An Actor-Network of the FDA Approval Process 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

In the United States today there are 6.3 billion prescriptions for prescription drugs, corresponding to an average of 19 prescriptions for every American (Ho, 2023). In total, there are over 20,000 types of prescription drugs that the FDA (Food and Drug Administration) has approved for marketing, implying that companies that have advertised the effects of their drugs have had these effects examined and validated by the FDA (Commissioner, 2024). This task of validation is an important one, with the process of drug approval gatekeeping claims of safety and effectiveness from ineffective products, thereby safeguarding public health and instilling confidence in the healthcare system, But the FDA has dual mandates: in addition to the responsibility of refuting ineffective and improper treatments, the FDA also has the responsibility to approve effective drugs expediently and broadly to ensure that patients suffering from disease can access potentially life-saving measures (Abraham, 2002). This has led to some conflicts over the years and changes in the immediate priority of the approval process, leading to alterations of how the concept of an "FDA approved" drug is constructed over time.

On June 7th, 2021, the FDA approved the drug Aduhelm for the treatment of Alzheimer's Disease to public and scientific outcry. This approval had come after weak results had led the drug sponsor, Biogen, to terminate Phase III trials in March of 2019, with no further research to support the approval. Three members of the advisory committee that recommended the FDA not to approve the drug resigned in protest. Separate investigations into the accelerated approval of Aduhelm were almost immediately started by the House Committee on Energy and Commerce and the US Department of Health and Human Services. The Centers for Medicare and Medicaid Services (CMS) decided to only have Medicare cover the costs of the drug in clinical trials, with

other health insurance providers following suit, leading to almost no patients using the drug due to its cost of $56,000 annually.

For almost all other drugs, FDA approval is a black box that the public, politicians, and health providers trust implicitly. But in this case approval was not accepted as a black box, it was instead thoroughly hacked open and investigated to expose its inner workings. It provides an excellent opportunity to analyze the actors and relationships that make up the modern FDA approval process by trying to see where it went wrong in convincing the world that it was right. The research question is then as follows: *What was the actor network for the FDA approval process of aducanumab (Aduhelm) and how does it reflect on the modern FDA approval process?*

Background

How the FDA operates its drug approval process can change depending on the whims of Congress. How frequently laws affecting the FDA are passed varies over time and depends on shifts in public health priorities and advancements in medical technology (Van Norman, 2020). Historically, the FDA has been subject to legislative updates on a semi-regular basis, with significant overhauls occurring in response to emerging public health crises or advancements in regulatory science. The most notable examples of such legislation being the Food, Drug, and Cosmetic Act of 1938 and the Prescription Drug User Fee Act of 1992, both of which have fundamentally reshaped the FDA's regulatory framework at the time (Hutt, 2018). In addition to changes in the law, however, the behavior of the FDA could be adjusted by internal cultural changes in the agency prompted by changes in federal administration and leadership. Changes to internal enforcement procedures were suspected to contribute to the difference between presidential administrations of the FDA’s rate of issuing notices of violation from the Office of

Prescription Drug Promotion to offending companies from the stretch of 1997-2011 (Nguyen et al., 2013).

The complex interplay of federal legislation, public health, advancements in regulatory capability, politics both from within and without the FDA, and potentially other subtle factors make studying the sociotechnical composition of the FDA approval process difficult. That has not stopped impressive attempts to study it. One such analysis honed in on the influence of the culture and cultural components of regulatory science within the FDA, its derivation from the adversarial political culture of the USA, and, within that framework, dissected three case studies of major FDA incidents from the 1970s-1990s (Abraham, 2002). Another examined the global shifts in drug development and regulatory environment from the 1980s and 1990s with a realist empirical program, and tried to delineate the impacts on micro-level approvals from macro-level societal shifts towards neoliberal business practices (Abraham, 2008). Alternatively, an analysis combining the work of Bruno Latour in science and technology studies with a further analysis of power relations within the pharmaceutical industry has examined how the FDA approval process constructs a conceptual black box around the drug and then further examines how that box is interacted with and exploited by other actors involved in the industry (Busfield, 2006). While these are all valuable contributions, they provide a generalized, top-down overview of the FDA approval process that primarily emphasizes human actors within the system. There would be novelty in examining the construction of the black box of FDA approval from a bottom up, component first perspective.

