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Editorial – Volume 3 – nº 01- 2025

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The **GHLJ** strives to offer an opportunity for interdisciplinary discussion on topics in health law, international health law, comparative health law, health policy, health cases, medical, and biomedical law.

The Journal targets a broad and diverse audience of academicians, professionals, and students in Law, Medicine, Biomedicine, as well as policy makers, law operators, and legislators in health care.

Articles must be related to health law, international health law, comparative health law, health policy, health cases, medical and biomedical law, Medicine, and Biomedicine.

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It has been created and raised in an innovative, cooperative and participatory spirit, and will always continue its commitment to these values.

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OFF-LABEL MEDICINES AND THE RIGHT TO HEALTH: REGULATORY CHALLENGES, LEGAL IMPLICATIONS AND COMPARISON BETWEEN BRAZIL, THE UNITED STATES AND THE EUROPEAN UNION[1]

Tatiana Barone Sussa [2]

Renato Braz Mehanna Khamis [3]

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Off-label medicines and the right to health: regulatory challenges, legal implications and comparison between Brazil, the United States and the European Union

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Abstract

The use of off-label medications, defined as the prescription of drugs for purposes not specified in the label approved by regulatory agencies, is a growing practice in contemporary medicine. This phenomenon is often linked to the lack of alternative therapies or the existence of favorable scientific evidence; however, it raises concerns regarding safety and efficacy. The central issue lies in the judicialization of healthcare, where patients seek access to off-label medications through legal action, burdening the healthcare system and creating complex legal precedents. This study aims to analyze the regulation, challenges, and legal implications of off-label drug use in Brazil, with a comparative analysis between Brazil, the United States, and the European Union. The methodology includes a literature review and documentary analysis of legislation, case law, and scientific studies on the topic. The results indicate that the lack of clear regulation in Brazil contributes to inconsistent and unsafe practices, in addition to intensifying judicialization. In contrast, the United States and the European Union adopt distinct but equally rigorous approaches to the regulation of off-label use. It is concluded that more robust regulation and the establishment of strict criteria for off-label prescriptions may reduce risks and mitigate the negative impacts of judicialization in Brazil, promoting greater safety for patients and healthcare professionals. The differences between the regulatory

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frameworks of the Brazilian Health Regulatory Agency (ANVISA), the United States Food and Drug Administration (FDA), and the European Medicines Agency (EMA) highlight the need for ongoing debate on the role of regulatory agencies, medical professional autonomy, and patient protection, especially in the face of increasing judicialization of healthcare.
Keywords: health´s judicialization, Brazilian health surveillance agency, United States Food and Drug Administration, off-label use, personal autonomy

Introduction[4]

The use of off-label medicines, i.e., the prescription of medicines for purposes not specified in the package insert approved by a Regulatory Body, is an increasingly common practice in contemporary medicine. Although this use may occur when there are no therapeutic alternatives for a specific condition or when there is scientific evidence that a particular medicine may be effective for cases not covered by the package insert, it also raises significant safety, efficacy and regulatory issues.

The judicialization of health is a frequent phenomenon, covering a wide range of demands, including the prescription of off-label medicines. This phenomenon occurs when patients resort to the judicial system to guarantee access to treatments

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not provided by the public health system or not covered by health plans. In Brazil, the Superior Court of Justice (STJ) has issued important decisions on the responsibility of the public authorities and health insurance companies in providing off-label treatments, imposing the need for rigorous criteria and scientific evidence to support their use.

The purpose of this article will be to explore the regulation, challenges and legal implications of off-label medicines, with a comprehensive overview of the Brazilian context and an international comparative analysis. By addressing the judicialization of the off-label use of medicines, we seek to deepen the understanding of regulatory practices and the judicial repercussions of this treatment option. The problem situation identified is the prescription of off-label medicines that may not be supported by robust clinical studies, raising concerns about the safety and efficacy of these treatments. The absence of clear and specific regulations for off-label use may result in inconsistent and unsafe practices, and legal action for off-label treatments may overwhelm the judicial system and create complex precedents in terms of medical and state liability.

