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Incorporation of non-registered medicines in the Brazilian Unified Health System (SUS): a study of the recommendations of the National Committee for Health Technology Incorporation, 2012-2016

Incorporação de medicamentos sem registro sanitário no SUS: um estudo das recomendações da Comissão Nacional de Incorporação de Tecnologias no período 2012-2016

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ABSTRACT

Introduction: Drug registration is an essential tool for assessing quality, safety, and efficacy. In Brazil, the current regulatory framework prohibits the incorporation of any technology into the Brazilian Public Health System (SUS) without prior registration with the Brazilian regulatory institution, the Brazilian Health Regulatory Agency (Anvisa). The National Committee for Health Technology Incorporation (Conitec) advises the Ministry of Health on which health technologies should be incorporated. **Objective:** Conitec's recommendations to incorporate non-registered medicines and their federal procurement between January 2012 and June 2016 were studied. **Method:** The study was based on the information available on Conitec's website and on purchases registered in the Integrated General Services Management System database. **Results:** Six out of the 93 drugs incorporated into SUS during the examined period were not registered with Anvisa. The main reasons for incorporation of non-registered medicines were severity of the disease, minor adverse events, and low budgetary impact. In 50% of the cases, medicines had already been made available at SUS for the approved indications, but in presentations that made it difficult for them to be used in pediatric patients or situations of greater severity. R$ 3,159,085.96 were spent on the purchase of these drugs. **Conclusions:** The recommendation of incorporation of medicines not registered with Anvisa contravenes the legislation related to Conitec and to the public acquisition of medicines. However, it is important to highlight the importance of drug incorporations that meet relevant therapeutic gaps.

KEYWORDS: Medicines; Drug Registration; Health Technology Assessment; Decision-making; Brazilian Unified Health System

RESUMO

Introdução: O registro sanitário de medicamentos é instrumento essencial na avaliação da qualidade, segurança e eficácia. O marco regulatório vigente veda a incorporação de novas tecnologias sem registro no Sistema Único de Saúde (SUS), cabendo à Comissão Nacional de Incorporação de Tecnologias (Conitec) assessorar o Ministério da Saúde nessas decisões. **Objetivo:** Foram estudadas as recomendações de incorporação de medicamentos sem registro sanitário realizadas pela Comissão entre janeiro de 2012 e junho de 2016, e suas compras pelos órgãos federais nacionais. **Método:** Usaram-se informações presentes no *website* da Conitec e as compras registradas no SIASG. **Resultados:** Seis dos 93 medicamentos incorporados pelo SUS no período não possuíam registro na Agência Nacional de Vigilância Sanitária (Anvisa). Somente duas das decisões foram submetidas à consulta pública. As principais justificativas associadas às recomendações foram a

gravidade da doença, a presença de menores eventos adversos e o baixo impacto orçamentário. Metade dos fármacos na situação estudada já era disponibilizada pelo SUS, mas em apresentações que dificultavam seu uso pediátrico ou em situações de maior gravidade. Foram gastos R$ 3.159.085,96 com a compra desses medicamentos. **Conclusões:** A recomendação de incorporação de medicamentos não registrados pela Anvisa contraria a legislação relativa à Conitec e às aquisições públicas de medicamentos. Por outro lado, ressalta-se a importância da incorporação de medicamentos que atendem a relevantes lacunas terapêuticas.

PALAVRAS-CHAVE: Medicamentos; Registro de Medicamentos; Avaliação de Tecnologias em Saúde; Tomada de Decisão; Sistema Único de Saúde

INTRODUCTION

Around the world, drug registration is a regulatory tool used by health authorities to evaluate the quality, efficacy, and safety of products that apply for commercialization or consumption. The initial drug registration and its renewals provide products available on the market with quality and aim to protect individual and collective health before the risks associated with these products, and at the same time guarantee a more rational use of resources[1].

Law no. 6,360 dated September 23, 1976 is one of the main standards on drug registration in Brazil and addresses several aspects of registration and inspection of services and products subject to sanitary control[2]. Since 1998, the Brazilian National Policy on Pharmaceuticals defined drug registration as an exclusive act of the competent institution of the Ministry of Health (MH)[3]. This activity is a responsibility of the Brazilian Health Regulatory Agency (Anvisa), created in 1999 and in charge of market regulation and control, safeguarding the Brazilian market against possible risks in drug commercialization and consumption[4].

Law no. 12,401 dated April 28, 2011, on the therapeutic care and incorporation of health technologies in the context of the Brazilian Public Health System (SUS), established the National Committee for Health Technology Incorporation (Conitec) to help the MH regarding decisions on the incorporation, exclusion, or alteration of new medications, products, and procedures, as well as the development/alteration of clinical protocols or therapeutic guidelines. This law prohibits, in all management spheres of SUS, the payment, refund, or reimbursement of medications, products, experimental clinical or surgical procedures, or procedures not authorized or registered by Anvisa[5].

