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Perspective Article

Medicinal, Not Alternative: Regulation, Access and Safety in the Therapeutic Use of Cannabis Derivatives in Brazil

Medicinal, Não Alternativa: Regulamentação, Acesso e Segurança no Uso Terapêutico de Derivados de Cannabis no Brasil

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The use of cannabinoid-based products, such as cannabidiol (CBD) and tetrahydrocannabinol (THC), compounds extracted from the *Cannabis sativa* plant, has spread worldwide in the field of medicine due to their therapeutic potential in diseases such as refractory epilepsies, chronic pain, and neurological disorders.[1] Despite the growing body of scientific evidence on the efficacy and safety of these products, the quality and extent of these studies vary in Brazil, which results in a lack of national data on their safety under real conditions of use.

The removal of CBD from the list of prohibited psychotropic substances and its inclusion in the list of drugs subject to special control represented an important regulatory milestone.[2,3] RDC No. 17/2015 authorized, albeit restrictedly, the exceptional import of cannabidiol-based products.[4] Subsequently, RDC No. 327/2019 established criteria for the manufacture, importation, commercialization, prescription, and inspection of these products in Brazil.[5] Products containing *Cannabis* derivatives can be registered in two distinct regulatory categories: as a medicine, following the standards for proof of efficacy and safety, or as a *Cannabis product*, which has a less rigorous regulatory process, with the non-requirement of clinical studies.[6] Although these regulations represent advances, they are insufficient to consolidate a robust policy for the safe, effective and accessible use of medical *cannabis*.

The classification as a *Cannabis* product, as currently defined by Brazilian legislation, limits the application of the classic regulatory mechanisms of the health system, such as the obligation to register as a medicine, proof of efficacy and safety, traceability, quality control and pharmacovigilance.[7] It is important to highlight that this regulatory process is transitory and aims to guarantee access while companies carry out studies for registration as a drug. However, while these products do not meet the strict criteria to be classified as medicines, the structuring of an effective pharmacovigilance system remains compromised, which can impact patient safety.

In view of this, legitimate doubts arise as to the safety of the products currently available on the market. One of the first points of attention is the origin of the products. The different flows of access to cannabis-based products in Brazil, including registered medicines, products

regulated by RDC No. 327/2019, exceptional importation, artisanal productions by associations, and obtaining them through the courts, have varying levels of sanitary requirements, directly impacting the quality, traceability, and safety of the products.[5] In this context, traceability should be understood as a process that begins in production/import and extends to dispensation to the patient, being fundamental to ensure health safety, supporting control in the scope of pharmaceutical services.

According to Brazilian health regulations, cannabis-based therapeutic products can be classified into three distinct categories, each with direct implications for quality, effectiveness, safety, and pharmacovigilance. The drugs follow the requirements of RDC No. 200/2017, including scientific proof of efficacy and safety, sanitary registration, standardization of formulation and mandatory pharmacovigilance.[8] Cannabis-based products, according to RDC No. 327/2019, are provisionally authorized for manufacture and commercialization, without the need for prior clinical studies, although they must present minimum quality and safety data and monitor adverse events.[5] Artisanal or associative preparations, produced by individuals or non-commercial organizations, do not have sanitary registration or standardized quality control, which entails risks to patient safety and hinders health surveillance actions.[9]

The distinction between these categories is fundamental for the formulation of evidence-based public policies and for the strengthening of pharmacovigilance in the country. There are products registered in Anvisa that are subject to all the rules related to the production of herbal medicines, including pharmacovigilance requirements.[7] On the other hand, imported products with exceptional authorization from Anvisa do not go through all the stages of quality, safety and efficacy evaluation required for registered medicines, and do not fall into the category of "cannabis products".[10] Another critical point is the formulations produced by individuals or patient associations, which use different varieties of the plant and extraction methods without standardization, which generates uncertainties regarding the standardization and quality control of the concentration of active ingredients, stability of the formulations and risk of contamination. Added to this is the lack of control over the route of administration, dosage, and frequency of use, further compromising the safety and effectiveness of treatments, especially in the absence of rational prescription and adequate control of dispensation.[11]

The solution to these challenges requires a joint effort between regulatory authorities, health professionals, universities and industry, starting with the conduct of clinical studies that allow the classification of certain cannabis-based products as medicines. A drug is any substance or preparation with therapeutic, diagnostic or prophylactic purposes, whose production and commercialization must comply with strict criteria of quality, safety and efficacy.[12] This reframing would allow these products to be subject to the applicable regulatory requirements, triggering control mechanisms such as sanitary registration, good manufacturing practices, pharmacovigilance and rational prescription based on standardized and validated information.

A third problem refers to the absence of public policies that guarantee equitable and safe access to these products.[13] The high costs involved in the import process significantly restrict access. Considering that cannabis-based products can have different concentrations of CBD, the price can reach R$2,600.00; evidencing the inequity of access by the population.[14,15] There are also patients who resort to illicit means of acquisition, without any quality control or safety guarantee, which increases clinical and health risks. In 2020, the National Commission for the Incorporation of Technologies in the Unified Health System (CONITEC) rejected the incorporation of cannabis-based medicines into the Unified Health System (SUS), due to insufficient robust and reliable scientific evidence to prove their efficacy and safety.[16.17]

Consequently, there are no Clinical Protocols and Therapeutic Guidelines (PCDTs) aimed at the therapeutic use of Cannabis-derived products in the SUS, since these protocols are designed exclusively for nationally standardized medicines and products. This normative gap makes it difficult to standardize clinical conduct, systematically monitor treatments, and train multiprofessional teams, especially pharmacists. In this context, the multiplication of municipal initiatives and specific judicial decisions con-

tributes to the fragmentation of care and insecurity in use. The implementation of PCDTs is essential to guide pharmacists and multiprofessional teams in rational prescribing, contribute to the effectiveness and safety of treatments, and promote the integration of care.

