Navigating Controversy: Political and Economic Dynamics Influencing the FDA Approval of Aduhelm

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On my honor as a University Student, I have neither given nor received unauthorized aid on this assignment as defined by the Honor Guidelines for Thesis-Related Assignments

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Introduction

After back-to-back failed clinical trials, Biogen, a leading biotechnology company, launched Project Onyx. Like the valuable gemstone it is named after, Project Onyx symbolized a prized strategy fabricated to carve a path to acquire FDA approval for a new Alzheimer's disease drug called Aduhelm. However, unlike the allure of its namesake, Project Onyx elicited extreme scrutiny rather than admiration. Once this secret project came into the public's attention, investigations were launched evaluating the complex relationship between the FDA and Biogen. The investigation found that there were over 115 meetings and calls over a year, with an additional 66 calls and email exchanges that were not memorialized, violating FDA guidelines (COA, 2022). To make matters worse, the FDA concluded after an internal review that there was usage of a joint briefing document that "afforded Biogen advance insight into FDAs responses," to which the FDA noted as an inappropriate approach (COA, 2022). Ongoing debates about the drugs clinical efficacy and safety rose to the forefront, exacerbated by leaders in the scientific community speaking out to condemn Aduhelm's approval.

With the approval of Aduhelm, which targets one hypothesized biomarker of Alzheimer's disease, the research community has begun flooding the field with new projects targeted at decreasing the same biomarker (Steenhuysen, 2023). This research accounts for the majority of attention and funding, despite experiencing multiple failures in confirming that this biomarker causes Alzheimer's disease. The approval of Aduhelm can halt the Alzheimer's disease research field as there needs to be a devotion of "the same amount of attention to other approaches that could slow, prevent, or even reverse Alzheimer's" (Fillit, 2017). Another grave concern is that the approval could "lower standards for future drugs, allowing them onto market before experts in the field are convinced the benefits outweigh any safety risks" (Belluck & Robbins, 2021).

Thus, an examination into Aduhelm's approval process is necessary to prevent these hypotheses from becoming reality.

To evaluate the approval process, I first provide an overview of the literature regarding the United States healthcare system and how this system created a need for medical advancements with an affordable price. The review also introduces the role and structure of the FDA which is needed to understand the reasoning behind the FDAs actions in this situation. Then analyze the events that occurred during and after the approval of Aduhelm, as well as the roles of relevant social groups. Through this analysis, I analyze what groups had an impact on the FDAs decision making process and what power imbalances were created. Finally, I end with a discussion of the long term impacts of the drug's approval and recommend actions that the FDA should consider to ensure that mistakes are not repeated in the future. Through this discussion, I assert that the accelerated approval of Aduhelm, marked by scandal and controversy, underscored the political and economic power imbalances that directly and negatively impact the FDA approval process.

Literature Review

In the years leading up to 2021, the United States healthcare system left something to be desired. The Commonwealth Fund reported that "people in the United States experience the worst healthcare outcomes overall for any high-income nation" (Gunja et al., 2023). To make matters worse, when compared to wealthy and equally developed countries, the US ranks the lowest in life expectancy at birth, has the largest mortality rates from treatable conditions, and has some of the steepest suicide rates (Gunja et al., 2023). Despite spending "a higher portion of its gross domestic product than any other country [on healthcare]," the current system falls short (World Health Organization, 2000). In 2006, the National Institutes of Health (NIH) conducted a

survey and found that 32% of Americans were “very worried about not being able to afford the health care services they thought they needed,” with these percentages jumping to 52% for low income households (Blendon et al., 2006). These concerns are well-founded, given that 66.5% of all personal bankruptcies in the US stem from the burden of medical bills, causing Americans to be left grappling with financial hardship and uncertainty (Fielding, 2023).

