacrolimus	Primary Nephrotic Syndrome	SAS/MS	Phase II and retrospective	No	No	Recommended	No	Yes
2013	Ambrisentan	Pulmonary Arterial Hypertension	Industry	Phase II and III	Yes	Cost minimization	Recommended (Price negotiation)	Yes	Yes
2013	Bosentan	Pulmonary Arterial Hypertension	Industry	Phase II and III	Yes	Cost minimization	Recommended (Price negotiation)	Yes	Yes
2013	Injectable Methotrexate	Ankylosing Spondylitis	SAS/MS	Phase II	No	No	Recommended	No	Yes
2014	Fingolimod	RR Multiple Sclerosis (third line)	SCTIE/MS	Phase III	Yes	Cost-effectiveness	Recommended	Yes	Yes
2015	Hydrocortisone Cypionate	Congenital Adrenal Hyperplasia in NB	SAS/MS	Not described	Yes	No	Recommended	No	Yes
2016	Golimumab	Ankylosing Spondylitis	Industry	Phase III	Yes	Cost minimization	Recommended	Yes	Yes
2016	Tobramycin	Cystic Fibrosis	Judiciary	Systematic reviews	Yes	No	Not recommended	Yes	Yes
2017	Certolizumab Pegol	Moderate to severe Crohn's disease	Industry	Systematic review	Yes	Cost minimization	Recommended	Yes	Yes

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Year	Medicine	Indication	Applicant	Study types	Budget Impact Analysis	Health Technology Economic Analysis	Initial recommendation	Was there a Public Consultation?	Incorporated?
2017	Desmopressin	Central Diabetes Insipidus	SCTIE/MS	Systematic review	No	No	Recommended (Price negotiation)	No	Yes
2017	Fingolimod	RR Multiple Sclerosis (second line)	Industry	Systematic review	Yes	Cost-utility	Not recommended	Yes	Yes
2017	Dimethyl fumarate	RR Multiple Sclerosis (second line)	Industry	SR, Phase III, and IV	Yes	Cost-utility	Not recommended	Yes	Yes
2017	Idursulfase	Type II Mucopolysaccharidosis	SCTIE/MS	Not described	Yes	No	Recommended	Yes	Yes
2017	Laronidase	Type I Mucopolysaccharidosis	SCTIE/MS	Phase III	Yes	No	Recommended	Yes	Yes
2017	Teriflunomide	RR Multiple Sclerosis (first line)	Industry	Phase III	Yes	Cost minimization	Not recommended	Yes	Yes
2017	Somatropin (with up to 30 IU)	Turner Syndrome and Hypopituitarism	SCTIE/MS	Not described	No	No	Recommended	No	Yes
2018	Secukinumab	Ankylosing Spondylitis	Industry	Phase III	Yes	Cost minimization	Recommended	Yes	Yes
2018	Tafamidis meglumine	Familial Amyloidotic Polyneuropathy	Industry	Phase III	Yes	Cost-utility e Cost-effectiveness	Recommended	Yes	Yes
2018	Eltrombopag olamine	Idiopathic Thrombocytopenic Purpura (ITP)	SCTIE/MS	Phase II and III, SR	Yes	No	Not recommended	Yes	Yes
2018	Eculizumab	Paroxysmal Nocturnal Hemoglobinuria	SCTIE/MS	Phase III and SR	Yes	Cost-effectiveness	Not recommended	Yes	Yes
2018	Adalimumab	Active Non-Infectious Posterior Uveitis	Industry	Phase III	Yes	Cost-effectiveness	Not recommended	Yes	Yes
2018	Ursodeoxycholic acid	Primary biliary cholangitis	Industry	Phase III and SR	Yes	Cost-effectiveness	Not recommended	Yes	Yes
2018	Sapropterin	Phenylketonuria	SCTIE/MS	Phase III	Yes	No	Not recommended	Yes	Yes

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Chart 1. Requests for medicines for rare diseases incorporated in the Unified Health System.