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To achieve the proposed objectives, this study adopted a qualitative approach, based on the analysis of legislation, jurisprudence and scientific literature. The methodology included a documentary analysis of laws, regulations and court decisions relevant to the use of off-label medicines in Brazil and other jurisdictions; a comparative study between regulatory and judicial practices in Brazil, the United States and the European Union, highlighting similarities and differences; and a literature review that consulted scientific articles and technical reports that address the off-label use of medicines, its implications and challenges. Through this methodology, we aim to provide a comprehensive and critical view of the regulation and judicialization of off-label medicines, contributing to a better understanding of the practices and challenges associated with this practice in contemporary medicine.

The hypothesis to be verified is that adequate regulation and strict criteria for off-label prescribing can reduce the associated risks and mitigate the negative impacts of the judicialization of health. Ultimately, this study is expected to provide practical recommendations to improve the regulation and safe use of off-label medicines in Brazil and other international contexts.

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1. The right to health in Brazil and the use of off-label medicines

In Brazil, the right to health is guaranteed by the Federal Constitution of 1988, which defines it as a fundamental right of all citizens and an essential obligation of the State. As provided for in article 196 of the Constitution, “health is a right of all people and a duty of the State, guaranteed through social and economic policies that aim to reduce the risk of disease and other injuries and universal and equal access to actions and services for promotion, protection and recovery”.

To guarantee universal access to health, through Law 8080/1990, the Unified Health System (SUS) was created, a regionally organized and hierarchical network of health actions and services, in which the Public Authority carries out activities to control substances of interest to health, in addition to several actions aimed at improving health services (SILVA, 2009, p. 770).

The implementation of the SUS represents a significant milestone in the quest for universal access to health in Brazil, and highlights the joint and participatory responsibility between the three levels of government in the management of health services. This structure allows for more effective coordination

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of public policies, facilitating the implementation of health and public assistance actions and services for the population. The participation of the private sector in the SUS occurs in a complementary manner, as provided for in article 199, Paragraph 1 of the Federal Constitution of 1988, and is carried out through agreements or contracts with the private sector. It is important to highlight that the private sector, permitted by the Federal Constitution, acts directly in private care or through the regulation established by Law No. 9.656/1998, which regulates health plans, and not comprehensively in the SUS.

Law 8080/1990 assigned the Unified Health System – SUS the responsibility of guaranteeing universal and equal access to health actions and services, including the provision of medicines among its attributions. In this context, section VI of article 6 specifies that it is the function of the SUS to “formulate the policy on medicines, equipment, immunobiologicals and other supplies of interest to health and participate in their production”. Given this regulatory provision, it is clear that the provision of medicines is fundamental for the treatment of diseases, being an essential element in health care, enabling the effective treatment of diseases, improving the quality of life

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of the population and preventing more serious complications and even death.

In Brazil, the Brazilian Health Regulatory Agency (ANVISA) is responsible for regulating and monitoring medicines. Law No. 14.313/2022 and Normative Resolution No. 465/2021 of the National Health Agency (ANS) establish important guidelines for off-label prescribing, reflecting the complexity and need for balance between the physician's therapeutic freedom and patient safety. ANVISA determines that, in the case of medicines, the package insert must include their indication, use and intended use, as authorized by the Regulatory Agency, to enable the prescription by the doctor and the correct guidance of the patient. The medicine package insert is a legal document, regulated by the Brazilian Health Regulatory Agency (ANVISA), whose function is to provide essential information for the safe and effective use of medicines. It plays a crucial role for both patients and healthcare professionals by providing detailed guidance on the composition, indications, contraindications, side effects and dosage of a medicine. There are two types of package inserts: the package insert for the Patient, which is written in accessible and objective language, making it easier for the end user to understand the instructions, and the package

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insert for the Healthcare Professional, which contains more technical and detailed information, intended for doctors and other healthcare professionals so that they can make therapeutic decisions based on more complex scientific and clinical data. Thus, the package insert is an indispensable instrument to ensure that the use of medicines is conducted in an informed and safe manner, respecting the parameters established by the health authorities (ANVISA, 2024).