With the healthcare system exerting a heavy economic strain on citizens, Americans turned their attention to the political landscape in hopes of assistance. With 4 out of 10 Americans delaying medical treatment due to the cost, and approximately ⅓ of Americans forced to stray from their medication regimen due to the cost of prescription medicine, healthcare quickly shifted to the forefront of political debates (Newport, 2023; Picchi, 2019). In a 2019 poll, 69% of Americans stated that minimizing healthcare costs should be a top priority for the national government, foreshadowing healthcare based issue voting in the upcoming election (ASH Clinical, 2021). Despite promises from lawmakers and former President Donald Trump to address and tackle the rising drug costs, over 3,400 commonly used medications experienced a 17% increase in prices in 2019 compared to 2018 (Picchi, 2019). Similar transparency and accountability concerns characterized the political climate, driven by accessibility disparities as well as the staggering increase in prescription drug costs.

While medical practices, policy, and drug prices within the healthcare system are not regulated by the U.S. Food and Drug Administration (FDA), the FDA impacts Americans' drug treatment options. The FDA is responsible for “protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices” (FDA, n.d.). Federal law mandates rigorous evaluation by the FDA of all new drugs, in order to ensure safety and effectiveness before becoming accessible to the general public.

Whenever there is an unmet medical need for serious conditions, the FDA has the power to grant accelerated approval for new medical devices and drugs (Largent et al., 2022). Accelerated approval is based on a surrogate marker in a clinical trial that occurs earlier, rather than endpoint markers that are used in traditional approvals (Lilly, 2023). These surrogate markers are able to predict a high level of clinical benefit. During the drug approval process, whether accelerated or not, a group of educated and specialized people come together in order to evaluate the therapy. This group is called the FDA advisory committee and is composed of leaders in the scientific community, industry members, and consumer representatives. Their job is to be an independent voice when reviewing new treatments and offer feedback surrounding the safety and efficacy (FDA, 2021). Since the 1970's, the advisory committee has been a powerful and influential committee when determining what is safe and effective for Americans.

In June of 2021 the FDA granted accelerated approval for an Alzheimer's drug developed by Biogen known as Aduhelm. Alzheimer's Disease is a neurodegenerative disease that results in memory loss and declining thinking skills. There are over six million Americans living with Alzheimer's Disease with zero treatment options, allowing the FDA to consider this disease as a substantial unmet need (Ercolano, 2021). Aduhelm was the first drug on the market that is proven to decrease a hypothesized peptide biomarker of Alzheimer's disease known as amyloid beta. The FDA decided the proven reduction of this peptide was enough to predict a clinical benefit to patients, therefore deemed it worthy of accelerated approval (FDA, 2021). The long term approval of Aduhelm is conditional on the success seen in post clinical studies, as well as monitoring and reporting side effects. For now, Aduhelm is for patients that are in the very early stages of Alzheimer's Disease, which accounts for about 1⁄4 of the diseased population in the

United States. With the approval of Aduhelm, Alzheimer's patients around the world were given hope about the prospect of a treatment.

The purpose of this research paper revolves around understanding the influences and motivations behind the accelerated approval of Aduhelm, as well as evaluating the response post-approval. My analysis of the events leading up to and after the drugs approval draws on the Social Construction of Technology (SCOT) framework, which allows me to identify and examine relevant social groups, and how these groups impacted the closure and stabilization of Aduhelm. The SCOT framework focuses on how technology is constantly influenced by social factors and the interactions between multiple social groups involved in its production and usage. In order to understand the developmental process, SCOT examines the meanings each group gives to the artefact. According to Pinch and Bijker (1984), two prominent SCOT theorists, "we need to have a detailed description of the relevant social groups in order to define the function of the artefact with respect to each group" (pg. 415). SCOT defines relevant social groups as "institutions or organizations, as well as organized groups or unorganized groups of individuals" that "share the same set of meanings, attached to a specific artefact" (Pinch & Bijker, 1984, pg 414). In the case of Aduhelm, relevant social groups could include the FDA, Biogen, patient advocacy groups, insurance companies, and experts in the neurodegenerative disease field. SCOT is particularly useful when analyzing the approval of Aduhelm as it adopts a multi-directional model, in comparison to a linear one, allowing me to examine how the social groups responded and shaped the approved drug, and the impact the drug had on the surrounding social groups. This multi-dimensionality is best understood using three key components of SCOT: interpretive flexibility, closure, and stabilization. Interpretive flexibility refers to a specific artefact having different meanings to different social groups, or that artefacts are