Year	Medicine	Indication	Applicant	Study types	Budget Impact Analysis	Health Technology Economic Analysis	Initial recommendation	Was there a Public Consultation?	Incorporated?
2018	Elosulphase Alfa	Type IVa Mucopolysaccharidosis (Morquio A Syndrome)	Industry	Phase III and SR	Yes	Cost-utility	Not recommended	Yes	Yes
2018	Galsulfase	Type VI Mucopolysaccharidosis	Industry	Phase I, II, and III	Yes	Cost-effectiveness	Not recommended	Yes	Yes
2018	Glatiramer acetate 40 mg	RR Multiple Sclerosis	Industry	Phase III and Metanalysis	Yes	Cost minimization	Not recommended	Yes	Yes
2019	Secukinumab	Psoriatic Arthritis	Industry	Phase III, SR, and MA	Yes	Cost minimization	Recommended	Yes	Yes
2019	Nusinersen	Spinal Muscular Atrophy	Industry	Phase II and III	Yes	Cost-utility	Recommended	Yes	Yes

Source: Authors' elaboration.

The rare diseases demanded

Multiple sclerosis had the highest number of requests among the 30 rare diseases with requests for drug incorporation, namely, twelve in total (20%), and only five of these were incorporated. We can also highlight ankylosing spondylitis [5 requests (8%), 4 incorporated]; acromegaly [4 requests (7%), 1 incorporated], pulmonary arterial hypertension [4 requests (7%), 2 incorporated] and mucopolysaccharides [4 requests (7%), 4 incorporated]. The different subtypes of each disease were not considered by grouping the number of claims by disease.

CONITEC's recommendations

Figure 2 shows the evolution of incorporation requests between July 2012 and June 2019 and the characterization of the applicants regarding CONITEC's initial and final recommendation. Only 20 (33%) of the 61 assessments of incorporation of medicines for rare diseases had a positive initial recommendation before public consultation. However, an inversion in these numbers was observed after the public consultation, and, thus, 32 (52%) medicines received a positive recommendation and were incorporated into the SUS. We can note that the initial years (2012 and 2013) had many requests to CONITEC, both by the government and the industry, and all initial recommendations were upheld. The initial negative recommendations were reversed as of 2016 and started to recur in the following years, regardless of the applicant type.

Concerning the 12 incorporation requests with reversed decisions after the public consultation, CONITEC's justifications for the initial negative recommendation were based on the lack of quality clinical evidence, uncertain effectiveness, not being cost-effective options vis-à-vis the options already included in the SUS, weak evidence, and modest clinical benefits that do not justify the high price. The clinical evidence presented by the applicants in these requests was, at a minimum, phase III clinical studies.

The initial negative recommendations that were reverted to positive built on the high number of contributions favoring the incorporation of medicines for rare diseases; for example, Paroxysmal Nocturnal Hemoglobinuria, which obtained 2,451 contributions. The main contributions of the public consultation were related to the presentation of new clinical studies, the availability of a generic drug on the market, the

Chart 2. Requests for drugs for rare diseases not incorporated into the Unified Health System.

Year	Medicine	Indication	Applicant	Study types	Budget Impact Analysis	Health Technology Economic Analysis	Initial recommendation	Was there a Public Consultation?	Incorporated?
2012	Ambrisentan	Pulmonary Arterial Hypertension	Industry	Phase III	Yes	Cost minimization	Not recommended	Yes	No
2012	Certolizumab Pegol	Crohn's disease	Industry	Phase II	No	No	Not recommended	Yes	No
2012	Everolimus	Subependymal giant cell astrocytoma (SEGA)	Industry	Phase II	Yes	Cost-effectiveness	Not recommended	Yes	No
2012	Fingolimod	RR Multiple Sclerosis (first line)	Industry	Phase III	Yes	Cost-utility	Not recommended	Yes	No
2013	Ursodeoxylic acid	Cystic Fibrosis	Industry	Phase II	Yes	Cost-effectiveness	Not recommended	Yes	No
2013	Canakinumab	Cryopyrin-associated Periodic Syndromes	Industry	Phase II and III	Yes	Cost-effectiveness	Not recommended	Yes	No
2013	Golimumab	Ankylosing Spondylitis	Industry	Phase III	Yes	Cost minimization	Not recommended	Yes	No
2013	Nadroparin	Recurrent Pulmonary Thromboembolism	State Government of Goiás	Phase II	No	No	Not recommended	Yes (no contributions)	No
2013	Natalizumab	RR Multiple Sclerosis (second line)	Industry	Observational	Yes	Cost-effectiveness e utilidade	Not recommended	Yes	No
2013	Pegvisomant	Acromegaly	Industry	Phase II	Yes	Cost-effectiveness e utilidade	Not recommended	Yes	No
2013	Sapropterin	Hyperphenylalaninemia with BH4 deficiency	State Government of Minas Gerais	Phase III	No	No	Not recommended	Yes (no contributions)	No
2013	Tadalafil	Pulmonary hypertension	Industry	Phase III	Yes	Cost minimization	Not recommended	Yes	No
2014	Fingolimod	RR Multiple Sclerosis (first and second lines)	Industry & Doctor	Phase III	Yes	Cost-effectiveness	Not recommended	Yes	No
2015	Icatibant	Hereditary Angioedema	Industry	Phase III	Yes	Cost-effectiveness	Not recommended	Yes	No