However, there are specific situations in which doctors feel it is necessary to use medicines for purposes that are not described in the package insert approved by the Regulatory Body. This may occur when there are no therapeutic alternatives for a specific condition or when there is scientific evidence that a particular medicine may be effective for a particular patient. In these cases, doctors use off-label prescriptions.

The use of medicines not specified in the package insert is based on the doctor's therapeutic freedom, which is essential to their professional experience, and they can choose the most appropriate treatment for the specificities of the case. According to Arruda (2022, p. 132), off-label use occurs when a medicine is administered outside the specifications of its package insert,

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ranging from supposed evidence to robust evidence. The practice is not necessarily inadequate, as it can be based on different levels of scientific certainty, from subjective inferences to consolidated clinical evidence.

The prescription of off-label medicines, according to article 4, item X, of Normative Resolution No. 465/2021 of the National Health Agency, refers to the “use of medicine, material or any other type of health technology, for an indication that is not described in the package insert or manual registered with ANVISA or made available by the manufacturer”. Using the concept defined by Michele Mello, the prescription of an off-label medicine is explained as “a therapeutic indication different from that stated in the Summary of Product Characteristics (SmPC), i.e., for a purpose that goes beyond the scope of the approved therapeutic indications, the approved age group, the approved dose, or the approved form of administration” (Mello et al., 2009).

Medical liability encompasses the obligation of healthcare professionals to provide the most appropriate and effective treatment for each patient. This responsibility includes the careful selection of medicines, considering not only those approved for a given condition, but also those that can be used

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outside the indications approved by regulatory authorities. Studies highlight that off-label prescription requires in-depth knowledge of the medicine on the part of the physician, in addition to clear communication with the patient about the risks and benefits involved (Soares; Dadalto, 2020; Rampazzo, 2020).

The use of off-label medicines is a common practice in several medical specialties, in which clinical and scientific evidence often suggests their effectiveness. Choosing a treatment that is not specified in the package insert requires that the doctor be confident about the use of the medicine and that the patient is aware of the risks and benefits of the treatment. This practice requires extra care on the part of doctors, who must closely monitor the patient's progress.

The Code of Medical Ethics (CFM Resolution No. 2.217/2018) establishes the principles and standards that govern the conduct of doctors in Brazil, determining that the doctor must always act for the benefit of the patient and based on the best scientific evidence available, in alignment with therapeutic freedom. The Code of Medical Ethics establishes fundamental principles that guide the conduct of health professionals, highlighting the commitment to the well-being

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and dignity of human beings. Among these principles, the following stand out: item II emphasizes that the focus of medical care must be the health of the human being, conducted with the utmost care and professional competence; item V requires the doctor to be constantly up-to-date scientifically, applying advances in medicine for the benefit of the patient and society; item VI establishes unconditional respect for the human being, even after death, prohibiting any action that causes suffering or violates the patient's dignity and integrity; and item XVI protects the doctor's therapeutic freedom, ensuring that the choice of diagnostic and therapeutic means is not limited by institutional rules, except when it is clearly for the patient's benefit. These principles reinforce the professional autonomy of the physician, ensuring that their decisions are always based on the best scientific evidence and focused on the well-being of the patient.

Law 14.313/2022 provides for the processes of incorporating technologies into the Unified Health System (SUS) and the use of medicines whose indication for use is different from that approved in the registration with the Brazilian Health Regulatory Agency (ANVISA). This Law establishes that the prescription of medicines with indications different from those provided in the package insert may be recommended by

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the National Commission for the Incorporation of Technologies into the Unified Health System (Conitec), but does not allow the SUS to issue prescriptions or directly administer the medicine. The legislation partially changes the SUS Law, but maintains the focus on regulating processes for incorporating new technologies and treatments, without changing the functions of prescribing and administering medicines.

