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ESSENTIAL DRUGS IN THE ONCOLOGICAL CONTEXT

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Abstract: The World Health Organization (WHO) Model List of Essential Medicines was first published in 1977 and since then it has been updated every two years. The last version was published in 2021 and contains the medicines considered most effective and safe to meet the most critical needs of a health system. Developed and developing countries have created national lists of essential medicines based on the WHO model list, in Brazil, for example, named RENAME and since 2011 has been updated by the National Commission for the Incorporation of Technologies in the SUS (CONITEC). Even though, the list faces challenges with inclusion of different types of medications to meet particularities of each population, such as cancer patients. Frequently, these patients are not fully covered by the list and need to pay for their own treatment or require judicialization. In this paper, we compared the real availability of cancer drugs which were in the WHO essential list in the Brazilian public health system. First, we consulted the 2021 version of the WHO list of essential medicines and then, checked which ones had recommendations by CONITEC for inclusion or not in the SUS. Finally, we compared the current recommendations with a list of health technologies adopted by a Brazilian network of university hospitals, which operates in the SUS. This article analyzes differences between the model list and CONITEC recommendations and the real-world practice, highlighting important aspects such as financing and real access to these drugs.

Keywords: Access to essential medicines and health technologies; Clinical oncology; Essential drugs.

The World Health Organization (WHO) Model List of Essential Medicines contains the medicines considered most effective and safe to meet the most critical needs of a health system. More than 155 countries, including developed and developing countries, have created national lists of essential medicines based on the WHO model list. The first list was published in 1977 and included 208 drugs; after that, it was updated every two years. The 22nd list, from 2021, includes 479 drugs (WHO, 2021).

In 1964, through Decree No. 53,612 of Dec 26th, 1964, Brazil began to draw up lists of essential medicines, which defined the Basic and Priority List of Biological Products and Materials for Human and Veterinary Pharmaceutical Use. In 1975, the list was named: the National List of Essential Medicines (RENAME). Since then, Brazil has invested in improving these lists to guarantee access to pharmaceutical care and promote the rational use of these drugs (BRASIL, 2022).

Decree No. 7,508, of Jun 28th, 2011, which regulates Law No. 8,080, of Sept 19th, 1990, states that "RENAME comprises the selection and standardization of medicines indicated for the treatment of diseases or injuries under the Unified Health System (SUS)" and also that "every two years, the Ministry of Health will consolidate and publish the RENAME updates and the respective National Therapeutic Form (FTN)." RENAME also complies with Consolidation Resolution No. 1 of Mar 30th, 2021, which presents the composition of this List according to the financing responsibilities of Pharmaceutical Assistance between - Union, states, and municipalities - in addition to presenting the medicines offered at all levels of care and in the SUS care lines. In addition, the permanent update of RENAME is a significant challenge for SUS managers, given the complexity and singularities of the population's health needs, the particularities of

the health system's organization and financing models (Figure 1) (BRASIL, 2020, 2022).

Subsequently, after Decree No. 7646 of Dec 21st, 2011, the National Commission for the Incorporation of Technologies in the SUS (CONITEC) became responsible for proposing the update of RENAME (Figure 2). CONITEC, responsible for evaluating the technologies to be made available in the Unified Health System (SUS), aims to define criteria and deadlines for the incorporation of new technologies in health, exclusion or alteration of new medicines, products, and procedures, as well as elaboration or revision of Clinical Protocols and Therapeutic Guidelines (PCDT). The RENAME update proposed by CONITEC consists of: "i) a reactive process in which the claimants are bodies and institutions, public or private, or individuals; and ii) an active process conducted by a CONITEC subcommittee – the Technical Subcommittee for Updating RENAME and the National Therapeutic Form." In both processes, medicines, and inputs are included, excluded, or changed in the SUS after evaluation by CONITEC and a decision by the Department of Science, Technology, Innovation and Strategic Health Inputs of the Ministry of Health (BRASIL, C. 2020; BRASIL, MS. 2022; RIBEIRO, 2020).

Outpatient medications in the SUS occur through the Components of Pharmaceutical Assistance, namely: Basic Component, Strategic Component, and Specialized Component, which have characteristics, a form of organization, financing, and a list of differentiated medications, as well as different criteria for the access and availability of drugs (BRASIL, 2022).

The complexity, bureaucracy, and time-consuming process of updating the RENAME according to the particularities of each population is what makes a list, in some circumstances, non-inclusive. In cancer treatment, many patients have to pay for treatments not covered by the list of medications, often requiring the judicialization of these medications. In this perspective, there is a clear need for a more plural list in order to contemplate the cancer patient since many oncological drugs considered essential by the WHO, unfortunately, are not available to those who need to receive treatment financed by the SUS, as can be seen in table 1.

