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FOR ALZHEIMER’S DISEASE: A COMPARATIVE STUDY
BETWEEN THE UNITED STATES AND BRAZIL ¹**

Célio Ramos Farias ^{2*}

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Marcelo Lamy ^{4}***

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Abstract

Context: Alzheimer's disease is one of the greatest public health challenges of the 21st century, due to population aging and the increasing prevalence of dementia worldwide. The arrival of disease-modifying therapies, especially anti-amyloid antibodies, has reignited debates on

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regulation, cost-effectiveness, and access. **Problem:** Although recent clinical results indicate progress, uncertainties remain regarding the magnitude of benefits, potential adverse risks, and, above all, the differences in regulatory models adopted by the United States and Brazil.

Objectives: This study aims to comparatively analyze the roles of the FDA and CMS, on the one hand, and Anvisa, Conitec, and ANS, on the other, highlighting approval timelines and criteria, evidentiary requirements, financial coverage policies, and access challenges. **Methods:** The research adopts a deductive approach, based on a literature review, as well as the analysis of national and international legislation, legal doctrine, and case law. It is a comparative law study in regulatory health, designed to identify convergences and divergences between the U.S. and Brazilian models.

Results: The analysis revealed that the United States applies accelerated approval pathways through the FDA, followed by clinical confirmation, with integration between regulatory processes and public coverage by CMS, although conditioned on continuous evidence generation. In Brazil, Anvisa recently approved donanemab, but the incorporation process into the SUS and by ANS is still underway, characterized by caution regarding cost-effectiveness, increasing judicialization, and structural limitations in the diagnostic network. **Conclusions:** The U.S. model ensures greater speed and integration between approval and funding, while Brazil shows regulatory progress but still faces barriers to guaranteeing broad and equitable access.

Keywords: Alzheimer's disease. Disease-modifying treatments. Health regulation. FDA. Anvisa. Comparative law. Health technology assessment.

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Introduction

Alzheimer's disease has emerged as one of the most significant contemporary public health challenges, driven by population aging and the steadily increasing global prevalence of dementia. This scenario generates not only substantial clinical and familial burdens but also profound economic and societal consequences, threatening the sustainability of healthcare systems. Historically, available therapeutic options have been limited to symptomatic treatments aimed at partially alleviating cognitive and behavioral decline, without altering the natural course of the disease.

The advent of disease-modifying therapies—particularly monoclonal antibodies targeting amyloid-beta protein—has introduced new regulatory and ethical challenges related to the assessment of clinical efficacy, cost-effectiveness, and equitable access. As Paim (2017) argues, health regulation and policymaking should be guided by the principles of comprehensiveness, therapeutic rationality, and social justice, ensuring that the adoption of new health technologies expands rather than restricts rights. Within this framework, the present study examines how different regulatory models, particularly those adopted by the U.S. Food and Drug Administration (FDA) and the Brazilian Health

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Regulatory Agency (Anvisa), influence the approval, adoption, and accessibility of innovative therapies for Alzheimer's disease, taking into account the strengths and limitations of each regulatory system.

A comparison of the regulatory frameworks in the United States and Brazil reveals distinct institutional approaches to health technology governance, particularly regarding the assessment of efficacy, safety, and cost-effectiveness. According to Viana (2018), health regulatory policies reflect the ways in which the state is organized and the interactions among science, the market, and the public interest, thereby explaining differences in decision-making processes and the pace of technology adoption.

In the United States, the Food and Drug Administration (FDA) has implemented accelerated approval pathways that allow earlier access to innovative therapies based on surrogate endpoints, while requiring post-marketing confirmation of clinical benefit through advanced-phase clinical trials (FDA, 2021a; FDA, 2021b). This strategy has been accompanied by timely public coverage decisions by the Centers for Medicare & Medicaid Services (CMS, 2022; CMS, 2023), illustrating a highly dynamic regulatory model characterized

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by close integration between regulatory oversight and healthcare financing.

In Brazil, the Brazilian Health Regulatory Agency (Anvisa) is responsible for evaluating the quality, safety, and efficacy of new therapies for marketing authorization, whereas the National Commission for the Incorporation of Health Technologies into the Unified Health System (Conitec) assesses cost-effectiveness and budget impact before recommending their incorporation into the Brazilian Unified Health System (SUS) (Brazil, 2022). As noted by Ocké-Reis (2018), the Brazilian regulatory model seeks to balance innovation with the long-term sustainability of the healthcare system; however, it tends to be slower because of the institutional separation between regulatory approval, technology incorporation, and private health insurance coverage decisions by the National Regulatory Agency for Private Health Insurance and Plans (ANS, 2021). Although this institutional structure provides more rigorous technical oversight, it also extends the interval between regulatory approval and the actual availability of new treatments to patients.