Subsequently, Decree no. 7,646 dated December 21, 2011 regulated the composition, responsibilities, and functioning of this committee, defining flows and deadlines for the evaluation and incorporation of technologies for the public health system, as well as a set of legal requirements for drugs to be considered for a potential incorporation into the SUS's procedure reimbursement table payment table. Some of the requirements to be met are the need for information on the number and validity of the registration of the health technology with Anvisa, for the presentation of scientific evidence on the efficacy, effectiveness, and safety of the technologies, and for complete economic evaluations, examining costs and benefits, and comparing the new alternatives to those technologies already incorporated into SUS, including the predicted financial-budgetary impact on the system. Lastly, medications must have their prices set by the Drug Market Regulation Chamber informed[6].

Additionally, the Brazilian legislation prohibits the purchase, dispensing, and funding of non-registered medications in all levels of the public health system, except in the cases provided for by law[2,5,7].

Nevertheless, the growing phenomenon of health litigation of propaedeutic or therapeutic procedures has led to judicial demands and the purchase of medications without sanitary registration in Brazil, often with no proven benefits, which poses risks to the health of patients who take them[8,9,10].

Consequently, the objective of the present study was to examine the recommendations on the incorporation of medications without active sanitary registration in Brazil proposed by Conitec from January 2012 to June 2016 and the purchase of these products by Brazilian federal institutions before and after the recommendations.

METHODS

The study was descriptive, retrospective, had a quali-quantitative approach, and focused on the recommendations for incorporation of medicines in Brazil proposed by Conitec between January 2012, date of implementation of the committee, and June 30, 2016. The present investigation is part of a more comprehensive study[10], but concentrated on the examination of the incorporation recommendation of drugs for human use without active sanitary registration.

Three main data sources were used. To check Conitec's requests and recommendations, the information presented on the website of the committee (http://conitec.gov.br/) was analyzed. Four types of data were extracted: a) registrations of requests for health technologies submitted during the studied period; b) Conitec's recommendation technical reports; c) decision administrative rules by the secretary of Science, Technology, and Strategic Supplies (SCTIE) published in the Federal Official Gazette (FOG); and d) contributions to public consultations.

Medicines without active sanitary registration were defined as those which did not had a registration at the date of publication in the FOG of the administrative rule that announced the decision of incorporation into SUS publicly. The registration status of each medicine was verified on Anvisa's website for medication

consultation, based on the name of the drug and its pharmaceutical presentation (https://consultas.anvisa.gov.br/#/medicamentos/). The data available on the website did not allow to know whether the lack of registration was due to the rejection of the request or the absence of its solicitation by the manufacturer. The existence of active registrations was confirmed again in August 2017, when the study was being concluded, to identify medicines that might have obtained Anvisa's approval for commercialization after the committee's decision.

The presence of public purchases of the medicines incorporated without valid registration carried out until December 31, 2016 was verified at the Integrated General Services Management System (SIASG), run by the Ministry of Planning, Development, and Management. This system contains information about all goods and services purchased by the federal public administration[11], and its data can be accessed publicly, in accordance with the Brazilian Access to Information Law[12].

For analysis purposes, the applicants for incorporation were registered and subsequently categorized into requests of (i) internal origin, when they originated from secretariats of the MH, its regulatory agencies (Anvisa and the Brazilian Regulatory Agency for Private Health Insurance and Plans), or municipal or state health secretariats; and (ii) external origin, when they originated from other institutions of the federal government, industries, the Judicial Branch, health organizations, teaching and research institutions, medical and professional societies, patient associations and other nongovernmental organizations, healthcare professionals, and patients or their relatives/caregivers.

Medicines without sanitary registration were examined according to the year of Conitec's recommendation and the clinical condition associated with the indication, presented in the request, by using the 10th version of the International Classification of Diseases (ICD) and the Anatomical Therapeutic Chemical Classification System (ATC) up to the fifth level (active substance) and applying the *World Health Organization Collaborating Centre for Drug Statistics Methodology*[13].

The registration of these medicines with the health regulatory agencies *Food and Drug Administration* (FDA), from the United States, and *European Medicines Agency* (EMA), from Europe, was also verified using the organizations' websites[14,15].

For each medicines under analysis, the authors checked whether a public consultation was carried out and the total number of received contributions, as well as whether the Conitec's recommendation was followed by the SCTIE secretary and had the final decision published in the FOG.

Last, all the justifications included in the reports to base the recommendation for incorporation by Conitec were identified, as well as potential restrictions related to the decisions.