Table 1 was built based on the WHO model list of essential medicines compared to the catalog of health technologies available from a network responsible for the administration of Brazilian federal university hospitals, which operate within the scope of the SUS. We consulted whether there were CONITEC recommendations for the drugs on the list to compare the CONITEC recommendation with the availability in hospitals that provide onco-hematological care in the context of the Brazilian public health system (ROMERO, 2022; BRASIL, 2022).

According to the Brazilian Constitution of 1988, the right to health is guaranteed to the entire population residing in Brazil, aiming at "reducing the risk of disease and other injuries and universal and equal access to actions and services for its promotion, protection, and recovery". However, even though the enactment of the Federal Constitution dates back more than 20 years, what is observed in the public scenario is the lack of full access to health, being restricted to a small portion of the population, subject to lack of health care (BRASIL, 2022; ROMERO, 2022).

In addition, the sophistication of health systems, after the development of innovative technologies that provide improvement in therapy and diagnosis of the population's health problems, a better understanding of the health-disease process, the increased need for safe and effective treatments, and an increased in the life expectancy of the population, have

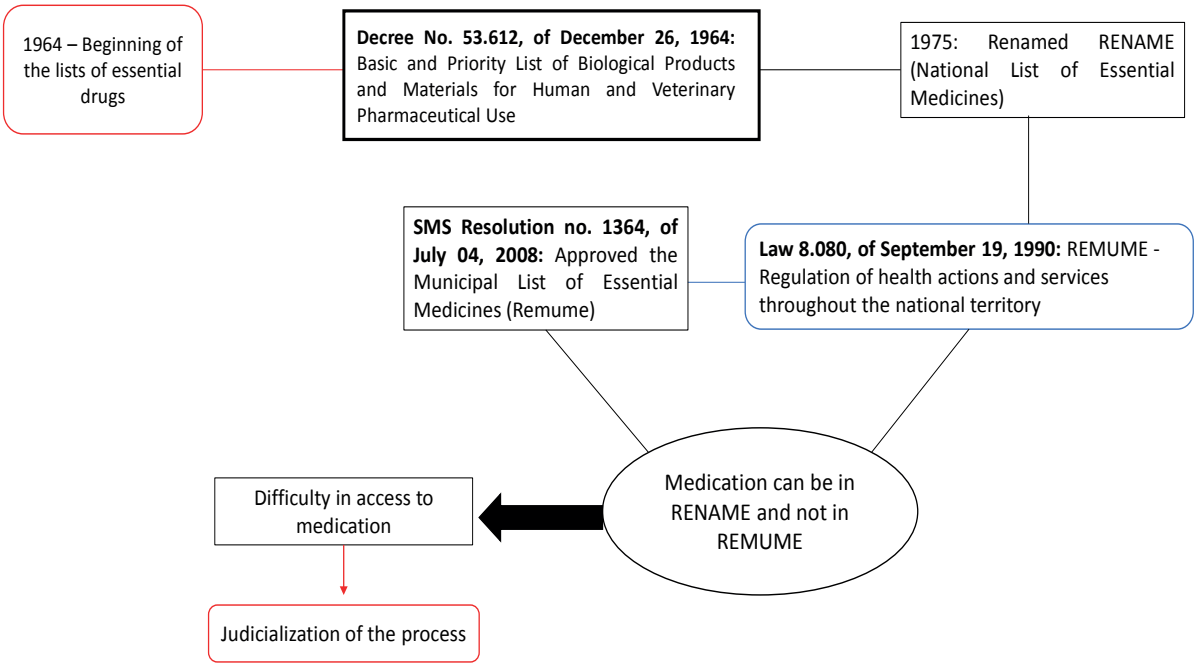

Figure 1 - Flow of access to medicines by the SUS.