As Boaventura de Sousa Santos (2002) argues, legal and institutional knowledge must be interpreted in light of its social function and the historical context in which it is produced, giving

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international comparative analysis a critical and emancipatory dimension. Accordingly, this study adopts a qualitative, deductive approach based on a review of the literature and an analysis of national and international legislation, legal scholarship, and case law, with the objective of providing both theoretical and practical contributions to the improvement of health regulatory policies and health technology incorporation.

Against this backdrop, the present study aims to comparatively examine the regulatory frameworks and access challenges associated with disease-modifying therapies for Alzheimer's disease in the United States and Brazil, highlighting their convergences, divergences, and legal and social implications. The research is grounded in the comparative analysis of public policies and draws upon theoretical perspectives that conceptualize law as a mediating force among science, the state, and society.

Methods

This study employed an exploratory, document-based qualitative design using a comparative legal approach within the fields of Health Law and Health Regulatory Policy. As Diniz (2019) notes, scientific legal research involves the systematic analysis of

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normative and doctrinal sources, integrating deductive reasoning with critical interpretation to understand legal phenomena within their broader social and institutional contexts. Accordingly, this investigation examines the normative, institutional, and jurisprudential foundations governing the regulation and financing of disease-modifying therapies for Alzheimer's disease through a comparative analysis of the U.S. and Brazilian regulatory frameworks.

The methodological approach combined a narrative literature review with documentary analysis, encompassing peer-reviewed scientific publications, legislation, regulatory instruments, and relevant judicial decisions. The literature search was conducted between January 2021 and September 2025 using both national and international databases, including the Virtual Health Library (VHL), SciELO, the CAPES Journal Portal, and Google Scholar, as well as institutional reports and official documents. Search terms were used in both Portuguese and English and combined with Boolean operators. These included *Alzheimer's disease*, *monoclonal antibodies*, *amyloid-beta*, *health regulation*, *coverage*, *cost-effectiveness*, *Conitec*, *FDA*, *CMS*, *ANS*, *Anvisa*, and *health judicialization*.

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Eligible studies included peer-reviewed articles and technical or institutional documents addressing the regulation of health technologies, health economic evaluation, and mechanisms for coverage and access to anti-amyloid-beta monoclonal antibodies. Regulatory instruments, technical reports, and official publications relevant to the study objectives were also included, as were judicial decisions concerning access to high-cost medications. Editorials, opinion pieces lacking documentary support, non-peer-reviewed preprints, duplicate records, and materials unrelated to the study scope were excluded.

At the international level, the analysis included reports and official communications issued by the U.S. Food and Drug Administration (FDA) (2018; 2020; 2021a; 2021b; 2023; 2024) and the Centers for Medicare & Medicaid Services (CMS) (2022; 2023). In the Brazilian context, the study examined regulatory documents and publications issued by the Brazilian Health Regulatory Agency (Anvisa, 2022), the National Commission for the Incorporation of Health Technologies into the Unified Health System (Conitec, 2011; 2025), and the National Regulatory Agency for Private Health Insurance and Plans (ANS, 2021), as well as Collegiate Board Resolutions (RDCs), clinical protocols, and guidelines related to the

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incorporation of disease-modifying therapies. The legal analysis was further supplemented by a review of recent judicial decisions concerning access to medications lacking Anvisa approval or authorized under restricted conditions, including precedents from the Federal District and Territories Court of Justice (TJDFT, 2025) and Brazil's higher courts, with the aim of examining the impact of health-related litigation on access to innovative therapies.

According to Lakatos and Marconi (2021), documentary analysis provides a means of understanding social and normative phenomena through the critical interpretation of secondary sources, making it particularly suitable for comparative legal research. Accordingly, the collected data were subjected to thematic content analysis, and a comparative analytical framework was developed to examine the United States and Brazil across four key domains: (i) regulatory pathways and approval requirements; (ii) coverage and reimbursement mechanisms, including *coverage with evidence development*; (iii) clinical evidence and cost-effectiveness assessment; and (iv) implications for patient access. The findings were synthesized through a critical comparative analysis highlighting regulatory convergences, divergences, and existing gaps. Because the study relied exclusively on publicly

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available secondary data, it did not involve human participants and therefore did not require review or approval by a research ethics committee.

Results and Discussion

Alzheimer's disease is one of the leading causes of dementia and poses an increasing challenge to healthcare systems because of its substantial clinical, social, and economic burden. As Paim (2017) argues, addressing complex chronic conditions requires public policies grounded in the principles of comprehensiveness, equity, and therapeutic rationality to ensure that scientific progress does not become a driver of social exclusion. Within this context, the development of disease-modifying therapies, particularly monoclonal antibodies targeting amyloid-beta protein, represents a major milestone in contemporary biomedicine. Unlike conventional symptomatic treatments, these therapies are designed to target the underlying pathophysiological mechanisms of the disease, with the goal of slowing disease progression while redefining the regulatory and ethical landscape of innovation in healthcare.