In the private sector, article 10, section I of Law No. 9.656/1998 prohibits coverage of experimental treatments, without explicitly mentioning off-label medicines. Health plans often try to use this legal provision to deny coverage for off-label medicines. In this sense, Josiane Araújo Gomes makes an important distinction, explaining that the treatment is experimental when the medicine has not yet completed the clinical research cycle, and off-label use does not mean that the medicine is experimental, but only that it does not have a specific indication with ANVISA (Gomes, 2024, p. 218).

In addition to the Brazilian context, it is relevant to compare how the regulation and use of medicines, including off-label ones, are treated in other jurisdictions, such as the United States and the European Union, which may provide an overview of the challenges faced in different health systems.

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2. Comparative analysis between Brazil, the United States and the European Union

2.1 Supervisory Bodies

The medicine regulatory processes in Brazil, the United States and the European Union have similarities, including the requirement for rigorous studies in three phases of clinical trials and safety, efficacy and quality criteria. These rigorous controls are essential to ensure that the medicines available on the market are safe and effective.

On the international scene, comparative analysis between the United States and the European Union reveals distinct, yet rigorous, approaches. The Food and Drug Administration (FDA) in the United States and the European Medicines Agency (EMA) in the European Union set high standards for evaluating and monitoring medicines, including those prescribed off-label. ANVISA, FDA and EMA play crucial roles in this process, establishing standards and guidelines that protect public health and ensure patient confidence in medical treatments.

In the context of the right to health, these regulatory bodies are essential, as their regulation and oversight serve as a basis for medical practices, directly influencing judicial decisions involving access to health. However, each regulatory system

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has its own particularities, reflecting the health policies of each location.

In Brazil, the regularization of medicines is authorized by the Brazilian Health Regulatory Agency (ANVISA), which aims to promote the protection of the population's health through sanitary control of the production and consumption of products and services subject to health surveillance, including related environments, processes, inputs and technologies, as well as the control of ports, airports, borders and customs areas (ANVISA, 2024).

Before a medicine is made available for prescription and sale, it must undergo a rigorous process, as established by Law No. 6.360/1976 - which provides for the health surveillance to which medicines, drugs, pharmaceutical and related inputs, cosmetics, sanitizing products and other products are subject, and provides other measures.

This process includes a rigorous protocol that involves several evaluation steps, starting with the submission of preclinical data, which includes laboratory and animal studies to assess the initial safety and potential efficacy of the medicine. If these studies are promising, the next step is to conduct clinical trials in humans, which are conducted in three phases to

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monitor efficacy and safety in a growing number of volunteers. After completing the tests, the company must submit a complete dossier to ANVISA with all research and manufacturing data. The Agency conducts a detailed review, which may include inspections of manufacturing facilities and additional evaluations of clinical and safety data (ANVISA, 2016).

In the United States, the Food and Drug Administration (FDA) is responsible for regulating medicines. According to the FDA, its mission is to "protect the public health by assuring the safety, effectiveness, and security of human and veterinary medicines, biological products, and medical devices; and by ensuring the safety of our food supply, cosmetics, and products that emit radiation" (FDA, 2024).

The assessment is carried out in accordance with the general requirements of Good Manufacturing Practices (GMP), known as Current Good Manufacturing Practices (CGMPs), which consists of a set of procedures that ensure that products are produced and controlled according to quality standards appropriate for their intended use and in accordance with registration requirements.

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CGMP regulations for pharmaceuticals ensure that products are safe and effective and establish minimum requirements for methods, facilities, and controls in the manufacturing, processing, and packaging of pharmaceutical products. The new medicine and generic medicine approval process includes review of the manufacturer's compliance with CGMPs. FDA reviewers and investigators verify that the company has the necessary facilities, equipment, and capacity to manufacture the medicine (FDA, 2024).

In the European Union, the European Medicines Agency (EMA) is responsible for the scientific evaluation of centralized marketing authorization (MAA) applications. According to the EMA, its mission is to "promote human and animal health by evaluating and monitoring medicines in the European Union (EU) and the European Economic Area (EEA)" (EMA, 2024). Once granted, the authorization is valid in all European Union (EU) Member States, Iceland, Norway and Liechtenstein (EMA, 2024).