"culturally constructed and interpreted" (Pinch & Bijker, 1984, pg. 421). These interpretations are subject to change and reshaping during interactions of multiple social groups. Closure and stabilization refers to dominant interpretations that become popular due to negotiations within social groups. By analyzing the drug approval through this lens, I am able to determine what key factors caused the FDA to push the dominant interpretation of Aduhelm's success by approving the drug, and why this closure was then reopened two years later, challenging the stabilization. Utilizing SCOT will enable me to sift through the economic and political power dynamics in place during and after Aduhelm's approval.

Methods

In this paper, I collected multiple reviews from scientists outlining Aduhelm research papers, as well as their interpretation of that research. I used these as secondary sources in order to evaluate how the healthcare and pharmaceutical system has impacted the approval process of Aduhelm. I collected research from the last 10 years to examine the economic and political climate before, during, and after the approval of Aduhelm. The research I collected also includes the clinical trial data from Biogen which I used in combination with reviews from leaders in the scientific community to draw claims on the efficacy of the FDAs decision to grant accelerated approval. I used the literature review to examine that political and economic factors were considered previously, and see what actors are most and least relevant. My literature review also consisted of secondary sources outlining the issues in the American healthcare system and how these issues relate to Alzheimer's research specifically. My main form of research revolved around a case study analysis in order to generate a rich and detailed picture of the dynamics between relevant social groups, such as insurance companies, Biogen, the FDA, public advocacy groups, and elected officials in positions of political power. I was very interested in the bounded

system revolving around Aduhelm's approval and used a case study analysis to understand the interactions and influences that shaped it. This case study analysis provided insights into the drug approval process and the impacts it has on a larger scale, beyond just this case.

Analysis

The grounds on which Aduhelm was approved were uncertain and widely debated within the scientific community. The FDA Advisory committee failed to approve Aduhelm, with 10 out of 11 members voting against its approval, and the 11th left undecided on the interpretation of the data. The advisory committee offers recommendations and feedback on all drugs approved by the FDA. Due to gaps in the clinical trial data, the committee's feedback to the FDA was not favorable to Biogen's new drug (Maulden, 2022). One of these gaps included the failure to produce statistically significant data to support that it improves a patient's cognitive function (Glymour et al., 2022). Although Aduhelm is proven to decrease the amount of amyloid beta plaques in the brain, a hypothesized precursor of Alzheimer's disease, there is no evidence to support that this reduction improves patients' cognitive function or prognosis. The lack of translation between reducing amyloid beta plaques with clinical benefits was unfounded, promoting widespread debate over the efficacy and reliability of the new drug. Additionally, multiple similar trials have demonstrated a reduction of plaques without statistically significant results indicating that the treatment has been successful. Dr. Samuel Ganfy, a member of the Scientific Advisory Council of the Alzheimer's Association as well as the Associate Director of the Mount Sinai Alzheimer's Disease Research Center commented that the "FDA has apparently applied what I can only speculate to have been bias, wishful thinking, and/or delusion as substitutes for science and data" (Gandy, 2021). Without the backing from the scientific

community, Aduhelm was under intense scrutiny from its conception that only continued to accumulate in the following years.