Actor-Network Theory (ANT) provides a unique lens through which to understand the complex interactions between non-humans and human entities within sociotechnical systems like the FDA approval process (Walsham, 1997). ANT challenges typical notions of causality by

emphasizing the role of both non-human and human actors in shaping social phenomena. ANT views systems as networks of heterogeneous actors, whether they be people, technologies, or ideas, that are interconnected through relationships of interaction and influence (Latour, 1996). By highlighting the agency of non-human actors and the ways in which they participate in shaping system outcomes in relation to human actors, ANT offers a useful framework for analyzing how sociotechnical systems are composed and constructed into representative entities. In this case, the translation of the actors and relationships involved in the FDA approval process into an accelerated FDA approval of the drug for the treatment of Alzheimer's.

The coalescence of an actor network into a representative entity is a process known as translation, and consists of four stages: problematization, interessement, enrollment, and mobilization. These stages are carried out by principal actors, typically researchers or advocates working on a scientific concept or idea. Problematization is the presentation of primary actors within the network and their motivations so that all actors have a common interest in the obligatory passage point (OPP), the aim that all actors seek to satisfy in pursuit of their own goals. Interessement is the process of locking actors into designated roles set out by the research program by negotiating alliances with them. Enrollment is the strategies that principal actors carry out to define and interrelate the roles of actors within the network. Mobilization is the set of methods the principal actors use to maintain enrollment and make sure that actors do not betray the network. A black box of accepted fact is eventually constructed following a successful mobilization (Callon, 1984).

Methods

To understand how the actor-network of the FDA approval process of Aduhelm was constructed, a literature review was conducted to gather data necessary for constructing an

overview of translation. Human actors were identified through media reports and papers detailing the controversy, with the text of some transcripts or interviews thematically coded to qualitatively analyze the position of actors within the network. The documents related to pre-clinical studies and Phase I and Phase III trials were also sought out to examine the materials, subjects, and methodology used in the study to be used as human and non-human actors. Retrospective review articles and media coverage detailing information related to the approval process were examined for information particularly related to Aduhelm to further consider alliances between actors during the process of interessement, enrollment, and mobilization. Biochemical information about the drug was also sought out to determine the complexities associated with the process of interessement of trials.

Most of the data was collected from accessdata.fda.gov, a website that contains documents for FDA drug approvals. Papers related to the pre-clinical or phase trials that were published online were obtained through their respective journals. Information from media coverage was obtained from articles from STAT, a news site dedicated to the biotechnology field. Legislation related to the FDA was obtained through Congress, and the FDA's policies were obtained from fda.gov.

The principal actor in the actor-network of the FDA approval of Aduhelm was Biogen, a biotech company that had developed the drug and worked with the FDA for a couple of years. More specifically, a small team under Dr. Alfred Sandrock and Dr. Samantha Budd Haeberlein served as representatives for Biogen when presenting to and interacting with the FDA, Aduhelm data from Alzheimer's patient trials, and healthcare professionals.