The process begins with the submission of a marketing authorization application which is reviewed by CHMP experts. They evaluate the safety, efficacy and quality of the medicine. After a positive evaluation, the European Commission issues

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the marketing authorization, allowing the medicine to be sold in all member states of the European Union. The EMA also conducts continuous post-market safety monitoring of medicines to ensure they remain safe and effective for patients (European Medicines Agency, 2019).

What is clear is that, despite the particularities in the regulations of each region, regulatory agencies, such as ANVISA in Brazil, the FDA in the United States and the EMA in the European Union, aim to protect, ensure safety and effectiveness of the treatments offered to patients. These bodies carry out rigorous evaluations to ensure that medicines are safe and effective before they are authorized for use. The priority of these agencies is to ensure that patients receive treatments with standards of quality, efficiency and safety. In the context of the right to health, these agencies play a crucial role in ensuring that all patients have access to effective and safe treatments, thus protecting the fundamental right to health.

2.2 Judicialization Involving Off-label Medicines

The judicialization of health is a growing phenomenon in Brazil, where patients turn to the judicial system to obtain access to treatments and medicines not provided by the public

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health system or to repair damages caused by inadequate treatments.

The Superior Court of Justice (STJ) has issued several relevant decisions on the subject. Regarding the use of off-label medicines and their supply by the Government, the Superior Court of Justice in the judgment of Special Appeal 1.657.156 (repetitive appeal) established the thesis that it is the obligation of the government to supply medicines for situations not provided for in the package insert registered with the Brazilian Health Regulatory Agency, provided that the following requirements are present: medical report proving the need for the product as well as the ineffectiveness report, for the treatment of the disease, of the medicines supplied by the SUS; financial incapacity of the patient; and registration of the medicine with the Brazilian Health Regulatory Agency.

Regarding the provision of off-label medicines by health insurance companies, the Superior Court of Justice, in the judgment of Special Appeal 1.721.705/SP, reported by Minister Nancy Andrighi, established that health insurance companies cannot deny coverage for prescribed treatment on the grounds that the medicine is outside the indications registered with the

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Brazilian Health Regulatory Agency (ANVISA) if there is a medical indication for the treatment (Brazil, 2018).

The Minister highlighted that Law 9.656/1998 (Health Insurance Law) authorizes health insurance companies to deny coverage for experimental clinical or surgical treatments, as per article 10, item I. However, it is important to highlight Paragraph 13 of this article, which establishes that, under no circumstances, may companies deny coverage for treatments prescribed by a physician, except when it is an experimental treatment. Furthermore, the National Supplementary Health Agency (ANS), through Normative Resolution No. 338/2013, in force at the time, defined that experimental treatments are those that do not have indications described in the package insert or in the manual registered with ANVISA, characterizing off-label use. It is also worth mentioning ANS Normative Resolution No. 465/2021, especially Annex I.6, which brings more specificity to the topic, clearly differentiating off-label use from experimental treatments, and highlighting that off-label use does not necessarily imply an experimental nature, as long as there is scientific evidence to support its efficacy and safety.

Regarding this point, it was highlighted that the STJ's case law is consolidated in the understanding that therapeutic

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guidance is a medical act, and the doctor is responsible for choosing the appropriate treatment for the patient, not the health plan operator. According to the Code of Medical Ethics (CFM Resolution No. 2.217/2018, modified by CFM Resolutions No. 2.222/2018 and No. 2.226/2019), therapeutic prescription is the exclusive prerogative of the doctor, who must act in the benefit of the patient based on their expertise and the best scientific evidence. Thus, by allowing the operator to deny coverage for clinical or surgical treatments that do not have the indications described in the package insert or manual registered with ANVISA (off-label use), the National Supplementary Health Agency (ANS) may be, in an abstract and prior manner, replacing medical expertise with administrative interference, which goes against the principle of autonomy of the medical act.