Extreme backlash was seen from the scientific community and advising members of the FDA after the FDA approved Aduhelm against the committee's recommendation. Three FDA Advisory Committee members resigned as a form of protest as the advisors were concerned that although the need was met for accelerated approval, the clinical trials did not meet requirements for approval (Largent et al., 2022). Aaron Kesselheim, a Harvard professor of medicine and one of the advisors that resigned, commented that this approval was "the worst drug approval in recent US history" (Mahase, 2021). David Knopman and Joel Perlutter, the other two advisors that quit, expressed that they were disappointed with how the FDA had treated its advisory committee's input and that the FDA had approved Aduhelm without any further discussion with the experts (Mahase, 2021). The response from the FDA's advisory committee prompted criticism of the accelerated approval. Knopman further iterated that "accelerated approval is not supposed to be the backup that you use when your clinical trial data are not good enough for regular approval" sparking further evaluation of the data submitted to the FDA (Mahase, 2021). The FDA attempted to force the closure of Aduhelm, as defined by SCOT, through its accelerated approval process, but the closure reopened after industry leaders and researchers heavily criticized the FDA's actions and motives.

The FDA approval process was further scrutinized as the integrity of the relationship between pharmaceutical companies and regulatory agencies was questioned, highlighted by an unofficial meeting prior to accelerated approval. Following controversy involving the FDA Advisory Committee members, Biogen and the FDA found itself under intense scrutiny from the public when allegations of "inappropriately close relationship[s] between the FDA and the

industry" hit the papers (U.S. Department of Health and Human Services, 2021). After the approval, news of Biogen launching an effort called Project Onyx in order to get FDA approval arose. Reports of an unofficial meeting between Al Sandrock from Biogen and Billy Dunn at the FDA's Office of Neuroscience a month before accelerated approval of Aduhelm was granted took everyone including Biogen's own executives by surprise (Terry, 2022). This meeting was against FDA policy as it was not considered a method of official contact between the industry and regulatory agency. *Science*, a peer- reviewed journal, commented that the proposal of accelerated approval took even the executives of Biogen by surprise (Lowe, 2021). To exacerbate suspicions, Biogen appeared to be "flush with money and new drug approvals" over the last few years, only to find itself financially relying on the approval of a drug for a disease that has not had any treatment breakthroughs since 2003. With a lack of clinical evidence to support Aduhelms approval followed by extreme criticism from the scientific community, FDA approval being granted a month after an unofficial meeting leaves many questions unanswered.

The refusal of insurance companies to cover Aduhelm, coupled with the extreme financial burden it would pose, intensified ongoing debates. The hot water Biogen found itself in became boiling when large insurance companies, including Medicare, refused to cover Aduhelm. Aduhelm costs $65,000 per year per patient and there are extreme risks of brain bleeds, seizures, and swelling (Largent et al., 2022). Assuming that patients only had to pay 20% of the cost and only 10% of these patients pursued treatment, Aduhelm would cost insurance companies $45 billion dollars annually (Glymour et al., 2022). This cost analysis does not include the cost of multiple doctors' visits, MRI scans, and follow-up treatment needed when taking Aduhelm. Without demonstration that Aduhelm is effective and safe, it is understandable that these large insurance companies refused coverage. The risk of the experimental drug causing financial loss

to Medicare's budget and high risk side effects was not acceptable in the eyes of large insurance companies. Obviously, this was a detrimental blow to Biogen's financial situation and only compounded public scrutiny. The combination of significant economic and health based risks associated with this new drug without certain benefits to the patient prompted debate from all parties involved in the development and usage of Aduhelm.

The economic landscape surrounding Alzheimer's care called for some solution to aid Americans, directly impacting the push for accelerated approval of Aduhelm. The cost of memory care can range from $13,740 to $115,007 per year, prompting extreme financial hardships on both patients and loved ones (Alzheimer's Association, n.d.). In addition to memory care costs, there are many indirect costs associated with Alzheimer's Disease such as loss in quality of life, diminished productivity, and augmented dependence on family members provided unpaid care (Skaria, 2022). With the large financial and emotional burden on American families to care for their loved ones affected with Alzheimer's, the public push for an effective treatment was tremendous. The financial strain was not only felt by American families, but by the national government. Total healthcare costs was estimated at $305 billion dollars in 2020 and is expected to increase to over $1 trillion (Wong, 2020). With the large quantity of baby boomers entering the age where Alzheimer's begins to onset, a solution was needed. The strain on individuals and national healthcare costs pivoted attention to any and all possibilities of a cure.