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The debate surrounding these therapies extends well beyond the biomedical domain and encompasses health regulation and public health policy, including the legal, economic, and institutional dimensions of health technology assessment and equitable access. From this perspective, the present study examines the regulatory frameworks governing anti-amyloid therapies in the United States and Brazil, focusing on the roles of the principal regulatory and reimbursement authorities—the U.S. Food and Drug Administration (FDA) and the Centers for Medicare & Medicaid Services (CMS) in the United States, and the Brazilian Health Regulatory Agency (Anvisa), the National Commission for the Incorporation of Health Technologies into the Unified Health System (Conitec), and the National Regulatory Agency for Private Health Insurance and Plans (ANS) in Brazil.

Comparative analysis emphasizes key regulatory and technical aspects, including approval timelines and criteria, clinical evidence requirements, reimbursement and coverage mechanisms, and challenges related to equitable access. The findings are derived from a comprehensive review of the scientific literature, regulatory documents, and judicial decisions and seek to elucidate how different institutional arrangements influence the effectiveness of

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regulatory oversight and the realization of the right to health in the context of therapeutic innovation.

1. U.S. Regulatory System

In the context of Alzheimer's disease, the coordinated roles of the U.S. Food and Drug Administration (FDA) and the Centers for Medicare & Medicaid Services (CMS) have been instrumental not only in the approval of novel therapies but also in establishing access and reimbursement policies for older adults, the population most affected by the disease. As Viana (2018) argues, health regulatory systems constitute arenas in which scientific innovation, economic sustainability, and the public interest intersect, making technical decisions inherently political and socially consequential.

The FDA, an agency within the U.S. Department of Health and Human Services (HHS), plays a central role in the regulation of pharmaceuticals, medical devices, and food products in the United States. For drug approval, the agency employs multiple regulatory pathways, including traditional approval and accelerated approval. The accelerated approval pathway, established in 1992 in response to the HIV/AIDS crisis, was designed to expedite patient access to

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promising therapies when no effective treatment alternatives are available (FDA, 2018; Friedman & Califf, 2019).

Applying this regulatory framework to Alzheimer's disease, the FDA granted accelerated approval to anti-amyloid monoclonal antibodies using the reduction of amyloid-beta plaques, measured by positron emission tomography (PET), as a surrogate endpoint (FDA, 2021b). Although this biomarker was considered reasonably likely to predict clinical benefit, the direct relationship between amyloid clearance and meaningful cognitive improvement remains the subject of ongoing scientific debate (Cummings et al., 2021).

A major regulatory milestone occurred in 2021 with the accelerated approval of aducanumab (Aduhelm), a decision that generated substantial controversy because of inconsistent clinical trial results and the negative recommendation issued by the FDA's independent advisory committee (FDA, 2021a; Knopman, Perlmutter, & Selkoe, 2021). In 2023, the FDA granted traditional approval to lecanemab (Leqembi), reinforcing the use of biomarkers as an initial regulatory criterion while emphasizing the importance of demonstrating clinically meaningful efficacy (FDA, 2023). The following year, donanemab (Kisunla) received traditional approval under a similar regulatory rationale, further establishing

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anti-amyloid monoclonal antibodies as disease-modifying therapies for Alzheimer's disease while maintaining stringent post-marketing safety surveillance (FDA, 2024).

The FDA operates within a regulatory framework characterized by transparency and public engagement, incorporating independent advisory committee meetings, publication of scientific review documents, and opportunities for public comment (FDA, 2020). Although the agency's final decisions do not always align with the recommendations of external experts, this process enhances both the scientific credibility and institutional legitimacy of its regulatory actions and is widely regarded as an international benchmark for regulatory accountability.

Regulatory approval, however, does not automatically guarantee patient access. In the United States, reimbursement decisions are determined by the CMS, which administers Medicare, the federal health insurance program covering approximately 65 million Americans. Following the approval of aducanumab, CMS adopted a restrictive coverage policy, limiting reimbursement to patients enrolled in qualifying clinical trials because of uncertainty regarding the therapy's clinical effectiveness and its substantial cost (CMS, 2022). After the traditional approval of lecanemab, CMS

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expanded coverage while requiring participation in national patient registries designed to monitor long-term safety and real-world effectiveness under a Coverage with Evidence Development (CED) framework (CMS, 2023).

This model reflects an effort to balance early patient access with fiscal responsibility by closely integrating regulatory approval and public reimbursement policy. Nevertheless, significant challenges remain. The high cost of disease-modifying therapies places considerable financial pressure on the Medicare program (Cubanski & Neuman, 2021), while the risk of amyloid-related imaging abnormalities (ARIA)—including cerebral edema and cerebral microhemorrhages—necessitates intensive safety monitoring and access to specialized diagnostic infrastructure (Salloway et al., 2022).