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Year	Medicine	Indication	Applicant	Study types	Budget Impact Analysis	Health Technology Economic Analysis	Initial recommendation	Was there a Public Consultation?	Incorporated?
2015	Pegvisomant	Acromegaly	Industry	Phase IV	Yes	Cost-effectiveness	Not recommended	Yes	No
2017	Alemtuzumab	RR Multiple Sclerosis (second line)	Industry	SR and Metanalysis	Yes	Cost-utility	Not recommended	Yes	No
2018	Belimumab	Systemic lupus erythematosus	SCTIE/MS	Phase II and III	Yes	No	Not recommended	Yes	No
2018	Pegvisomant	Acromegaly	SCTIE/MS	Phase III	Yes	No	Not recommended	Yes	No
2018	Romiplostim	Idiopathic Thrombocytopenic Purpura (ITP)	Industry	Phase I, II, III, and SR	Yes	Cost-utility	Not recommended	Yes	No
2018	Alpha and beta-agalsidase	Fabry disease	SCTIE/MS	Phase III	Yes	No	Not recommended	Yes	No
2018	Nintedanib	Idiopathic pulmonary fibrosis	Industry	Phase II and III	Yes	Cost-effectiveness e utilidade	Not recommended	Yes	No
2018	Adalimumab	Inactive Non-Infectious Posterior Uveitis	Industry	Phase III	Yes	Cost-effectiveness	Not recommended	Yes	No
2018	Alemtuzumab	RR Multiple Sclerosis (third line)	Industry	Phase III, Metanalysis and Observational	Yes	Cost-utility	Not recommended	Yes	No
2018	Pirfenidone	Idiopathic pulmonary fibrosis (IPF)	Industry	Phase II and III	Yes	Cost-effectiveness e utilidade	Not recommended	Yes	No
2019	Efmoroctocog Alfa	Hemophilia A	Industry	Case Reports	Yes	Cost minimization	Not recommended	Yes	No
2019	Eftrenonacog Alfa	Hemophilia B	Industry	Phase III	Yes	Cost-effectiveness	Not recommended	Yes	No
2019	Ocrelizumab	RR Multiple Sclerosis	Industry	SR and Metanalysis	Yes	Cost-effectiveness	Not recommended	Yes	No
2019	Ocrelizumab	PP Multiple Sclerosis	Industry	Phase III	Yes	Cost-effectiveness	Not recommended	Yes	No
2019	Vedolizumab	Crohn's disease	Industry	Phase III, SR, and MA	Yes	Cost minimization	Not recommended	Yes	No

Source: Authors' elaboration.