Although the scientific community and insurance companies shared similar opinions about placing this unfounded drug on the market, public advocacy groups, made up of individuals experiencing financial and emotional hardships, held a very different opinion. For centuries, patients and families suffering at the hands of Alzheimer's disease had no hope. The desperation for some relief both financially and emotionally prompted Alzheimer's advocates

from around the US to march in Washington DC to fight for the reversal of the Medicare block (Alzheimer's Association, 2023). The public advocacy groups surrounding Alzheimer's disease marched to convey that they desired the right to choose to use a drug whose scientific efficacy remained on shaky grounds in hopes of a working treatment. Each relevant social group employed interpretive flexibility as outlined in the SCOT framework. Aduhelm meant nothing but wishful thinking and financial instability to insurance companies and leading members of the scientific community. To Biogen, the drug was seen as a medical breakthrough and entrance into an empty yet desperate market. The FDA viewed Aduhelm as a release from public or political pressure for an Alzheimer's drug to be approved after years of failed clinical trials. However, to these advocacy groups, it was seen as a light at the end of the tunnel. The advocacy groups efforts were futile as in 2022 Biogen halted Aduhelm marketing, and in January of 2024, Biogen announced the discontinuation of the development of Aduhelm in (Biogen, 2024; Langreth, 2022). The combination of media backlash, outbreaks of scandals, and lack of support from major insurance companies forced Biogen to halt continuation of Aduhelm production. The controversy surrounding the approval of Aduhelm, from leading scientists, insurance companies, and public advocacy groups, disrupted the stability of the perception of Aduhelm. When Biogen announced that Aduhelm would be taken off of the market, closure was yet again implemented, reflecting the ongoing concerns surrounding the approval.

Patient advocacy groups and leading experts in the neurodegenerative diseases field used their political power in order to drive the accelerated approval of Aduhelm. A FDA advisory committee meeting in January 2021 revealed that the amount of risk patients would accept was relatively high to test a new treatment with unknown benefits (Largent et al., 2022). Input from patients and families directly affected by the disease prompted decision makers to allow for

accelerated approval in spite of shaky clinical trial evidence. A patient advocacy group, called The Alzheimer's Association, released a statement in favor of Aduhelm's approval, dividing the Alzheimer's patient community (Park & Law, 2021). Many patients expressed that it should be their decision, once introduced to the risks, to take a chance on the new drug or not. These patients expressed outrage that the FDA might create access barriers by not approving the drug. The pro-approval side of the community was very vocal in pushing to make their own decisions, as seen on multiple interviews, news outlets, and even protests. Others in the community believed that it was the FDAs responsibility to protect family members and patients from harmful treatments, as well as not give hope to patients when the drug has not been shown to improve cognitive function. Dr. Billy Dunn who is the director of the FDA's office of neuroscience, strongly pushed for Aduhelm in opposition to statistician's concerns (Largent et al., 2022). Some advocates from the scientific community directly involved with the FDA pushed for Aduhelm, prompting discourse among experts and causing confusion to people in positions of political power.

The drug approval process through the FDA gives power to pharmaceutical companies by creating economic incentives in exchange for faster drug approvals. After slow progress during the AIDs epidemic in the 1980's, the FDA allowed pharmaceutical companies to pay fees for faster approval processes (Lupkin, 2020). Drug development experts are concerned that this policy has created a culture where the primary client is the industry rather than patients. Faster approval processes are advantageous when supplying the public with effective and safe drugs, however, there is a significant danger that decisions are being made too quickly to ensure a high quality of new drugs. Perhaps this policy is a contributing factor as to why there has been a significant increase in recalled drugs over the last few decades. Through indirect costs, the

amount of money owed to the FDA to obtain accelerated approval is larger than traditional approval methods. The cost after accelerated approval of a new drug on the market is also significantly higher than those with traditional approval (Skydel et al., 2022). The structure of the accelerated approval process prompts industry to pay more money at the beginning of the process in order to receive faster approval, knowing that their profits will be larger due to higher drug costs when it hits the market.