Finally, substantial structural disparities in access persist, influenced by supplemental insurance coverage, geographic location, and socioeconomic barriers. The requirement for advanced diagnostic and monitoring infrastructure, including amyloid PET imaging and serial magnetic resonance imaging (MRI), is likely to exacerbate regional disparities by concentrating access in major academic and specialized medical centers, thereby

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reinforcing ongoing concerns regarding equity in access to biomedical innovation.

1.1. Critical Synthesis

The U.S. regulatory experience illustrates a framework characterized by procedural flexibility and the use of expedited approval pathways, particularly accelerated approval, combined with relatively efficient coordination between the U.S. Food and Drug Administration (FDA) and the Centers for Medicare & Medicaid Services (CMS) regarding reimbursement decisions. This institutional arrangement seeks to balance timely access to innovative therapies with regulatory accountability through robust post-marketing surveillance mechanisms. Nevertheless, considerable debate persists regarding whether the clinical evidence available at the time of initial approval is sufficient to justify market authorization.

This policy reflects the enduring tension among biomedical innovation, public demand for rapid access to new therapies, and the financial sustainability of healthcare systems. As Ferraz (2009) argues, judicialization and the incorporation of new health technologies without distributive criteria may create systemic

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imbalances and exacerbate inequities in access, thereby challenging the principle of health justice. In the U.S. context, this tension is particularly evident, as the regulatory system seeks to reconcile access to innovative treatments with the long-term fiscal sustainability of Medicare, which provides coverage for the majority of eligible patients.

The case of aducanumab illustrates the vulnerabilities inherent in this regulatory model. The drug's approval based on limited clinical evidence, followed by widespread clinical skepticism and its subsequent commercial discontinuation (ICER, 2021; Alzheimer Europe, 2024), underscored the importance of transparent decision-making processes supported by robust, reproducible, and continuously reassessed evidence. In this regard, regulatory innovation must be accompanied by rigorous post-marketing surveillance to ensure that procedural efficiency does not compromise the legitimacy, credibility, or safety of regulatory decisions.

The high cost of disease-modifying therapies for Alzheimer's disease further intensifies the ethical debate surrounding distributive justice and equitable access. Their substantial financial burden places increasing pressure on public healthcare budgets

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while creating additional socioeconomic barriers, particularly for vulnerable populations that lack access to advanced diagnostic infrastructure and specialized longitudinal care. Consequently, the U.S. regulatory framework serves as an institutional laboratory for regulatory innovation, while simultaneously exposing the structural limitations of efforts to reconcile rapid access, cost-effectiveness, and equity.

For Brazil, where the constitutional principle of universal healthcare under the Unified Health System (SUS) coexists with significant budgetary constraints, the U.S. experience offers both valuable lessons and important cautions. It demonstrates the potential benefits of more agile pathways for incorporating emerging technologies while highlighting the risks associated with accelerated regulatory decisions that may ultimately compromise the long-term sustainability and social equity of the healthcare system.

2. Regulation and Health Litigation in Brazil

In Brazil, the Brazilian Health Regulatory Agency (Anvisa) plays a central role in the regulation of new medicines, evaluating applications on the basis of quality, safety, and efficacy. The

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enactment of Collegiate Board Resolution (RDC) No. 753/2022, which updated RDC No. 200/2017, introduced more objective and transparent prioritization mechanisms, allowing expedited review of innovative therapies and treatments intended for rare or serious diseases (Brazil, 2022). This regulatory reform, aligned with international best practices, sought to enhance regulatory predictability and strengthen health oversight while promoting the principles of rationality and administrative efficiency.

In 2025, Anvisa granted marketing authorization for donanemab (Kisunla) for the treatment of early-stage Alzheimer's disease, restricting its indication to the genetic subgroup considered at lower risk for severe adverse events (Brazil, 2025). This decision represented a regulatory milestone, marking the first approval of a disease-modifying monoclonal antibody for Alzheimer's disease in Brazil. By contrast, lecanemab (Leqembi) has not yet received marketing authorization, and the absence of regulatory approval has served as the basis for judicial decisions denying compulsory access to the therapy (TJDFT, 2025).

According to Viana (2018), health regulation is a political and institutional process that integrates scientific evidence, economic considerations, and social values. Consequently, the incorporation

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of new health technologies should be accompanied by systemic planning and distributive criteria. Marketing authorization, although a prerequisite for commercialization, does not by itself ensure universal access. Within the Brazilian Unified Health System (SUS), the effective availability of new therapies depends on evaluation by the National Commission for the Incorporation of Health Technologies into the SUS (Conitec), established under Decree No. 7,646/2011, which assesses clinical efficacy, cost-effectiveness, and budget impact before recommending incorporation into the public healthcare system (Brazil, 2011).

The 2025 update of the Clinical Protocol and Therapeutic Guidelines (PCDT) for Alzheimer's Dementia illustrates Conitec's incremental and evidence-based approach. The expansion of donepezil eligibility to include patients with severe disease (Brazil, 2025) reflected the SUS commitment to the gradual and responsible expansion of therapeutic coverage in accordance with the best available scientific evidence, while avoiding disproportionate financial and public health risks.