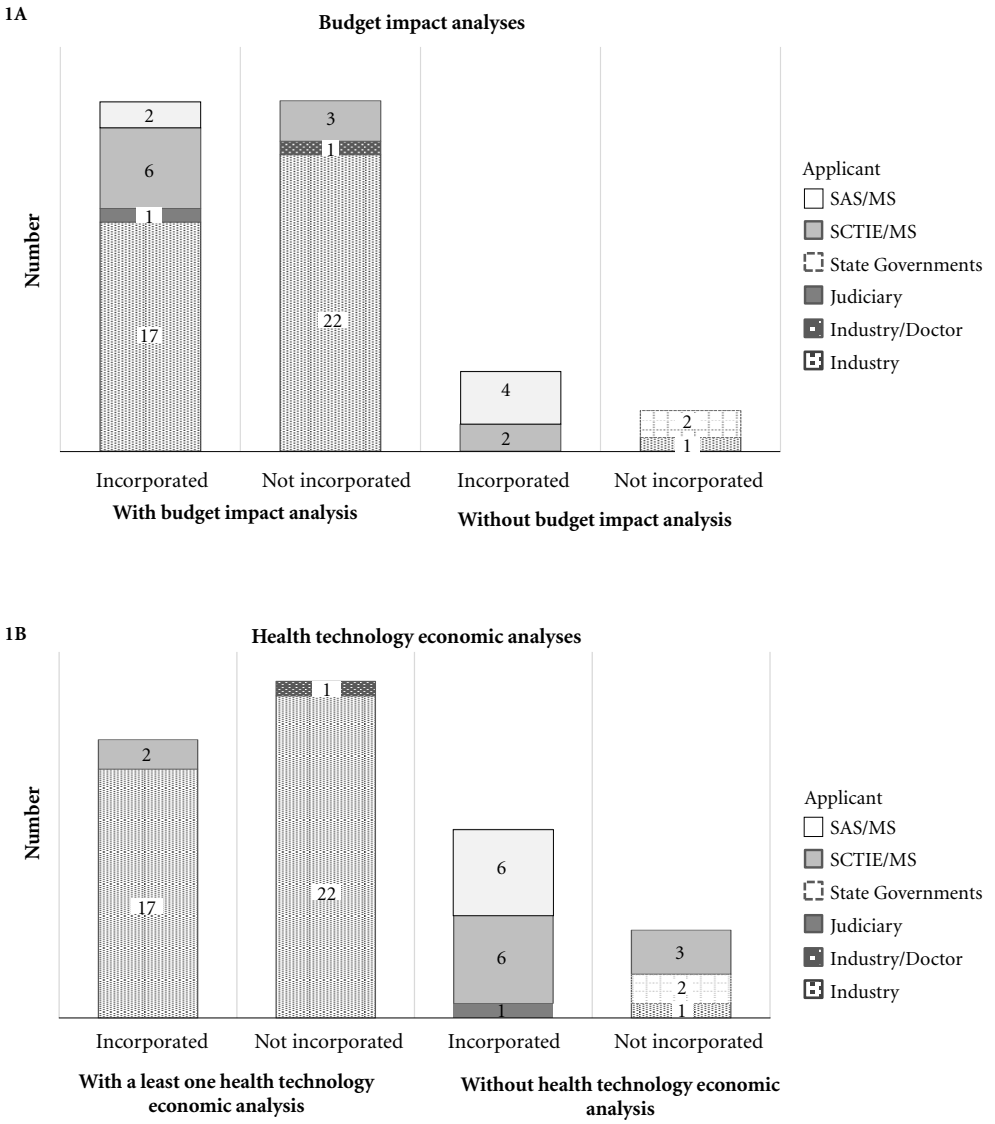

Figure 1A and 1B. Number of budget impact analyses and health technology economic analyses in requests incorporated or not by CONITEC. SCTIE/MS: Secretariat of Science, Technology and Strategic Inputs/Ministry of Health; SAS/MS: Health Care Secretariat/Ministry of Health.

Source: Own preparation based on the survey of applications for incorporation with CONITEC.

requested medicine was the only available treatment for the disease, and price negotiation with the industry.

Criteria used by international HTA agencies to incorporate medicines for rare diseases

A study by the Canadian agency CADTH[19] compared several HTA processes for rare diseases in some countries, including England, France, Australia, and Canada. Table 1 is an adaptation of data from the CADTH report, and the Brazil column was answered based on the bibliographic survey carried out to develop this work, with only public data from the CONITEC website itself.

We observe that only NICE uses the six criteria adopted in the assessment, although it does not define the exact prevalence of a rare disease. Among the others, only PBAC has a differentiated process for submitting a request for inclusion for