In this sense, the regulation highlighted that the experimental nature referred to in Article 10, I, of Law 9.656 concerns clinical or surgical treatment that is incompatible with health control standards or that is not recognized as effective by the scientific community. Therefore, the operator's interference, in addition to having no basis in Law 9.656/98, consists of unfair and abusive action in the contractual

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relationship, and specifically places the consumer at an exaggerated disadvantage (art. 51, IV, of the CDC).

In light of these important decisions, the Superior Court of Justice recognized the importance of off-label medicines as well as the autonomy of the physician who prescribed the treatment, ensuring that patients had access to appropriate therapies proven through scientific studies, contributing to access to healthcare.

Similarly, court decisions in other countries, such as the United States v. Caronia case in the United States and the Avastin/Lucentis case in the European Union, illustrate the challenges and legal solutions adopted to deal with this practice.

In the United States, the judicialization of off-label use of medicines has led to important decisions involving the supply and relevance of these medicines. On February 11, 2022, the U.S. Court of Appeals for the 11th Circuit reversed a lower court decision in Dobson v. Secretary of Health & Human Services. Florida resident Donald Dobson was denied Medicare Part D coverage for dronabinol, a medicine needed to treat severe nausea and vomiting resulting from a spinal cord injury and related surgeries.

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Dronabinol had been prescribed off-label by Dobson's doctors after standard medicines failed to relieve his symptoms. Although Medicare Part D allows coverage of off-label medicines when supported by citations in medicine compendia specified by Medicare law, coverage has been denied on the basis that the prescription is for a use not approved by the FDA.

The Court ruled that the denial of coverage was improper, stating that off-label prescribing should be covered when supported by citations in medicine compendia, even if the patient's specific diagnosis does not exactly match that described in the compendium. The decision highlighted that the interpretation of the term support should tend to show or help prove the efficacy and safety of the prescribed medicine, without requiring a hyper-specific correspondence between the patient's case and the citation in the compendium (Center for Medicare Advocacy, 2022).

Another important case is United States v. Caronia. Alfred Caronia, a sales representative for a pharmaceutical company, was accused of promoting off-label use of the medicine Xyrem, which is FDA-approved only to treat symptoms in patients with narcolepsy. Caronia has been recorded promoting its use for other unapproved conditions.

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The U.S. Court of Appeals for the Second Circuit reversed Caronia's conviction, arguing that promoting off-label uses of FDA-approved medicines is a form of expression protected by the First Amendment. The court concluded that conviction based solely on off-label promotion was unconstitutional, noting that the FDCA (Food, Drug, and Cosmetic Act) does not explicitly prohibit such promotion, but rather the use of such claims as evidence of intentional use. The court stated: "Caronia's conviction for promoting off-label use of an FDA-approved medicine violates the First Amendment. Current law does not explicitly prohibit such promotion, and using it as evidence of intended off-label use is unconstitutional" (Justia Law, 2012).

These decisions reflect the nature of the common law system in the United States, where judgments based on judicial precedent allow judges to interpret and apply legislation in ways that protect the rights of individuals.

Finally, in the European Union, litigation involving off-label medicines is less frequent due to the rigor imposed by the European Medicines Agency (EMA) and the European Commission. One case worth highlighting is the Avastin/Lucentis case, which involved the use of the medicine

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Avastin, initially approved to treat cancer, but which was prescribed for the treatment of age-related macular degeneration (AMD). In 2014, Italy's Autorità Garante della Concorrenza e del Mercato (AGCM) imposed fines on pharmaceutical company Roche and Novartis, alleging that the companies had implemented an agreement to restrict off-label use of Avastin in favor of Lucentis, a more expensive medicine approved for AMD.

The Court of Justice of the European Union (CJEU) has ruled that off-label use of a medicine may be permitted when there are no suitable alternatives and when it is in the public interest, provided that the established safety and efficacy conditions are met. The decision emphasized that Member States have the responsibility to organize and manage their health services, including setting prices for medicines and their inclusion in the national health insurance system. According to this decision, member states are responsible for organizing and managing their health systems, which includes setting medicine prices and determining which treatments or medicines will be included in the national health insurance system. This autonomy allows each country to adapt its health policies according to its needs and capabilities, within the limits

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established by European Union standards, ensuring that decisions regarding financing and access to medicines reflect both the public interest and local conditions (CJEU, 2018).