A search was performed in SIASG's website to determine the presence of purchase registrations in the five years that preceded the date of recommendation for incorporation of the analyzed medicines and in all the subsequent years after the approval until December 31, 2016. Data on the quantities acquired, the public institution responsible for the purchase, the acquisition modality, justifications for the purchase, hired suppliers, and unit prices were collected.

To compare information from all the years covered in the examined period, the unit prices extracted from SIASG's website were corrected to December 2016 by using the annual variation of the Brazilian Consumer Price Index, obtained directly from the Institute for Applied Economic Research. The corrected prices of each purchase were multiplied by the acquired quantities to determine the contracted expenditure on each medication.

Data obtained from all the sources were organized in a database designed for this purpose with the Epidata® program. The Stata® version 12 software was used for tabulation and data analysis.

Information on requests, recommendation technical reports, and contributions to public consultations is open and available on Conitec's websites. Similarly, data obtained on Anvisa's website and information about the purchases registered at SIASG did not require the previous approval of the study proposal by a research ethics committee.

RESULTS

In the examined period, Conitec received 485 applications, from which 267 (55.1%) corresponded to requests for incorporation of new medicines into SUS. Seventeen applications (3.5% of the total number of requests) did not present a final decision as of June 30, 2016 and 148 (30.5%) had an early conclusion due to documentary nonconformity or at the request of the applicant or the committee.

Among the 201 requests related to medicines that were brought to the plenary, 93 medications, including six vaccines and two immunobiologicals, received a recommendation favorable to the incorporation (30.9%). Recommendations for the incorporation of six medicines not registered with Anvisa (6.5% of the total number of incorporated drugs) in eight different presentations were found: biotin 10 mg and 10 mg/mL, hydrocortisone cypionate 10 and 20 mg, chloramphenicol palmitate 125 mg/5 mL, hydroxocobalamin hydrochloride 5 mg, doxycycline 100 mg, and hydroxyurea 100 mg.

Table 1 shows the profile of the medicines without sanitary registration with Anvisa which received a recommendation for incorporation by Conitec. These medicines belong to four therapeutic subgroups (A11 – Vitamins, H02 – Corticosteroids for systemic use, J01 – Antibacterials for systemic use, and L01 – Antineoplastic agents). Two of them — chloramphenicol palmitate 125 mg/5 mL and doxycycline 100 mg — were recommended for the same indication: spotted fever. Regarding the presence of registration with international health agencies, it was found that only the medicine hydroxocobalamin 5 g has a registration with both the FDA and EMA, for the same indication approved in Brazil. Biotin (10 mg and 10 mg/mL) does not have a registration with any of the international regulatory agencies.

Table 1. Profile of the medicines without active sanitary registration with Anvisa which received a recommendation for incorporation by Conitec, January 2012 to June 2016.

Medicine	Presentation	ATC	ICD	FDA registration	Approved indication at FDA	EMA registration	Approved indication at EMA
Biotin 10 mg	Capsule/pill	A11HA05	Endocrine, nutritional, and metabolic diseases	No	NA	No	NA
Biotin 10 mg/mL	Oral solution						
Hydrocortisone cypionate 10 mg	Pill	H02AB09	Diseases of the blood and hematopoietic organs and immunological disorders	Yes	Congenital adrenal hyperplasia, among others	No	NA
Hydrocortisone cypionate 20 mg	Pill						
Chloramphenicol palmitate 125 mg/5 mL	Oral suspension	J01BA01	Some infectious and parasitic diseases	Yes	Anti-infective	No	NA
Doxycycline 100 mg	Injectable solution	J01AA02	Some infectious and parasitic diseases	Yes	Anti-infective	No	NA
Hydroxocobalamin hydrochloride 5 g	Capsule	V03AB33	Respiratory system diseases	Yes	Cyanide poisoning	Yes	Cyanide poisoning
Hydroxyurea 100 mg	Capsule	L01XX05	Diseases of the blood and hematopoietic organs and immunological disorders	No	NA*	Yes	Sickle cell disease

ATC: *Anatomical Therapeutic Chemical classification system*; ICD: International Classification of Diseases; Conitec: National Committee for Health Technology Incorporation; FDA: Food and Drug Administration; EMA: European Medicines Agency; NA: not applicable.

Table 2. Characteristics of the medicines without active registration with Anvisa recommended for incorporation by Conitec, January 2012 to June 2016.