This approach highlights the ethical and economic dilemma inherent in health technology incorporation within the SUS: ensuring access to innovation without compromising the long-term

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financial sustainability of the public healthcare system. As Barroso (2021) argues, the right to health, when enforced without appropriate technical and distributive criteria, may lead to judicial decisions that disrupt public health policies and exacerbate regional inequalities. Indeed, health-related litigation has become a defining feature of the Brazilian healthcare system. The constitutional right to health, established under Article 196 of the 1988 Federal Constitution, has frequently been invoked to secure access to high-cost medications, including therapies that have not yet received Anvisa approval or have not been incorporated into the SUS or the mandatory coverage list established by the National Regulatory Agency for Private Health Insurance and Plans (ANS). This tension between legal entitlement and policy implementation reflects the ongoing challenge of balancing judicial protection of individual rights with the collective interest and the rational allocation of public resources (Barroso, 2009).

In addition, structural inequalities continue to limit access to innovative therapies. Disease-modifying monoclonal antibodies such as donanemab and lecanemab require sophisticated diagnostic and monitoring resources, including amyloid positron emission tomography (PET) imaging and serial magnetic resonance

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imaging (MRI), which remain concentrated in major urban centers and predominantly within the private healthcare sector. According to Alencar et al. (2024), the unequal distribution of healthcare infrastructure and advanced diagnostic equipment undermines the constitutional principle of universality, widening regional disparities and restricting access in underserved areas. This raises a fundamental question of distributive justice: how can advances in biomedical innovation be translated into equitable benefits for patients across different geographic regions and socioeconomic groups? As Barroso (2021) contends, the answer lies in integrating sound technical regulation with long-term health system planning and evidence-informed public policies, ensuring that scientific innovation ultimately promotes both health equity and the effective realization of the right to health.

2.1. Critical Synthesis (Brazil)

The Brazilian regulatory landscape reflects a trajectory marked by meaningful progress alongside persistent structural challenges. Among the most significant advances are the expansion of symptomatic treatment options—including the incorporation of donepezil into the Brazilian Unified Health System (SUS) for patients

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with severe Alzheimer's disease in 2025—and Anvisa's approval of donanemab (Kisunla) in the same year, representing the first disease-modifying therapy for Alzheimer's disease to receive marketing authorization in Brazil (Brazil, 2025). These developments demonstrate a concerted institutional effort to align clinical protocols with advances in international scientific evidence while responding to the growing societal demand for therapeutic innovation.

Despite these advances, a substantial gap remains between regulatory approval and the actual availability of therapies to patients. The health technology assessment process conducted by Conitec and reimbursement decisions involving the National Regulatory Agency for Private Health Insurance and Plans (ANS), although essential for ensuring budgetary sustainability and cost-effectiveness, often significantly delay patient access. In this respect, the pace of regulatory decision-making in Brazil contrasts with the U.S. experience, where closer coordination between regulatory approval and reimbursement has facilitated more rapid access to innovative therapies (CMS, 2023; FDA, 2024).

Another major challenge concerns the high cost of anti-amyloid monoclonal antibodies, which places considerable pressure on both

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the SUS and the private health insurance sector. Economic impact analyses have shown that therapies of this nature may threaten the long-term financial sustainability of universal healthcare systems, particularly in middle-income countries such as Brazil (Friedman & Califf, 2019; ICER, 2021). Consequently, decisions regarding the incorporation of these technologies require a careful balance between fostering biomedical innovation and maintaining fiscal responsibility.

An additional concern relates to the need for highly specialized diagnostic and monitoring infrastructure, including amyloid positron emission tomography (PET) imaging and serial magnetic resonance imaging (MRI). As reported by Alencar et al. (2024), these resources remain concentrated primarily in Brazil's South and Southeast regions, reinforcing longstanding regional disparities in healthcare infrastructure. As a result, even when incorporated into clinical practice, these novel therapies are likely to benefit predominantly patients receiving care in large urban centers, thereby limiting both geographic and socioeconomic equity in access.

From a legal perspective, health-related litigation continues to play a central role in shaping access to high-cost therapies.

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Although litigation serves as an important mechanism for enforcing the constitutional right to health established under Article 196 of the Federal Constitution, it may also generate systemic distortions by prioritizing individual claims over technically grounded and collectively oriented public health policies (Barroso, 2009). Judicial decisions have varied between ordering immediate access to innovative therapies and reaffirming the prohibition against publicly funding medications that have not received Anvisa approval, illustrating the ongoing tension between regulatory legality and urgent societal demands.

This dilemma underscores the need for stronger institutional coordination among the judiciary, regulatory agencies—including Anvisa, Conitec, and ANS—and administrators of the SUS. Only through such integrated governance can the protection of individual rights be reconciled with the requirements of fiscal sustainability and evidence-based public policymaking, thereby fostering judicial decisions that are both scientifically informed and socially balanced.