Source: elaborated by the author (2022)

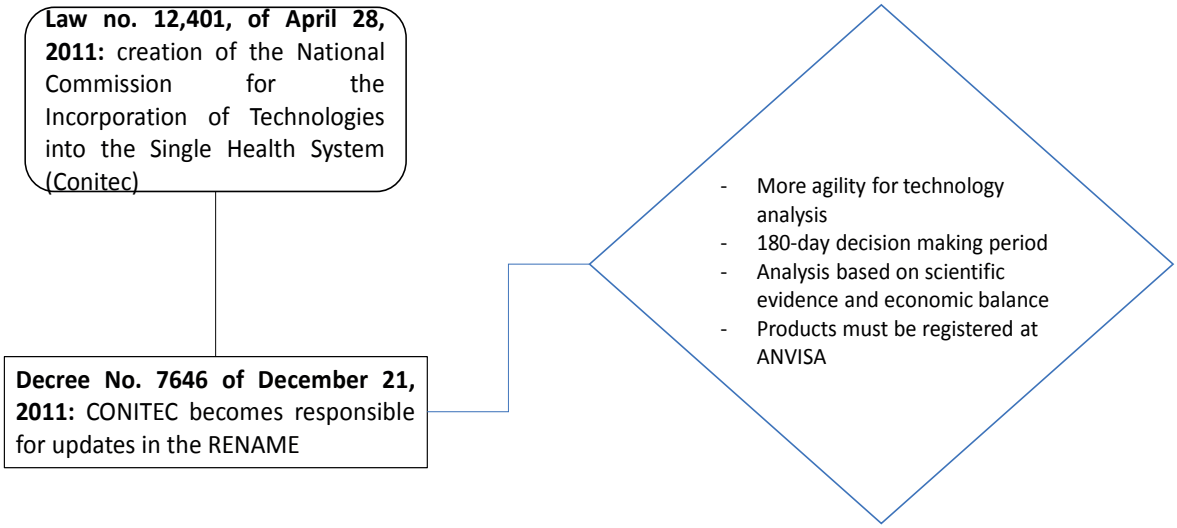

Figure 2 - CONITEC's role in RENAME.

Source: elaborated by the author (2022).

MEDICINE	AVAILABILITY BY SUS*	RECOMMENDATION CONITEC	OBSERVATION
Abiraterone	Yes	Recommended by incorporation.	Approved for metastatic castration-resistant prostate in patients with prior use of chemotherapy. Date of protocol [1]: 07/25/2019.
Bortezomib	Yes	Recommended by incorporation.	Approved for the treatment of multiple myeloma. Date of protocol [1]: 09/28/2020.
Dactinomycin	No	-	No active registration in Brazil. Import-dependent medicine.
dasatinib	Yes	Recommended due to non-expansion of use.	Evaluated for adults with Philadelphia chromosome-positive acute lymphoblastic leukemia resistant/intolerant to imatinib mesylate. Date of protocol [1]: 12/31/2020.
erlotinib	Yes	Recommended by incorporation.	Approved for treating advanced or metastatic non-small cell lung cancer EGFR mutation Protocol date [1]: 11/08/2013.
Everolimus	No**	Recommended for non-incorporation.	Evaluated for advanced postmenopausal breast cancer. Date of protocol [1]: 01/30/2014.
Gefitinib	Yes	Recommended by incorporation.	Approved for advanced or metastatic non-small cell lung cancer with EGFR mutation in 1st line. Date of protocol [1]: 11/08/2013.
hydroxycarbamide/ hydroxyurea	Yes	Recommended for incorporation into the SUS.	Approved for children with sickle cell disease. Date of protocol [1]: 06/13/2013.
imatinib	Yes	Recommended for incorporation into the SUS.	Approved for adjuvant chemotherapy of gastrointestinal stromal tumor. Date of protocol [1]: 07/07/2014.
lenalidomide	No	Recommended due to non-incorporation in SUS.	Evaluated for treatment of multiple myeloma. Date of protocol [1]: 03/14/2022.
Leuprorelin	Yes	Recommended for incorporation into the SUS.	Approved for central precocious puberty. Date of protocol [1]: 11/03/2021. Available from CEAF.
nivolumab	No	Recommended for incorporation into the SUS.	Approved for first-line treatment of advanced non-surgical and metastatic melanoma. Date of protocol [1]: 05/08/2020 0.
Pembrolizumab	No	Recommended for incorporation into the SUS.	Approved for 1st-line treatment of advanced non-surgical and metastatic melanoma. Date of protocol [1]: 05/08/2020 0.
rituximab	Yes	Recommended for incorporation into the SUS.	Approved for treating 1st and 2nd line CD20 positive B-cell non-Hodgkin's lymphoma. Date of protocol [1]: 12/30/2013.
Thalidomide	Yes	Recommended due to increased use.	Approved for the treatment of the myelodysplastic syndrome. Date of protocol [1]: 12/17/2014.
trastuzumab	Yes	Recommended for incorporation into the SUS.	Approved for first-line treatment of early, advanced, and HER-2 positive metastatic breast cancer. Date of protocol [1]: 07/26/2012 and 08/03/2017.
arsenic trioxide	Yes	Recommended due to non-incorporation in SUS.	Evaluated for the treatment of Acute Promyelocytic Leukemia. Date of protocol [1]: 12/17/2014.

triptorelin	Yes	Recommended for incorporation into the SUS.	Approved for central precocious puberty. Date of protocol [1]: 03/17/2022.