Medicine	Date of recommendation by Conitec	Proposed indication	Applicant	Public consultation	Number of contributions in the public consultation	Estimated price per PU	Estimated annual budgetary impact
Biotin 10 mg	Sep/2012	Biotinidase deficiency	MH/ SAS	Yes	None	R$ 0.79	R$ 915,520.00[a]
Biotin 10 mg/mL							
Hydroxyurea 100 mg	Jun/2013	Sickle cell disease	MH/ SAS	No	NA	R$ 0.85[b]	R$ 1,530,000.00[b]
Chloramphenicol palmitate 125 mg/5mL	May/2014	Spotted fever	MH/SVS	No	NA	US$ 1.50	US$ 6,000.00[c]
Doxycycline 100 mg	May/2014	Spotted fever	MH/SVS	No	NA	US$ 5.00	US$ 120,000[d]
Hydrocortisone cypionate 10 mg	Mar/2015	Congenital adrenal hyperplasia	MH/ SAS	No	NA	R$ 0.43	R$ 805,497.64[e]
Hydrocortisone cypionate 20 mg						R$ 0.99	
Hydroxocobalamin hydrochloride 5 g	Jan/2016	Cyanide poisoning	MH/SAS and MH/SCTIE	Yes	5	R$ 2,064.48	R$ 3,334,135.20[f]

Conitec: National Committee for Health Technology Incorporation; MH: Ministry of Health; SAS: Secretariat of Health Care; SVS: Secretariat of Health Surveillance; SCTIE: Secretariat of Science, Technology, and Strategic Supplies; NA: not applicable; PU: pharmacotechnical unit.
[a] Estimated budgetary impact of biotin taking into account the posology of one capsule with 10 mg per day, with an average price of the monthly treatment (30 capsules) of R$ 23.84. Special values for the liquid presentation of biotin 10 mg/mL were not established in the estimative[26].
[b] Estimated budgetary impact of hydroxyurea 100 mg based on a daily dose of 200 mg/day patient at the mentioned price of R$ 0.85 transferred by the MH to states per capsule of hydroxyurea 500 mg[22].
[c] Estimated budgetary impact of chloramphenicol palmitate taking into account a centralized purchase via direct importation by the MH at the price of US$ 1.50 per container of chloramphenicol solution 125 mg/5 mL[19].
[d] Estimated budgetary impact of injectable doxycycline 100 mg based on a centralized purchase via direct importation by the MH at the price of US$ 5.00/ampoule[19].

There were recommendations favorable to the approval of medicines without active registration in all the years of activity of Conitec. The indications of use accepted by the committee for the medicines matched those described by the consulted international health agencies, for the drugs that presented a registration with them. All the requests were internal and originated from secretariats of the MH. Only two medicines had their recommendation for incorporation submitted to a public consultation, in accordance with the period provided by for the law. One of the drugs received no contribution and the other underwent a simplified process. The drugs which showed the highest estimated budgetary impact were hydroxocobalamin hydrochloride 5 g, hydroxyurea 100 mg, and biotin 10 mg and 10 mg/mL (Table 2). All the recommendations for incorporation by Conitec were followed by the SCTIE secretary.

Regarding the justifications for recommendations for incorporation presented in the reports, reasons related to the severity/lethality of the underlying disease, presence of minor adverse events, and lower cost or low budgetary impact stood out (Table 3).

Table 4 shows the purchases of medicines without active registration with Anvisa registered at the SIASG database. Seventeen acquisitions of drugs without registration were carried out, with a predominance of purchases of chloramphenicol palmitate 25 mg/mL and biotin 10 mg, each with six purchases. Acquisition of doxycycline or hydroxyurea was not identified. Half the purchases occurred before the medicines had their recommendation for incorporation approved by Conitec and 47% were performed in the past two years. The Ministry of Education (ME) was responsible for 41% of the acquisitions, requested mostly by teaching hospitals, and the MH accounted for 29% of the purchases. The prevalent purchase modality was reverse auction (78%). Only two purchases had the fulfillment of a legal action as a justification,

Table 3. Justifications presented in Conitec's recommendation reports favorable to the incorporation of medicines without active sanitary registration with Anvisa, January 2012 to June 2016.

Medicine	Justifications for recommendation for incorporation
Biotin 10 mg and 10 mg/mL	Relevant unmet clinical need, low budgetary impact, and lack of alternatives at SUS
Hydroxyurea 100 mg	Relevant unmet clinical need, greater ease of use, and lack of alternatives at SUS
Chloramphenicol palmitate 125 mg/5 mL	Severity of the underlying disease, minor adverse events, and lower cost
Doxycycline 100 mg	Severity of the underlying disease, minor adverse events, and lower cost
Hydrocortisone cypionate 10 mg and 20 mg	Additional clinical benefit and minor adverse events
Hydroxocobalamin hydrochloride 5 g	Relevance and severity of the underlying disease, evidence of safety and cost-effectiveness, and low budgetary impact

Table 4. Purchases of medicines without active registration with Anvisa with a favorable recommendation for incorporation by Conitec present at SIASG, January 2012 to June 2016.