As an agency of the United States government, the FDAs decision to approve Aduhelm was may have been influenced by outside political agendas. Congress is able to set the FDAs budget and create legal procedures that the agency has to follow. There is a concern that these checks result in political officials being extensively involved in healthcare science with partisan motivations. With congress setting the FDA's budget, high priority issues to congress can translate as primary concerns to regulatory agencies. I have demonstrated previously that the federal government, especially elected officials, felt extreme pressure from the public to relieve the burden of Alzheimer's disease. Congress may have been more inclined to increase FDA funding due to the prospect of a new Alzheimer's drug getting approved.

The story I have written implies that the political and economic landscape, as well as the influence from individual relevant social groups, had a large impact on the approval of Aduhelm. However, scientific and clinical considerations may have been a larger contributor. The FDA is responsible for "advancing public health by helping to speed innovations that make medical products more effective, safer, and more affordable and by helping the public get the accurate, science-based information they need to use medical products and foods to maintain and improve their health" (Fleming et al., 2017). The FDAs decision making process is based on scientific standards revolving around the safety and efficacy of new drugs. While political pressure and

economic incentives may have been felt by individuals within the agency, Aduhelm's approval was not directly impacted by these factors. The political and economic climate had a limited direct impact on the FDA's evaluation of Aduhelm, while the promising clinical trial data that showed a decrease in amyloid beta plaques was the primary driver of the accelerated approval.

Conclusion

I began this paper by introducing the pitfalls of the United States healthcare system. Despite spending more money on healthcare than any other developed nation, citizens are forced to put their own health aside due to the extreme cost of daily medication. The FDA is responsible for ensuring that the medical devices and drugs available to the public are safe and effective, yet, as this paper highlights, this is not always the case. Aduhelm should never have been approved. Biogen's drug poses a high risk to patients, is rejected by leaders in the scientific community, and places a substantial financial burden on Alzheimer's patients and families who already suffer gravely.

The approval process of Aduhelm was impacted by a variety of relevant social groups who all viewed this approval differently. The FDA approved Aduhelm, not based on clinical trial data or founded scientific evidence, but because of outside influences. The FDA fell short on its responsibility to protect the public and allow only safe drugs to enter the market. It is no surprise that three members of the FDA advisory committee quit after the FDA ignored their input, that large insurance companies refused to cover this unfounded and high risk drug, and a scandal erupted revealing unofficial meetings between Biogen and the FDA coincidentally a month before accelerated approval was granted.

I recognize that this paper is limited in terms of perspective and generalizability. I focus on the controversies and criticisms surrounding Aduhelm's approval, disregarding the potential

benefits. Additionally, there are multiple relevant social groups and factors that I have not had the ability to address, resulting in the complexity of this situation to be oversimplified. Other factors besides scientific rigor and external influences may have impacted Aduhelm's approval, creating a different narrative. In the future, there are opportunities for research to be conducted that takes into account alternative influences.

The FDA as a regulatory agency needs to be independent from outside influences. The political pressure experienced by the FDA to approve any Alzheimer's treatment resulted in an unsafe and unsuccessful drug entering the market. Outside pressures as seen in this study emphasize the need for protocol to be established in technology-oriented spaces. Outside influences, especially political in nature, have no space in healthcare and methods to overcome these influences should be created to avoid a situation similar to this in the future. Stricter criteria needs to be developed in order to ensure that the amount of risk exposed to the public is minimized and tolerable. Real regulations backed by real power need to be established for when industry and agencies relationships become too close. Without these regulations, the trust between citizens and their government will continue to fracture. The FDA policy in reference to their drug approval process, accelerated or not, needs to be reshaped in order to ensure that the pharmaceutical industry is not prioritizing profits over patient safety. There will always be relationships between relevant social groups that have the potential to impact healthcare and the pharmaceutical industry. However, corrective actions should be taken in terms of the FDAs policy so that the next time political and economic influences come too close to healthcare, the agency can navigate the situation in a way that is ethical and prioritizes the people.

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