From an analytical perspective, the Brazilian experience represents a paradigmatic example of the tension among scientific innovation, fiscal responsibility, and distributive justice. On the one

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hand, substantial regulatory advances have been achieved in establishing pathways for the incorporation of disease-modifying therapies for Alzheimer's disease. On the other hand, persistent structural barriers continue to impede the translation of these regulatory milestones into equitable and effective patient access. Addressing this challenge will require the development of integrated public policies grounded in rigorous cost-effectiveness analyses, robust clinical evidence, and sustainable financing strategies. Only through such a coordinated approach will it be possible to establish a responsible framework for health technology incorporation that promotes equitable access, efficient stewardship of public resources, and the ethical, rational, and socially just realization of the constitutional right to health.

3. Regulation and Access: Contrasting the United States and Brazil

In the United States, regulatory decisions are generally reached more rapidly, largely because of the accelerated approval pathway, a mechanism established in 1992 in response to the HIV/AIDS crisis and subsequently applied to Alzheimer's disease. This pathway allows earlier authorization of promising therapies in areas of

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significant unmet medical need by accepting surrogate endpoints, such as reductions in amyloid-beta plaque burden, as evidence reasonably likely to predict clinical benefit. It was through this mechanism that the FDA approved aducanumab in 2021, a decision that generated substantial controversy because of the lack of scientific consensus regarding the relationship between biomarker reduction and meaningful cognitive improvement (FDA, 2018; Cummings et al., 2021).

In contrast, Brazil follows a more sequential and cautious regulatory process, as illustrated by Anvisa's approval of donanemab (Kisunla) in 2025. The agency restricted the indication to specific genetic subgroups—patients who are either non-carriers or heterozygous carriers of the APOE ϵ 4 allele—owing to differences in the risk of serious treatment-related adverse events. This decision reflects a more conservative regulatory approach that conditions patient access on robust clinical evidence while prioritizing patient safety (Brazil, 2025). Thus, whereas the U.S. model emphasizes regulatory flexibility and timely access to innovation, the Brazilian framework places greater weight on precaution and the protection of public health.

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A further distinction concerns the evidentiary standards required for regulatory approval. Initially, the FDA accepted biological surrogate markers as sufficient evidence of therapeutic efficacy despite the absence of definitive proof of clinically meaningful cognitive benefit. By contrast, Anvisa adopted a more stringent position, requiring stronger clinical evidence before granting marketing authorization. This divergence reflects not only different regulatory philosophies but also the realities of Brazil's universal publicly funded healthcare system, in which each regulatory decision has direct implications for the long-term financial sustainability of the Brazilian Unified Health System (SUS).

According to Ferreira and Magalhães (2020), health-related litigation in Brazil highlights persistent gaps between health regulation and public policymaking, revealing insufficient integration between scientific and legal decision-making. The authors argue that the fragmented operation of these sectors encourages reactive and isolated decisions, ultimately undermining both the effectiveness of access policies and the rational incorporation of new health technologies. From this perspective, Anvisa's cautious regulatory stance represents not merely a technical choice but also an institutional response aimed at

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ensuring therapeutic safety and distributive justice within a universal public healthcare system.

Differences between the two countries become even more apparent with respect to reimbursement and healthcare financing. In the United States, the Centers for Medicare & Medicaid Services (CMS) implemented the Coverage with Evidence Development (CED) policy, which provides conditional reimbursement for selected therapies while requiring the systematic collection of real-world evidence through national patient registries. This approach links early patient access to continuous evaluation of long-term effectiveness and safety (CMS, 2023; *Health Affairs*, 2023). In Brazil, public reimbursement depends on cost-effectiveness and budget impact assessments conducted by Conitec, while coverage decisions within the private healthcare sector are made by the National Regulatory Agency for Private Health Insurance and Plans (ANS). Although these processes are essential for ensuring the efficient allocation of public resources, they are typically more complex and time-consuming, often prompting patients to seek judicial intervention as an alternative means of obtaining access to therapies that have not yet been incorporated into coverage policies.

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Despite their structural and regulatory differences, both countries face similar challenges regarding financial sustainability and healthcare infrastructure. In the United States, the high annual cost of anti-amyloid monoclonal antibodies places substantial pressure on the Medicare budget, limiting the widespread adoption of these therapies (Cubanski & Neuman, 2021). In Brazil, the barriers are even more pronounced. Beyond the economic burden, the effectiveness of these treatments is constrained by the limited availability of specialized diagnostic infrastructure, particularly amyloid positron emission tomography (PET) imaging and serial magnetic resonance imaging (MRI). These resources remain concentrated primarily in the South and Southeast regions, contributing to significant geographic and socioeconomic disparities in access to specialized care (Alencar et al., 2024).