Medicine	Year of purchase	Organization responsible for the purchase	Purchase modality	Quantity of purchased PUs	Contracted expenditures (in R$)*
Acquisition before the incorporation administrative rule					
Chloramphenicol palmitate 25 mg/mL	2009	ME	Reverse auction	100	3,568.82
Chloramphenicol palmitate 25 mg/mL	2009	MD	Reverse auction	100	1,661.76
Chloramphenicol palmitate 25 mg/mL	2013	MD	Reverse auction	20	315.18
Hydrocortisone cypionate 10 mg	2011	ME	Reverse auction	600	2,862.34
Hydrocortisone cypionate 10 mg	2011	MH	Exemption of bidding	300	989.19
Hydrocortisone cypionate 10 mg	2013	MH	Exemption of bidding	400	2,162.96
Hydrocortisone cypionate 10 mg	2013	MD	Reverse auction	500	2,741.25
Hydroxocobalamin hydrochloride 5 g	2015	MH	Unenforceability of bidding	1,615	3,107,977.42
Subtotal				3,755	3,122,278.92
Acquisition after the incorporation administrative rule					
Chloramphenicol palmitate 25 mg/mL	2014	ME	Reverse auction	524	8,752.70
Chloramphenicol palmitate 25 mg/mL	2016	MH	Reverse auction	400	25,530.51
Chloramphenicol palmitate 25 mg/mL	2016	MD	Reverse auction	35	284.16
Biotin 10 mg	2014	ME	Reverse auction	500	314.66
Biotin 10 mg	2015	MD	Reverse auction	1,000	1,041.64
Biotin 10 mg	2015	ME	Reverse auction	500	308.24
Biotin 10 mg	2015	MH	Exemption of bidding	150	103.63
Biotin 10 mg	2015	ME	Reverse auction	500	170.06
Biotin 10 mg	2016	ME	Reverse auction	500	301.44
Subtotal				4,109	36,807.04
TOTAL				7,864	3,159,085.96

Conitec: National Committee for Health Technology Incorporation; MD: Ministry of Defense; ME: Ministry of Education; MH: Ministry of Health; SIASG: Integrated General Services Management System; PU: pharmacotechnical unit.
* Annual values (in reais) as per the correction to December 2016. The purchases of medications without active registration resulted in a total cost to public coffers of R$ 3,159,085.96 as per the correction to December 2016. A single medication accounted for 98% of this cost: hydroxocobalamin 5 g.

and they consisted of the acquisition of the drug or medicine hydrocortisone 10 mg by the MH in 2011 and 2013, totaling 700 pills and R$ 3,152.15 as per the correction to December 2016.

DISCUSSION

Authorizing the commercialization of medicines in a country or its distribution in the public system is a major sanitary and social responsibility. Law no. 12.401/2011, which instituted Conitec, clearly stated in article 19-T, subsection II, that "the release, payment, refund, or reimbursement of Brazilian or imported medicines without registration with Anvisa" are prohibited in all management spheres of SUS[5].

In disagreement with the rules defined by the regulatory framework that supported Conitec and the procedures for submitting applications, there was recommendation for incorporation by this committee of six medicines without active registration with the Brazilian health agency.

It was not verified whether there were requests for the registration of these medicines with the agency, whose average analysis time was long in the study period[16]. However, information on the registration status and its number with the agency is mandatory to submit incorporation applications and must be verified in the initial conformity analysis. Without this data, applications should not be analyzed[5]. Additionally, a new examination of the registration status, carried out over one year after the end of the study period, did not show the existence of active registration for any medicines with recommendation for incorporation by Conitec.

Half the cases referred to medicines already available at SUS for the same indications, but in different presentations, with recommendations aiming to facilitate their use by pediatric populations or in situations of high severity.

The medicine doxycycline 100 mg injectable solution and chloramphenicol 25 mg/mL oral suspension, requested by the Health Surveillance Secretariat to treat spotted fever, are an example of this situation. This multisystemic infectious disease, caused by bacteria of the genus *Rickettsia* and transmitted by ticks, was responsible for 17,117 suspected and 1,245 confirmed cases between 2007 and 2015[17]. Some cases evolve to high severity and lethality, which may reach 85% when not treated properly[18]. The antimicrobial agent of choice to treat suspected cases of infection, regardless of the age group of the patient and severity of the disease, is doxycycline, either in oral or injectable presentation; chloramphenicol is an alternative when the first option is impossible. The Guide to Epidemiological Surveillance of the MH has recommended these antibiotics in the new presentations to treat spotted fever since 2009, but they were not available in Brazil, for lack of commercial interest of manufacturing laboratories and unavailability of registration[19]. The financial impact of the importation of products for a one-year treatment with the two new presentations was estimated at US$ 126,000. Conitec endorsed the two incorporations, and the products would be acquired centrally by the MH and sent to Brazil's endemic areas[20].