These challenges involve technical, economic, and political barriers, ranging from the scarcity of robust clinical evidence to institutional resistance and limitations in the training of the professionals involved. Data on the preparation of pharmacies for the dispensation and clinical monitoring of cannabis-based products are still scarce, and the existence of systematized internal protocols is uncertain. Added to this is the absence of clinical protocols for rational prescription, adequate dispensation, and systematic pharmacovigilance mechanisms, which constitutes a significant risk to patient safety, especially in view of the lack of clinical studies that support registration as a drug.

Judicialization, increasingly common as a means of access, has made it possible to obtain these products without guarantee of traceability, standardization of formulation or clinical monitoring.[18] This scenario highlights structural weaknesses in the mechanisms of regulation and sanitary surveillance, which still do not ensure, even in judicial cases, the necessary control over the quality, safety and rational use of these products. In addition, individualized acquisition by judicial decision compromises the planning and programming of pharmaceutical services, contributing to shortages, disorganization of the supply of standardized drugs and increased public costs, since judicial purchases do not follow economic criteria or consolidated clinical protocols. Frequently, medicines obtained through legal means are often not entered into pharmacovigilance systems, which makes it difficult to detect adverse reactions, drug interactions and other clinical complications early.[19,20]

The structuring of robust pharmacovigilance systems for cannabis-based medicines is therefore essential. Although there is evidence to support the effectiveness profile of the use of CBD in epilepsy, for example, it is known that the risk of adverse events may increase in patients with comorbidities, complex family history, or concomitant use of other drugs.[21,22,23] In Brazil, data from the Vigimed pharmacovigilance system can be consulted through the Open Data Portal. However, such information often has gaps or inconsistencies, making it difficult to accurately analyze the use of cannabis-based medicines.[24] The development of specific pharmacovigilance systems will enable the continuous monitoring of cases, the production of relevant epidemiological data, and the improvement of clinical and regulatory practices. This includes updating package inserts, developing new products, conducting new clinical trials, and, when necessary, withdrawing drugs from the market. [25,26]

In this sense, understanding the safety profile of CBD in different clinical contexts is essential to guide these pharmacovigilance strategies and ensure safe use. Studies indicate that isolated use of CBD is generally well-tolerated, with mild to moderate adverse reactions in specific populations.[27,28] However, co-administration with other drugs may alter the pharmacokinetics and therapeutic profile, requiring care and monitoring.[29] In view of this, effective public policies must contemplate not only rational access, but also the structuring of care networks with rational prescription and adequate dispensation, in addition to integrated pharmacovigilance and health information systems. In this context, the importance of integrating pharmaceutical services into the health care network is highlighted, with the qualified performance of the clinical pharmacist in therapeutic follow-up, in the execution of pharmacovigilance and in the promotion of rational use, through the guidance and education of users. Public and private pharmacies play a strategic role in guiding users and in the safe dispensing of these products and can also act as spaces for health education and pharmacotherapeutic monitoring.

The consolidation of the therapeutic use of cannabis-based products in Brazil requires more than specific regulatory advances. It is necessary to build a national plan that covers the cycle of access to medical *cannabis*, which integrates cultivation, research and development, production, logistics, selection, dispensation and rational use. Regulation must be thought of in conjunction with the health care network, considering the principles of the SUS and the constitutional right to health.[30] The absence of the-

se products in the public offer restricts treatment to portions of the population with greater purchasing power or exposes patients to the parallel market, where risks related to low quality, lack of standardization and insecurity of use predominate, deepening health inequities.

Given the complexity of the topic, it is essential to observe international experiences and foster regulatory cooperation with other countries, especially in Latin America and Europe. The sharing safety data, regulatory experiences and good practices can accelerate the construction of a more efficient, fair and secure national model.

It is therefore considered that the classification of cannabis-based products as medicines is not a merely semantic or administrative issue, but a fundamental strategy to ensure the safe, effective and equitable use of these treatments. Regulatory recognition of these products as medicines paves the way for strengthening pharmacovigilance, encouraging clinical research, and developing more inclusive public policies. Although RDC No. 327/2019 provides for compliance with standards for specific drugs, its transitory nature and the absence of a requirement for clinical studies make it impossible to fully establish the control mechanisms of drugs, such as structured pharmacovigilance and therapeutic standardization. The proposal of this article is distinguished by defending the definitive reclassification as a drug, with all the corresponding regulatory requirements. We argue that this regulatory change is essential to protect patients, reduce inequities in access, and consolidate *Cannabis* as a legitimate, evidence-based therapeutic option safely inserted into the health system.

Ethical and legal aspects
The authors declare exemption from ethical approval by the Research Ethics Committee because it is a perspective article.

Authorship statement and authors' contributions
TPS, MLDAS, MDL, DMM, RP and CMR: Conception and development of the text, writing and critical review and approved the final version to be published. TPS and CMR: Responsible for all aspects of the work, ensuring the accuracy and integrity of any part of the study.

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All authors declare the absence of conflicts of interest.

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The contents underlying the research text are contained in the manuscript

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