Overall, the comparative analysis of the U.S. and Brazilian regulatory and reimbursement frameworks demonstrates that the U.S. system prioritizes the rapid adoption of innovative technologies, albeit with a greater degree of regulatory uncertainty, whereas the Brazilian model emphasizes cautious decision-making and patient safety, constrained by structural and fiscal limitations. Despite these differences, both countries confront the same

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fundamental challenge: reconciling the incorporation of innovative biomedical therapies with the long-term financial sustainability of their healthcare systems while upholding the principle of distributive justice, a cornerstone of contemporary health law and health policy.

4. Comparative Analysis of the U.S. and Brazilian Regulatory Frameworks

The analysis presented in the preceding sections demonstrates that both the United States and Brazil have established regulatory mechanisms for the approval and incorporation of novel therapies for Alzheimer's disease. Nevertheless, each system reflects the distinctive institutional, economic, and legal characteristics of its respective healthcare environment, resulting in different pathways for regulatory approval, reimbursement, and patient access.

According to Caetano et al. (2021), "health regulation and health technology incorporation are complex and dynamic processes that integrate scientific, economic, and social dimensions" (p. 5428). This perspective underscores that comparisons between regulatory systems should extend beyond their formal legal frameworks to encompass the institutional

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culture and structural determinants that shape regulatory decision-making in each country.

To facilitate a clearer and more systematic comparison, the following section summarizes the principal similarities and differences between the United States and Brazil with respect to their regulatory frameworks, health technology incorporation processes, and the practical conditions governing patient access to disease-modifying therapies for Alzheimer's disease.

Table 1. Comparison of Regulatory Pathways for Alzheimer's Disease Therapies in the United States and Brazil

Aspect	United States	Brazil	
Regulatory authority	The FDA (Center for Drug Evaluation and Research [CDER]) employs both accelerated and traditional approval pathways. Recent approvals include Leqembi (traditional approval, 2023) and Kisunla (2024).	Anvisa regulates drug approval under RDC No. 753/2022 (which revised RDC No. 200/2017). Kisunla received marketing authorization on April 22, 2025, whereas Leqembi has not yet received regulatory approval.	
Public coverage	Medicare/CMS expanded coverage for Leqembi following its	Conitec avalia custo-efetividade e impacto Conitec evaluates cost-effectiveness and budget impact	

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	traditional FDA approval, contingent upon patient enrollment in a national data registry.	before therapies can be incorporated into the Brazilian Unified Health System (SUS) under Decree No. 7,646/2011. Donepezil for severe Alzheimer's disease was incorporated in 2025, whereas anti-amyloid therapies have not yet been incorporated.	
Risk management and monitoring	Clinical protocols require serial MRI monitoring for amyloid-related imaging abnormalities (ARIA), with risk stratification based on APOE ε4 status. These requirements are reflected in prescribing information and clinical practice guidelines.	The Brazilian prescribing information for Kisunla includes restrictions based on APOE ε4 genotype and specifies monitoring requirements, creating additional demands for advanced diagnostic infrastructure within the healthcare system.	
Speed of access	The accelerated approval pathway enables earlier patient access while confirmatory evidence is generated. Coordination between the FDA and CMS facilitates more rapid implementation of coverage decisions.	Following marketing authorization, patient access depends on multiple decision-making bodies (Anvisa, Conitec/SUS, and ANS), which may prolong access timelines and contribute to increased health-related litigation.	

Source: Prepared by the authors

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The comparative analysis of the regulatory frameworks in the United States and Brazil reveals legal and public policy implications of considerable importance for public health and health law. The case of aducanumab (Aduhelm), approved by the FDA in 2021, represents a paradigmatic example of the risks associated with relying on surrogate endpoints as the basis for regulatory approval without robust confirmation of clinically meaningful benefit. Although the initial authorization generated considerable expectations among patients and their families, the limited strength of the supporting clinical evidence ultimately led to restricted Medicare coverage and the drug's subsequent commercial discontinuation. This trajectory underscores the importance of regulatory prudence and rigorous scientific standards when granting early access to therapies that lack well-established empirical evidence (Alzheimer's Association, 2024).

Another important consideration concerns the integration of regulatory approval and reimbursement policy. In the United States, close institutional coordination between the U.S. Food and Drug Administration (FDA) and the Centers for Medicare & Medicaid Services (CMS) allows regulatory approval to be followed rapidly by conditional public reimbursement through Coverage with

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Evidence Development (CED), under which continued access is linked to the systematic collection of additional clinical evidence. By contrast, the Brazilian system separates regulatory approval from health technology incorporation: marketing authorization is the responsibility of Anvisa, whereas decisions regarding reimbursement and incorporation into the public and private healthcare systems are made by Conitec and the National Regulatory Agency for Private Health Insurance and Plans (ANS), respectively. This institutional separation lengthens the overall decision-making process and contributes to increased health-related litigation, as patients frequently seek judicial remedies to obtain access to therapies that have not yet been incorporated into coverage policies (Brazil, 2011; CMS, 2023). Within this context, the central legal challenge lies in balancing the collective interests of public health protection and fiscal sustainability with the immediate realization of the individual right to health.