Another medicine that meets the cited characteristics is hydroxyurea 100 mg. It is used to treat sickle cell disease in children, a genetic problem marked by the structural alteration of the beta-globin chain, leading to the production of an abnormal hemoglobin denominated HbS. This illness has a high incidence in Brazil: according to the Brazilian Neonatal Screening Program, 3,500 children are born with sickle cell disease (approximately 1:1,000 live births) and 200,000 children are born with sickle cell trait per year in the country, with a significant variation among states due to different proportions of afro-descendants[21]. There is evidence supporting the efficacy of the drug or medicine to reduce the number of vaso-occlusive crises, hospitalizations, transfusions, and episodes of acute chest syndrome, showing a positive impact on survival and quality of life[22], which caused the drug to be indicated for patients older than two years old. Although the 500 mg capsule for adult use was included in the National Relation of Essential Medicines (Rename), the children-oriented presentation did not exist on the market, which resulted in the need to dilute the drug or medicine with water to administer a proportional dose, causing the handling of the drug at home and the disposal of the remaining of the product and increasing the chances of mistakes in the administered doses. The 100 mg presentation is available in other countries, which could make its importation possible via an international institution. The Conitec's report also mentions that the Department of the Industrial Complex and Innovation in Health of the MH was evaluating the possibility of production of the children-oriented presentation by the Air Force Research Laboratory as of the approval[23], which does not seem to be occurring.

The incorporation of three medicines — biotin 10 mg, hydroxocobalamin 5 g, and hydrocortisone cypionate 10 mg and 20 mg — was recommended for indications that were not covered by the existing therapeutic alternatives available at SUS at the moment or required compounded formulas or preparations for patients who needed treatment.

Hydrocortisone cypionate 10 and 20 mg was incorporated into SUS to treat congenital adrenal hyperplasia in newborns. This is an autosomal recessive hereditary disorder which affects the synthesis of adrenal steroids, and its incidence ranges from 1:7,500 to 1:20,000 live births[24,25]. Over 90% of the cases result from the deficiency of the 21-hydroxylase enzyme, which impairs the normal production of cortisol and aldosterone and redirects metabolic intermediates to the excess synthesis of androgens. The disease is associated with significant morbidity and mortality rates in affected children and adults[25]. The inclusion of screening for this condition in the Brazilian Neonatal Screening Program occurred only after the Administrative Rule no. 2,829 dated December 14, 2012 was enacted[26], but since 2010 a clinical protocol published by the MH has been including the injectable administration of hydrocortisone 100 mg or 500 mg in cases of glucocorticoid and mineralocorticoid deficiency and symptoms of hyperandrogenism. The recommendation for incorporation of hydrocortisone cypionate for use in newborns was

justified by the fact that the drug has a short half-life, which would not interfere with child development, conversely to what occurs with prednisone[24].

Biotin, another non-registered medicine whose incorporation was recommended, is indicated for the treatment of biotinidase deficiency (BD), an inborn error of metabolism caused by an autosomal recessive inheritance which shows a varied phenotypic expression. The recommendation report mentions that there were approximately 3,200 patients with BD in Brazil in 2012[27], but examination of 225,136 newborns from several Brazilian regions in 2004 showed a prevalence of 1:9,000 of some level of BD[28]. Cases of severe deficiency usually manifest early, with neurological and cutaneous problems, such as epileptic seizures, hypotony, microcephaly, and delayed neuropsychomotor development. In less severe cases, which usually have a late diagnosis, visual and hearing disorders and delayed motor and language development are frequent[29]. As for congenital adrenal hyperplasia, the screening for BD was included in the Brazilian Neonatal Screening Program only in 2012[26]. All the people with the deficiency, even those with some residual enzymatic activity, must be treated through supplementation with oral biotin in its nonconjugated form. The treatment is simple, inexpensive, and based on the reposition of biotin at the doses of 5 mg/day and 10 mg/day for patients with a diagnosis of partial and total BD, respectively, for life, orally and regardless of the body mass. Some products containing biotin in polyvitamin mixtures were available in Brazil at doses lower than those indicated for the treatment of BD, but there was no registration with Anvisa for the isolated form, and it could be obtained at compounding pharmacies only. Despite limited evidence reported in observational studies with a reduced number of patients, considering the lack of alternatives for the treatment of the disease, the affordable price of the therapy, and the low budgetary impact on SUS, the drug or medicine was recommended for incorporation by Conitec in July 2012[27].