Results

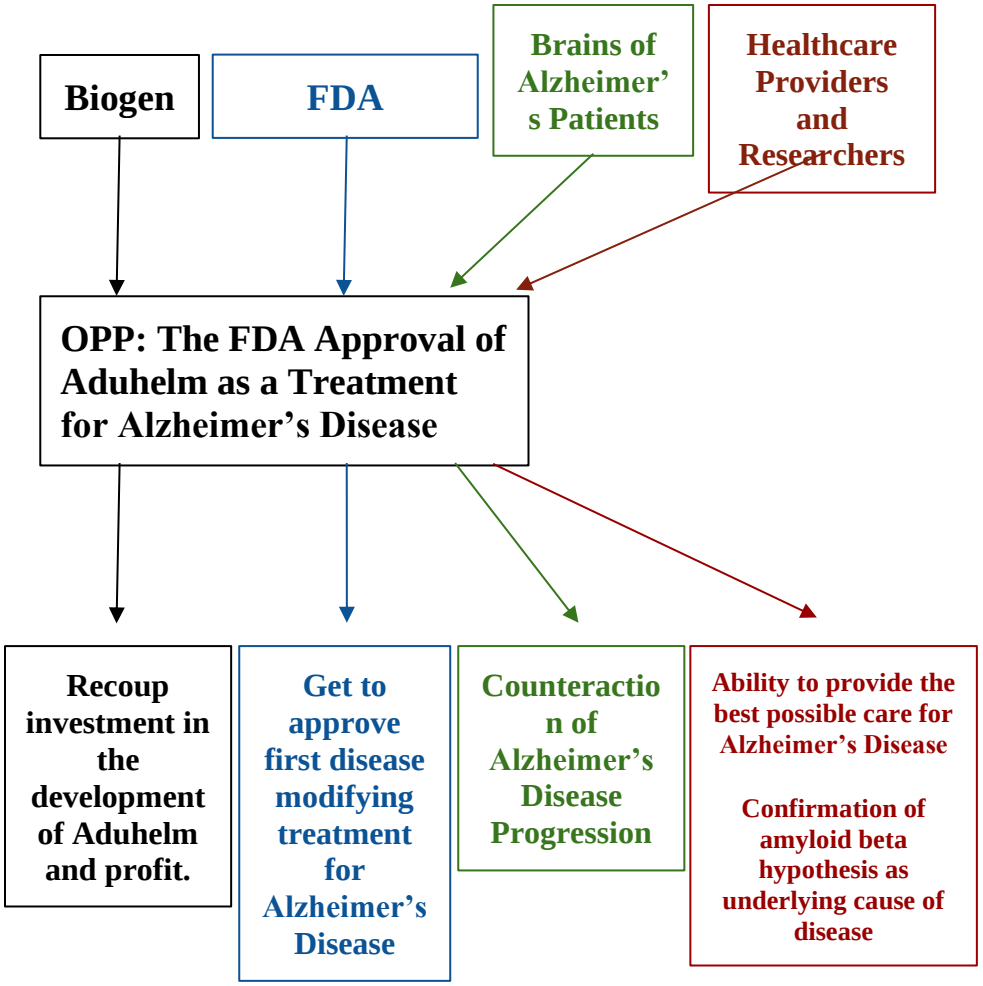

Figure 1. A depiction of Biogen's problematization of the primary actors within the network and their motivations in relation to the OPP.

Problematization

In March of 2019, an independent group of physicians returned the results of their futility analysis on the two Phase III trials (ENGAGE and EMERGE) of aducanumab's (Aduhelm) effect on Alzheimer's disease progression to Biogen. Biogen had high expectations based off of the massive reductions in both the Clinical Dementia Rating-Sum of Boxes (CDR-SB) and the mean PET standard uptake value ratio (SUVR) of amyloid plaques relative to control in their smaller Phase I trial, PRIME (Sevigny et al., 2016). To their disappointment, the pooling of both trial results resulted in a futile result that suggested that aducanumab would not achieve

statistically significant differences in CDR-SB reduction compared to placebo by the end of trials, and lead them to cancel the Phase III trials on March 21, 2019. Their stock fell 30% in response and there was talk of the company being acquired and spun off (Feuerstein, 2019).

However, while conducting statistical analyses to determine what could have gone wrong during the trials, they were surprised to find out that there was a clear significance with CDR-SB scores for EMERGE, but not ENGAGE. By separating trial data rather than pooling them together, the team under the head of research Dr. Sandrock gained confidence in the effectiveness of Aduhelm as a treatment and sought out help to recover from their canceled Phase III (Garde, 2021). As the principal actor of the network, the team at Biogen had to construct the presentation of the network in such a way to recruit the interests of primary actors to support the passage of the "indispensable" OPP: the FDA approval of Aduhelm as a treatment for Alzheimer's disease. The primary actors they targeted were the FDA itself, the brains of Alzheimer's patients and their response to Aduhelm, and the broader community of healthcare providers and researchers (**Fig. 1**).

At a convention of the American Neurological Association in May 2019, an off the books meeting took place between Sandrock and Dr. Billy Dunn, the director of the FDA's Office of Neuroscience within the Center for Drug Evaluation and Research (CDER). In it, Sandrock presented to Dunn that Aduhelm was a promising drug to serve patients suffering from a disease that did not have access to any drug that could affect disease progression, and that the FDA has a duty to support efforts to bring a drug like Aduhelm to market.