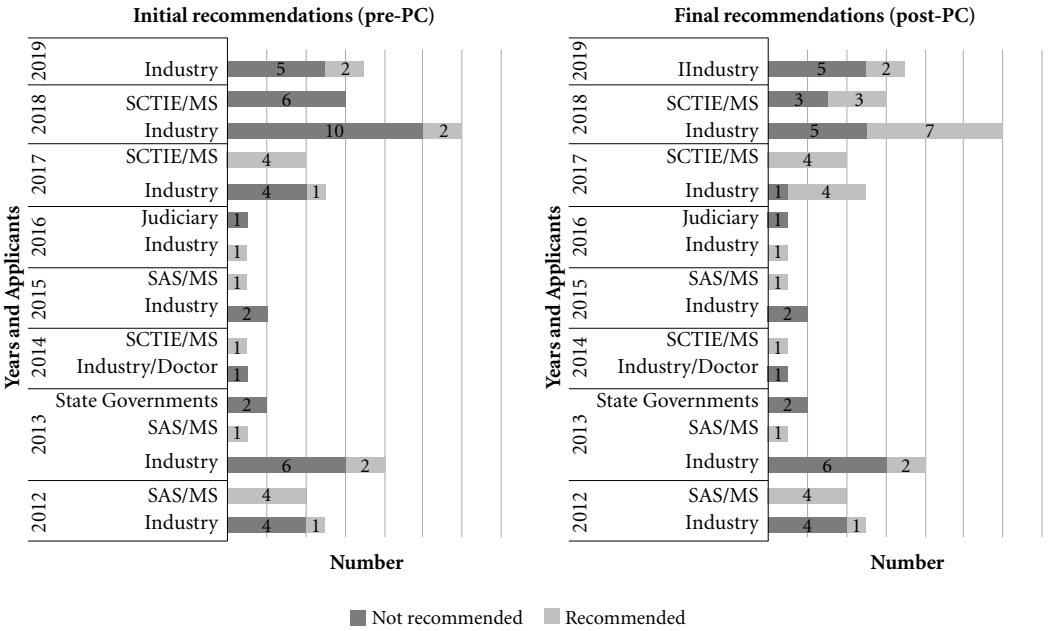

Figure 2. Evolution of CONITEC's initial (pre-PC = pre public consultation) and final (post-PC = post public consultation) recommendations from July 2012 to June 2019. SCTIE/MS: Secretariat of Science, Technology and Strategic Inputs/Ministry of health; SAS/MS: Health Care Secretariat/Ministry of Health.

Source: Own preparation based on the survey of applications for incorporation with CONITEC.

rare diseases. All four international HTA agencies use as criteria different considerations regarding economic assessments. It is worth noting that only England and Brazil report being willing to enter into risk-sharing agreements with technology applicants.

Discussion

Given the data presented in this study and considering that until the beginning of the publications of the evaluations by CONITEC, most drugs for rare diseases attended by the SUS treated only the symptoms[20], an important advance can be seen in the way in which patients with rare diseases are treated. Most technologies evaluated between July 2012 and June 2019 by CONITEC were orphan drugs that could interfere with disease progression.

The National Policy for the Comprehensive Care of People with Rare Diseases guided paths and goals for prioritizing some clinical protocols and therapeutic guidelines (PCDT)[13]. Based on the need to accelerate the arrival of orphan drugs created after this 2014 Policy[13], the National Health Surveillance Agency (ANVISA) stipulated a procedure for the registration of orphan drugs under RDC N° 205/17: drugs registered through pre-established criteria would be prioritized with a period of up to 365 days to be marketed.[21] Then, the way the Brazilian health system addresses diseases takes shape gradually. Among other factors, there may be a causal relationship between the rising number of incorporation requests from 2017 and this new setting for rare diseases, as occurred in the U.S. after introducing incentives and legislation (Orphan Drug Act)[22,23].

With the advances through Policies and Resolutions, patients could be treated by the health system in a more dignified manner. There is, then, an attempt to enforce two of the three SUS[1] principles: equity, since patients who suffer from rare conditions should have the same opportunity to receive treatment as other patients with more frequent disorders[22]; and universality, including this group of patients in public health policies. On the other hand, due to the difficulty of organizing a system that can take care of the patient in its entirety, whether in rare or more prevalent diseases[24], comprehensiveness is still one of the desired aspects.

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Table 3. Criteria used by international HTA agencies for incorporating medicines for rare diseases.

Criteria used by international HTA agencies	Countries and their HTA agencies				
	Canada	England	France	Australia	Brazil
	CADTH	NICE	HAS	PBAC	CONITEC
Is there a separate HTA process for rare diseases? Or does the standard process have different criteria for rare diseases?	No	Yes	No	Yes	No
Are there definition criteria for medicines for rare diseases?	No	Yes*	No	Yes	Yes
Is there a special committee to assist with the assessment?	No	Yes	No	No	No
Are patients or groups of patients part of the special review committee?	NR	Yes	NR	NR	No
Are any differentiated considerations made for economic evaluation?	Yes	Yes	Yes	Yes	No
Are shared risk arrangements considered?	NR	Yes	NR	NR	Yes

* Despite having the criterion of being a rare disease, there is no well-defined prevalence for its definition.
NR: Not reported.

Source: Own preparation based on the survey of criteria from international agencies.