Hydroxocobalamin was recommended for incorporation in January 2016 for the use in the treatment of cyanide poisoning, a relatively rare condition but with high severity and lethality, given that hydrogen cyanide causes severe hypoxia, with systemic toxic effects and a quickly set cardiovascular collapse. Inhalation of smoke originating from domestic and industrial fires is the most common source of exposure to cyanide, but there are cases of chronic poisoning caused by occupational exposure. The drug, considered a first-class antidote, acts by chelating cyanide into the cyanocobalamin (vitamin B12) form, which is excreted by the kidney. The administration must occur as early as possible, still in a pre-hospital setting. Each 5 g of hydroxocobalamin neutralizes around 40 micromoles of cyanide per liter of blood, thus the administration of 10 to 15 g may be necessary[30,31]. Other antidotes such as amyl and sodium nitrites and sodium thiosulfate are not available for commercialization in the country either[32].

The fire at the nightclub Kiss in Santa Maria, state of Rio Grande do Sul, Brazil in January 2013, which resulted in 242 deaths, exposed the need for the country to have ready availability of products to deal with unpredictable incidents like this. Hydroxocobalamin was included in the list of non-registered medicines authorized by Anvisa for importation on an exceptional basis, intended for hospital use. This simplified process makes the provision of medicines by SUS possible in situations of "high risk to health" and unavailability of approved therapeutic alternatives[33].

Decree no. 8,077 dated August 14, 2013 permits SUS to supply medicines with indications different from those approved by Anvisa, if requested by Conitec, which will be compelled to provide scientific evidence that attest the need for the new intended use[7]. It is noteworthy that, in some cases, the evidence of efficacy and safety presented in recommendation reports was limited to observational studies and even case series, usually considered of lower quality. This may be related, at least partially, to the intrinsic characteristics of the listed clinical indications, often referring to orphan diseases, which present specific difficulties regarding the evaluation of technologies in health[34], or to situations to which the possibility of randomized clinical trials was not applicable.

All the requests for incorporation of medications not registered with Anvisa originated from secretariats of the MH, which may be related to the fact that the requests were not rejected in the documentary conformity evaluation. Additionally, most of them were evaluated in a simplified process and were not submitted to public consultation.

Public consultations have the objective to expand the discussion about the subject from contributions, opinions, and criticisms from society and support the decision on the formulation and definition of public policies. Decree no. 7,646/2011, which normalized Law no. 12,401/2011, addresses the possibility of this simplified administrative process in cases of "relevant public interest" (Art. 29) without explaining, however, the criteria that characterize this interest[6]. Reports related to simplified processes refer to proposals that address the extension of use of technologies, new presentation of medications, or incorporation of established medicines whose use is traditional, involving low-cost technologies and low budgetary impact on SUS. These proposals relate to the development or update of clinical protocols and therapeutic guidelines.

All the medicines examined in the present study met these conditions. In the two cases submitted to public consultation, hydroxocobalamin and biotin, the number of contributions was low (seven)[32] or nonexistent[27] in the period provided for by law.

Economic evaluation studies, a criterion required in the examination for incorporation of new technologies, were carried out for hydroxocobalamin only. The cost-effectiveness analysis performed revealed that its use would correspond to an incremental cost-effectiveness ratio of R$ 62,474.34 per life saved and R$ 2,126.45/quality-adjusted life years. The budgetary impact, around R$ 3,334,135.20, resulted from the high acquisition cost of the intravenous infusion sets — R$

2,064.48 when the estimate was obtained — and need to supply two sets to each of the 600 advanced support units of the Mobile Emergency Care Service, as well as 405 sets to be distributed to state health secretariats and a strategic stock of ten sets for the MH[32].

None of the medicines identified in the present study had a registration with Anvisa until September 2017. Biotin obtained a registration in January 2016, but for a different presentation: gelatin capsules with 2.5 mg. In this sense, all the purchases of these medicines after the recommendation remain to be carried out without registration.

The Rename 2016, published in August 2017, lists some of the non-registered medicines examined in the present study — chloramphenicol palmitate, doxycycline, and hydroxocobalamin, all included in the Strategic Component of Pharmaceutical Care — but not all of them[35]. This absence is even more surprising when it is known that since the release of Rename 2012 the document has no longer been a classic list of essential medicines and has become a positive list of funding, which catalogues publicly provided items[36].