Additionally, Biogen represented themselves as integral to the advancement of science around Alzheimer's disease. There have been a number of competing theories about how the cognitive decline of Alzheimer's disease is mechanically caused in the brain, as while there are

associated protein plaques with the disease it is unknown if they are the actual cause of neurological issues or just merely a result of compromised neurons affected by the true cause (Agarwal et al., 2020). Aduhelm is an antibody that specifically targets and removes the malformed protein plaques of amyloid-beta, a transmembrane protein essential for neuron health. By associating a reduction of amyloid-beta plaques with less cognitive decline Biogen would have provided strong evidence for amyloid-beta as a cause, not a side effect, of Alzheimer's progression. And by using this drug after it is approved, physicians would be able to provide a disease modifying treatment that will make an actual difference in the course of the disease, rather than just treating symptoms like normal Alzheimer's medications. To provide the best care possible to patients, healthcare providers should be convinced by the evidence presented and support the FDA approval.

Biogen then also positioned itself as a drug with the only theoretical potential to slow down and reverse the damage caused by Alzheimer's disease to Alzheimer's patients. This should also make the OPP integral to the goal of counteracting the disease for patients and their brains, although in their role as data they are more instrumental than active actors in the network.

Interessement & Enrollment

Dunn was convinced that Aduhelm should be further supported and organized a meeting in June 2019 between regulators that would be reviewing the drug and the Biogen team developing and studying it. The FDA apparently eagerly accepted the role proposed in the problematization, even going beyond with the offer to help Biogen in the form of a collaborative working group. Meeting almost daily, regulators and Biogen employees would review the clinical data from Phase III trials to determine how to best rectify the inconsistent results between the two Phase III trials, even offering to potentially consider accelerated approval based

off of a proxy metric. This was essentially an offer to help the principal actor in their recruitment of the other actors, namely the response of Alzheimer's brains to Aduhelm and the community of healthcare providers and researchers, represented by the Phase III clinical data and an FDA advisory committee composed of outside experts, respectively.

To the Phase III data they had collected until cancellation, representing the clinical effect of Aduhelm on brains with Alzheimer's disease, Sandrock and Haeberleinn began to tease apart certain elements of the data to determine what was associated with clinical significance and what was not in collaboration with the FDA. In both ENGAGE and EMERGE, SUVR measures of the amyloid as well as tau plaques significantly decreased in response to higher doses, indicating that there was a clear clinical effect on the reduction of plaque in Alzheimer's patients. Additionally, they found that by just looking at high doses administered after a change in protocol in ENGAGE to line up with EMERGE, there actually was evidence for improved CDR-SB scores, providing some explanation of the discrepancies between EMERGE and ENGAGE (Budd Haeberlein et al., 2022; Wang, 2023).

After a year of analyzing data, a meeting by the Peripheral and Central Nervous System Drugs Advisory Committee took place on November 6th, 2020. With both the FDA and the clinical data accepting their locked position and enrolled in the network, the evidence was presented and the role was offered to the outside experts to support the findings of Biogen and the FDA about the muddled Phase III results. However, this alliance did not occur due to several disagreements about the conclusions of the data analysis by the joint FDA-Biogen presentation. The committee agreed that there was substantial evidence for reduced alpha-amyloid plaques based on SUVR values, but disagreed that this would be an acceptable alternative to a good clinical improvement in CDR-SB and held that the evidence provided did not necessarily support

the amyloid-beta cause hypothesis. The use of Aduhelm was also associated with increases in permeabilization of the brain, leading to local swelling and even mild brain bleeding in 40% of patients enrolled in trials, requiring that strong effects of treatments be presented to justify exposing patients to harmful side effects (Salloway et al., 2022). The detail about the change in protocol 4 leading to improved CDR-SB scores in the ENGAGE trials was disputed due to the low numbers of eligible patients to robustly represent that change. Additionally, some on the panel were concerned about the information packet about Aduhelm being jointly produced by the FDA and Biogen, which was highly unusual. A few members also resented that the line of questioning seemed to be targeted towards disputing the validity of ENGAGE and seemed to take the results of EMERGE at face value, rather than potentially EMERGE to be a false positive and ENGAGE to depict a true relationship between Aduhelm and CDR-SB scores. Ultimately, all on the advisory committee voted against the FDA approval of Aduhelm, excepting one abstention (Final Summary Minutes of the Peripheral and Central Nervous System Drugs Advisory Committee Meeting for aducanumab, n.d.).