We should highlight that, while most incorporation requests submitted to CONITEC have a favorable decision, access to treatment may be more difficult than expected. Logistics, distribution, and supply problems are frequent in specialized component pharmacies, impacting the availability and, thus, the treatment of medicine users[25].

The fundamental issue when discussing this topic is the budgetary impact of such incorporations to the system since these are medicines for a limited number of patients and generally have high manufacturing and sale costs. According to estimates by the Ministry of Health published by Interfarma[20], in 2016 alone, the Federal Government's spending on lawsuits reached BRL 1.3 billion, up 23% from the previous year.

The participation of orphan drugs in these expenses through the courts already represents 90% of the total cost, and half of the most legalized medicines in 2016 were for the treatment of rare diseases[20]. Thus, there is already a high expenditure on acquiring medicines for this group of diseases by the Federal Government, besides the lack of predictability in the allocation of resources, lower bargaining power with industries, and a reduced number of benefited patients. Given this scenario, incorporating these drugs into the SUS could bring more significant control over expenses with lawsuits and enable treatment to more patients.

The comparison of criteria used by international HTA agencies makes it clear that the way a rare disease is evaluated is a current issue and still requires maturation. No matter how much the country invests in health, it is impossible to pay everything for all[7]. For this reason, debating more effective ways to evaluate new technologies besides the cost-effectiveness and budget impact methodology is crucial. As observed in the five HTA agencies included in this work, differentiated criteria (using utilitarian principles less and considering both the vulnerability of the affected population and the society's position regarding this inclusion) and setting priorities may be the most indicated way to evaluate medicines for rare diseases[8] and, thus, improve access to medicines for this very different population. Also, some new specific programs to evaluate medicines for rare diseases are emerging in Europe to cope with the challenging setting of more significant political pressure for more transparency in the HTA processes[26], such as the Patient and Clinician Engagement (PACE) Meeting and the decision-making program by the Scottish Medicines Consortium (SMC), the National Institute for Health and Clinical Excellence (NICE) highly specialized technology program in England, and a European initiative, the Mechanism of Coordinated Access (MoCA)[27].

Understanding comprehensiveness as a principle that permeates decision-making and guarantees the right to health, some crucial questions emerge: are drug incorporations being carried out based on criteria that consider health needs and the perspective of comprehensiveness? Is it

possible to provide comprehensive care to patients with rare diseases using current health technology assessment criteria? An initial, albeit complex path for decision-makers could be identifying the value factors they deem relevant for each decision, the preferences of the groups involved, which value propositions support the decisions, and the construction of a consensus among all the parts[26,28,29]. Therefore, making the work process more transparent and participatory is necessary to facilitate collective decisions considering minority and even individual perspectives without compromising majority groups. This would allow differentiating the still widely used criteria for both high and low prevalence diseases.

In three of the 12 requests in which there was an inversion in the initial recommendation, CONITEC justified the final positive recommendation after public consultation as follows: *scientific evidence concerning rare diseases must be analyzed differently when compared to high disease prevalence. Likewise, there was a need to monitor these patients so that the treatment results are monitored and documented*, found in the reports of Mucopolysaccharidosis IVa and VI[30,31]. Also, *the decision was reconsidered upon compliance with provisionally established criteria for rare diseases* – Paroxysmal Nocturnal Hemoglobinuria report[32].

Conclusion

The setting of rare diseases has changed in the Brazilian public health system since the establishment of CONITEC. We cannot deny the advances achieved that have already been observed from the data in this study, in which most medicines (52%) that CONITEC has evaluated in the last seven years have been incorporated into the SUS. However, there are still challenges and opportunities in Brazil and countries whose HTA agencies were pioneers; such is the topic's relevance and timeliness. Countries like England and Australia, for example, already have significant differentiated criteria in their HTA agencies. On the other hand, limited health resources and the economic-political setting are points of attention and difficulty in the country. However, so that advances are not slowed down, it is crucial to bring to the light of conscience the Federal Government's spending, above all, with judicialization. This point, associated with differentiated criteria and relevant value factors for rare diseases, besides policies with well-defined objectives, will possibly strengthen decision-making and provide more significant potential for patients to access life-changing treatments.

Collaborations

LV Biglia and PM Aguiar participated in the project design, data analysis and interpretation, paper writing, and critical review of the intellectual content. SJ Mendes and TM Lima collaborated to discuss the data and the critical review of the text.

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