The purchase volume, regarding both the quantity of acquired items and costs, was barely significant. Biotin and hydroxocobalamin stood out in terms of purchased pharmacotechnical units. All the 3,165 biotin units were acquired as magistral formulas with Brazilian compounding pharmacies, even after its incorporation by SUS. In the case of hydroxocobalamin, which accounted for 98% of the total expenses, a single purchase of 1,615 units of the lyophilized product was carried out by the MH, via importation, with a unit price for the infusion set of R$ 1,810.55 as per the correction to 2015. The acquisition via importation was scheduled, from the centralized purchase by the MH, taking into account the procedures laid out in Decree no. 8,077/2013, according to which Anvisa may exempt from registration immunobiologicals, insecticides, medications, and other strategic supplies when these are acquired via international multilateral organizations, for use in public health programs by the MH and affiliated entities[7]. Because the company Merck® was the only producer, its purchase occurred by means of unenforceability of bidding, which in some cases may tend to increase costs significantly given the situation of commercial monopoly[37].

The ME was identified as the main purchaser of non-registered medicines, mostly through their teaching hospitals, which may be explained by the indication profile of the drugs and the use of new technologies in their teaching and research activities.

Regarding public purchases of these medicines, it is noteworthy the reduced proportion of acquisitions motivated by legal action. Teodoro et al. analyzed federal purchases of medicines without active sanitary registration in Brazil between 2004 and 2013 and verified that 51.0% were products that obtained a sanitary registration after the acquisition, which could cause tension in the registration granting and the subsequent incorporation by SUS. The authors showed that legal actions accounted for 81.9% of the purchases, with a growing trend in the last examined years[9]. The constitutional imposition to the state regarding the right to health, often resulting in judicial intervention, explains how the needs of the population are linked to commercial registration interests of producing companies. In addition, registrations can also be construed as an expression of the guarantee of the right to health to users, and aim to provide sanitary protection and safety[8].

The legislation that regulates Conitec establishes a period of 180 days for SUS to offer new incorporated technologies, and this availability must be supported by the Clinical Protocols and Therapeutic Guidelines. The use protocol of hydroxocobalamin was published in 2015, establishing criteria for diagnosis and inclusion in treatment, doses and administration plan, aspects of monitoring and availability, and forms of implementation and use at SUS[38]. The PCDT related to biotinidase deficiency was submitted to public consultation in May 2017 and recommended the use of gelatin capsules with 2.5 mg, already approved by Anvisa for commercialization, but remained unpublished as of the period of completion of the present manuscript[39]. The latest version of the 2016 Guide to Epidemiological Surveillance already pointed to the availability of injectable doxycycline and oral suspension of chloramphenicol in the guidelines for the treatment of spotted fever in Brazil[40]. Regarding the other medicines, the update of the existing protocols related to sickle cell disease and congenital adrenal hyperplasia, both published in January 2010, was not found.

Lastly, it is worth asking why therapeutic alternatives considered effective were not made available earlier. Most medicines in the situation under discussion are “old” products, which already lost patent protection, and are inexpensive, which results in little commercial interest for registration and production by the pharmaceutical industry. Santana et al. studied aspects related to the sanitary registration and incorporation of technologies at SUS oriented toward the so-called “diseases of poverty” and identified that, among the 132 medications listed in Rename 2014 to treat these diseases specifically, more than one third had only one Brazilian producer and 24 (18.2%) did not have registration in the country[41]. Thus, the authors point up the need for the Brazilian state to invest in offering medicines of low commercial interest, making a national production feasible via public laboratories or establishing productive development partnerships.

CONCLUSIONS

The sanitary registration of medicines is a fundamental tool to the evaluation of new technologies that apply for inclusion or permanence on the market, aiming to protect people’s health.

Conitec has the function defined by law to advise the MH on the decisions related to the incorporation of new medicines into SUS so the system can make these products available to users. It is not the committee’s responsibility to evaluate medicines applying to enter the Brazilian market, a role known to be played by Anvisa, with the subsequent funding authorization by SUS. However, the incorporation of medicines into the payment table represents an effective way to enter the market, given the universal nature of the Brazilian public health system.

Although the legislation in force prohibits the purchase and funding of non-registered medicines in all the levels of the Brazilian public health system, except in cases provided for by law, this fact occurred in the studied situation, before and after Conitec's recommendation.

The authors recognize the importance of the incorporation of medicines that meet relevant therapeutic gaps, for instance hydroxocobalamin. Nevertheless, taking into consideration the regulatory framework about registration of medicines, their incorporation into SUS, and public purchases in force in Brazil, evaluations of medicines without sanitary registration should have not happened, let alone incorporations.

The activity of the state is indispensable to guarantee the public interest and access to treatment required by the needs of the population, thus ensuring the safety and efficacy of products to which users are exposed, and developing and executing economic and social policies that facilitate the production of drugs, reduce iniquities, and follow the established constitutional principles.

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Conflict of Interest

Authors have no potential conflict of interest to declare, related to this study's political or financial peers and institutions.