Beyond regulatory considerations, significant structural and logistical challenges remain regarding the healthcare infrastructure required to implement disease-modifying therapies for Alzheimer's disease. Dependence on advanced diagnostic technologies—including amyloid positron emission tomography (PET) imaging and

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serial magnetic resonance imaging (MRI) for the detection and monitoring of amyloid-related imaging abnormalities (ARIA)—creates substantial barriers to access in both countries. In the United States, these obstacles are primarily associated with socioeconomic and geographic disparities, whereas in Brazil they reflect the concentration of advanced diagnostic resources in the South and Southeast regions, together with shortages of specialized healthcare professionals in underserved areas (Alencar et al., 2024).

From this perspective, even following regulatory approval and potential incorporation of therapies such as donanemab, there remains a substantial risk that effective access will continue to be concentrated in major urban centers, thereby reproducing longstanding patterns of geographic inequality and socioeconomic exclusion (PMC, 2023). Consequently, therapeutic innovation may paradoxically reinforce the very health inequities that universal healthcare systems seek to reduce.

Overall, the legal and public policy implications of regulating disease-modifying therapies for Alzheimer's disease extend well beyond the question of marketing authorization. The contemporary challenge is to reconcile the responsible incorporation of biomedical innovation with fiscal sustainability and distributive

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equity, ensuring that the constitutional right to health is realized in a manner that is universal, safe, evidence-based, and socially just.

Conclusion

The comparative analysis of the regulatory frameworks governing disease-modifying therapies for Alzheimer's disease in the United States and Brazil highlights both significant progress and persistent structural challenges. The U.S. model, characterized by the FDA's expedited approval pathways and close institutional coordination with the Centers for Medicare & Medicaid Services (CMS), has demonstrated a strong capacity to facilitate the early introduction of innovative therapies. At the same time, this regulatory agility exposes important scientific and economic risks, particularly when approval decisions rely on clinical evidence that remains preliminary. The case of **aducanumab** exemplifies these concerns, as its early approval generated substantial controversy regarding both its clinical effectiveness and the long-term sustainability of public reimbursement.

In Brazil, meaningful regulatory advances have been achieved through Anvisa's approval of **donanemab** and the revision of clinical protocols governing symptomatic therapies for Alzheimer's

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disease. Nevertheless, the slow pace of health technology incorporation, the high cost of innovative treatments, and persistent structural and regional disparities continue to constrain both the effectiveness of implementation and equitable patient access. These findings suggest that the principal challenge extends beyond the formal approval of new therapies to the development of public policies capable of ensuring social effectiveness, financial sustainability, and distributive justice.

From a legal perspective, both regulatory systems confront similar challenges in balancing the right to health with the competing demands of biomedical innovation, fiscal responsibility, and social justice. In the United States, debate has centered on the speed of regulatory approvals and their budgetary implications for Medicare. In Brazil, concerns have focused on the lengthy technology incorporation process and the growing reliance on health-related litigation as a means of obtaining access to therapies that have not yet been incorporated into public or private coverage. In both settings, regulatory approval alone is insufficient when not accompanied by coordinated policies addressing reimbursement, healthcare planning, and service delivery infrastructure. These

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findings underscore the importance of integrated governance and institutional coordination in health policy.

The evidence presented in this study indicates that the contemporary challenge of health regulation extends well beyond the binary decision of whether to approve or reject new medicines. Rather, it requires institutional, economic, and social conditions capable of translating regulatory advances into timely, safe, and equitable access to care. In the Brazilian context, achieving this objective will require the combination of scientifically rigorous regulation, expanded diagnostic capacity, fair and sustainable pricing strategies, and continued strengthening of the Brazilian Unified Health System (SUS) as a universal and redistributive public healthcare system.

From the perspective of comparative law, the experiences of the United States and Brazil demonstrate that neither regulatory model is without limitations; however, each offers valuable and complementary lessons for improving health policy in the era of biomedical innovation. The U.S. framework illustrates the benefits of regulatory agility and early access, albeit accompanied by greater clinical uncertainty and substantial financial pressures. By contrast, the Brazilian model emphasizes gradual implementation,

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regulatory caution, and equity, although its effectiveness continues to be constrained by structural barriers and persistent regional disparities.

Ultimately, the comparison between these two regulatory systems reaffirms that the central challenge lies not in the regulatory act itself but in the effective realization of the right to health. The future of public policies for Alzheimer's disease will depend on the ability to reconcile scientific innovation, fiscal responsibility, and social justice, ensuring that advances in biomedicine are translated into meaningful and equitable health benefits for the population as a whole rather than remaining accessible only to selected groups.

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