Furthermore, the CJEU mentioned that disseminating misleading information about the safety of off-label use of a medicine to reduce competitive pressure could be considered a violation of European Union competition rules. In the Avastin/Lucentis case, it was determined that the off-label use of Avastin, even after it was repackaged in accordance with rules set by the Italian authorities, did not violate EU law, allowing the medicine to be reimbursed by the Italian healthcare system.

In this case, it is possible to note that the CJEU rigorously applied the rules established by European Union legislation reflecting the nature of civil law. The decision followed the codified legal precepts and the legal normative application, typical characteristics of the European legal system.

Final Considerations

Analysis of off-label medicine use revealed the complexity and challenges inherent to this practice, which has become increasingly common in contemporary medicine. Although off-

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label prescribing may be essential in situations where there are no therapeutic alternatives or when there is scientific evidence of its efficacy, this practice raises critical safety, efficacy and regulatory issues that require careful attention.

In Brazil, the judicialization of healthcare has been a frequent phenomenon, with patients resorting to the judicial system to obtain access to off-label treatments not available through the public healthcare system or not covered by health plans. The decisions of the Superior Court of Justice (STJ) highlighted the responsibility of the public authorities and health plan operators in providing off-label treatments, imposing the need for rigorous criteria and scientific evidence to support their use. These decisions highlighted the importance of a balance between the physician's therapeutic freedom and patient safety.

The regulation of off-label medicines in Brazil, through ANVISA, has proven to be rigorous, but still faces significant challenges. Law No. 14.313/2022 and Normative Resolution No. 465/2021 of the ANS were important steps to ensure the safety and effectiveness of these prescriptions. However, the absence of specific and clear regulations can lead to

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inconsistent and unsafe practices, exacerbating the judicialization of health.

The comparative study with the United States and the European Union showed that, although there are differences in regulatory approaches, all jurisdictions face similar challenges.

In the United States, the common law system, exemplified by cases such as United States v. Caronia and Dobson v. Secretary of Health & Human Services, highlighted the judicial flexibility in addressing the promotion and supply of off-label medicines. These decisions reflected the importance of scientific documentation to justify off-label use, balancing medical innovation with careful regulation.

In the European Union, the civil law approach, illustrated by the Avastin/Lucentis case, showed how the rigorous application of the rules of the European Medicines Agency (EMA) and the Court of Justice of the European Union (CJEU) aimed to guarantee the safety and efficacy of treatments, protecting public health. The decision to allow off-label use in certain circumstances, when there are no suitable alternatives and it is in the public interest, highlighted the ability of the European system to respond to emerging medical needs.

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Regulatory agencies, such as ANVISA, FDA and EMA, have played crucial roles in establishing standards and guidelines that ensure the protection of public health and patient confidence in medical treatments. Prioritizing the safety and efficacy of the treatments offered was essential to ensure patients received high-quality care. The judicialization of health care, both in Brazil and in the United States and the European Union, reflected the ongoing need for a balance between rigorous regulation, medical autonomy, and patient rights. The court decisions highlighted the importance of a health system capable of integrating new scientific evidence and ensuring that patients have access to the best available treatments.

In response to the hypothesis formulated at the beginning of this study, it appears to be confirmed that adequate regulation and strict criteria for off-label prescribing could reduce the associated risks and mitigate the negative impacts of the judicialization of health. It was observed that, in contexts where regulation was clear and based on robust scientific evidence, there was a decrease in insecurity and inconsistency in practices, promoting better protection for patients and more efficient management of legal demands.

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This study reaffirmed the relevance of an in-depth understanding of regulatory practices and the legal implications of off-label use of medicines. When exploring the different approaches adopted internationally, it became clear that, regardless of the legal system, the ultimate goal must always be to protect and promote the health of patients, ensuring that they receive safe, effective treatments based on the best available scientific evidence.

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