Mobilization

The failure to recruit the support of external scientists did not stop the process towards FDA approval, however, as the Office of Neuroscience and the in-depth analysis of the phase III trials were mobilized to seek broader support within the CDER. Medical Policy and Program Review Council (MPPRC) meetings were held from March 21-April 7th, 2021 to discuss both the positive reviews done by the reviewers in the Office of Neuroscience as well as the decisions of the advisory committee in advising against the approval of Aduhelm. Persuaded by Dr. Dunn, the council eventually came to the agreement that there was substantial evidence to support Aduhelm's effectiveness against Alzheimer's disease. A center director briefing meeting

consisting of senior leaders in the CDER was held on April 26th to review an approach on approving Aduhelm using accelerated approval based on the evidence for the removal of alpha-amyloid plaques in SUVR results. There was broad agreement for accelerated approval across most of the directors within the CDER, with only the Director of the Office of Biostatistics, Dr. Sylva Collins, dissenting (Wang, 2023). On June 7th, 2021, Aduhelm received an accelerated approval for the treatment of Alzheimer's disease.

Accelerated approval based on a surrogate endpoint is originally intended to use clinically correlated markers to survival as a way to expedite the approval process for life saving drugs to save lives as fast as possible. A good example of a surrogate endpoint is reduction in tumor size as a surrogate point for the effectiveness of an anti-cancer drug as opposed to reduced mortality, which would cruelly require waiting for deaths to occur (Fleming, 2005). The use of a reduction in protein plaque of uncertain significance as a surrogate endpoint over an improvement in clinical symptoms as represented by the CDR-SB score was condemned by healthcare professionals, with many writing op-eds in journals to protest both the potential dangers of prescribing Aduhelm as well as the perceived corruption of the FDA approval process (Ebell & Barry, 2022; Karlawish, 2022). The broader community of healthcare providers and researchers may not have had an ultimate say against whether or not Aduhelm received FDA approval, but they were mobilized to betray the network by highlighting the irregularities in the FDA approval process as well as irreparably tarnish the reputation of Aduhelm as scandalous. The OPP was no longer accepted as a black box and it became suspect.

Conclusion

The ability for the FDA to construct a black box of verified safety around a product that the healthcare industry can rely on is contingent on the collective buy-in by professionals and

experts in the industry that the FDA is doing its due diligence. In the actor-network theory devised, the principal actor behind FDA approval was Biogen, the sponsor company behind the development of Aduhelm, however Billy Dunn's team within FDA was likely the most active and influential within the network to mobilize and influence others to have Aduhelm achieve FDA approval. Even during the advisory committee meeting, Dr. Dunn would sometimes step in to help Dr. Haeberlein from Biogen answer a question posed by the committee (Garde, 2021). The highly unusual practice of collaborative teams of Biogen and FDA workers making sense of the discrepancy between the ENGAGE and EMERGE trials raises questions about the independence of the FDA and the interests of Dr. Dunn.

The use of accelerated approval, which is becoming more and more common recently, allows for a company to run another Phase IV trial while also profiting from having their drug on the market. Almost a third of all accelerated approvals are overdue the deadline for the results of their Phase IV trial, and some worry that the accelerated approval program is being abused to sidestep a requirement of clinical benefit for some drugs. There is little enforcement to either take these drugs off the market or compel the drug sponsors to finish their studies, and so it presents a loophole for some companies to sell drugs that are unproven to unambiguously improve clinical results (Benjamin & Lythgoe, 2023).

If the FDA wants to preserve the faith that the system has in its authority and good judgment, it should be more adversarial against its drug sponsors. That is not to say that there can not be justified accelerated approvals, but the system should be reformed to be more stringent and strict. The FDA should not ask questions to review panels on the same side as a drug sponsor, but should instead be impartial and take the input of the review panel in good faith. As for Aduhelm, it was voluntarily taken off of the market by Biogen due to the lack of medicare

funding and bad press from healthcare professionals (Dyer, 2024). However, Biogen's approved successor drug Leqembi also targets alpha-amyloid plaques and has led to unambiguously improved CDR-SB scores, perhaps implying that Aduhelms similar mechanism of action may actually have worked and the ENGAGE trial was flawed. But it doesn't change the flaws that surrounded the approval process of Aduhelm.

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