Table 1 - Availability in a network of university hospitals of essential onco-hematological drugs, according to the *World Health Organization* (WHO), with opinion available from CONITEC.

Source: BRASIL, 2022a.

CEAF: Specialized component of pharmaceutical assistance; CONITEC: National Commission for the Incorporation of Technologies in the Unified Health System; SUS: Unified Health System.

1: Date of publication of the CONITEC decision. As determined by article 25 of Decree 7646/2011, from the publication of the decision to incorporate technology in health, the technical areas of the Ministry of Health will have a maximum period of 180 days to effect the offer to the SUS.

*Consulted the Health Technologies Catalog of the Ebserh Network (Brazilian Company of Hospital Services).

**Not available for oncological indications.

an impact on rising health-related costs (LIMA, 2022).

According to Decree No. 7646, for the incorporation, alteration, or exclusion of health technologies by the SUS, it is necessary to initiate an administrative process in which documentation of the number and validity of the technology registration with the National Health Surveillance Agency (Anvisa) must be filed; presentation of scientific evidence demonstrating that the guided technology is at least as effective and safe as those available in the SUS for the intended indication; economic evaluation study comparing the requested technology with those already available in the SUS; and, in the case of medicines, the price set by Anvisa's Medicines Market Regulation Chamber (BRASIL, 2011).

When the result is favorable to the incorporation, the new technology is not readily available to the population after being published in the Official Gazette of the Nation. It must be accessible by the Ministry of Health for 180 days. In the case of oncological drugs, funding for Medium and High Complexity Health Care (MAC) is expected, which has the function of reimbursing the establishment qualified in Oncology, after inclusion of the technology in the chemotherapy procedures registered in the Subsystem of Authorization of Procedure of High Complexity of the Outpatient Information System (APAC-SIA) (BRASIL, 2011; CAPUCHO, 2022).

However, Brazil is among the unequal countries in the world. Consequently, the parameters for providing adequate treatment will not be satisfactorily achieved. Added to this, CONITEC's performance has limitations. It comes up against conditions that make it difficult to carry out the policy and dispense a broader range of medications to the population, not being sufficient to respond to the epidemiological dimension of cancer in Brazil, with difficulties in access and failures in cancer treatment in patients using the SUS (BATISTA, 2020; KOZAN, 2022).

The publication of the inclusion of SUS drugs does not confer the immediate availability of the drug for the oncology area in the SUS since the acquisition of medication is the responsibility of the qualified health service. In some cases, they may choose not to purchase it. In practice, the period for making the technology available can exceed the 180 days provided for, and there are no guarantees of enforcing the principle of equity of the SUS regarding the availability of technology in the area of Oncology in all services enabled in Brazil (CAPUCHO, 2022).

The drugs recommended by CONITEC are only sometimes available in clinical practice. As an example, we have Nivolumab and Pembrolizumab, drugs recommended by CONITEC for the 1st line treatment of advanced non-surgical and metastatic melanoma since Aug 5th, 2020, but still unavailable today for free use in the SUS setting of this pathological condition (Table 1). As Capucho *et al.* (2022) pointed out, this delay in making technology available can mean loss of life, especially in the field of Oncology, since there is a worse prognosis when the start of treatment is delayed.

The leading cause of the lack of access for SUS users to these technologies already incorporated by CONITEC is the amount paid by the Ministry of Health for the treatment of advanced melanoma, for example, considering that this does not cover the cost of treatment. According to the Ministry of Health, the amount reimbursed by APAC for the treatment of melanoma is 7,500 reais. However, according to Tanaka *et al.* (2017) the recommended dose of 200 mg of Pembrolizumab costs an average of 22,000 reais, leaving the responsibility of hospitals qualified in oncology to make the financial contribution for the residual amount.

Therefore, the technology incorporation policy needs to be improved to make what was incorporated available and within the foreseen period (BRASIL, 2022).

Differences between drug financing and distribution processes may impact compliance with the deadlines established in the legislation for releasing the technology included by CONITEC. Currently, there need to be more studies discussing the time required for the technology to become widely available, especially in the release of oncological drugs. Faced with the ineffectiveness of public policies implemented by other powers and the lack of assistance regarding the availability of essential therapies, it becomes relevant to discuss medications recommended by CONITEC in contrast to those genuinely available in services linked to the SUS.

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