What Could Explain the Delay for Age-Reversal Clinical Trials?

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Abstract

This is a commentary article using data reported by the United States Drug Approval (FDA) system for clinical trials. The data show continued delays that impact drugs reaching patients. Instead of increasing drug approval, the statistics showed a trend of increased numbers of drugs on hold. The reasons for these delays need to be evaluated, and perhaps new technologies need to be applied to evaluate the data. This editorial summarizes some of the ways to resolve these needless delays.

Keywords: Food and Drug Administration, drug approval, clinical trials, investigational new drug.

The topic of the United States Food and Drug Administration (FDA) overregulation has been debated for decades. In recent years, however, the volume of novel biomedical approaches has overwhelmed the FDA to the extent that record numbers of human studies are placed on "clinical hold" [1]. I have protested these delays since the early 1980s, but the FDA now admits that it is stopping certain human research because the "technology is just so new" [2]. These new technologies are desperately needed for scientists to engage in

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Table 1 Timeline: Clinical Trials on Hold

Years	Average Clinical Trial Holds/Year
2002–2021	664
2017–2020	557
2021–2022	747

Shown are the data of reported clinical trials that were placed on hold.

novel research to slow and reverse pathological aging. To accomplish this goal, the Food, Drug and Cosmetic Act will require amendments. Alternatively, the FDA can enact internal "opt out" regulations, similar to the method applied with HIV in the 1980s–1990s. This "opt-out" FDA policy enabled effective treatments to quickly develop for what was then a universally fatal disease, as advanced aging is today.

Table 1 summarizes the current clinical trial holds as reported in the *Wall Street Journal* on January 11, 2023. The table shows the FDA's increased propensity to halt clinical trials due to the inability of the agency to understand the innovations, since the technology is 'new'. The FDA's admissions of its technology deficits are not new. Current and former FDA commissioners have complained that the agency is incapable of understanding or evaluating novel approaches to disease prevention and treatment. The former FDA commissioner, Dr. Andrew von Eschenbach agreed that the FDA needs modernization for rapid and efficient approval for patients (https://www.lifeextension.com/magazine/2012/12/former-fda-commissioner-admits-risk). This sentiment was echoed by Dr. Margaret Hamburg, who believed the outdated method was causing a significant delay in drug approval (https://www.lifeextension.com/magazine/2012/12/former-fda-commissioner-admits-risk).

The FDA's rejection or delay of innovation has been an ongoing discussion. The CATO Institute (cato.org) and other think tanks have harshly criticized the delay and outright denials of lifesaving therapies caused by inappropriate FDA policies for many decades. Similar concern was reported by peer-reviewed journals that supported needed reform at the FDA [3, 4].

In 2023 at the HEALINC conference in Nassau, Bahamas, I revealed the historic and current data showing that humans are needlessly suffering because of inappropriate delays or outright rejections by an antiquated bureaucracy. Indeed, the FDA continues to be considered by many to be the world's foremost institutional authority for evaluating and approving

controlled clinical trials. To put the clinical trials model in perspective, it was only in the early 1900s that concepts of well-controlled clinical trials were seriously conceived. Prior standards often relied on medical observations and weak methodological design. Execution and analyses often lacked the rigor of randomized placebo-controlled double-blind studies considered the gold standard of research today. Throughout the 20th century, incremental improvements were made in attempts to better evaluate safety and efficacy of new drugs and other medical technologies. The FDA was given increasing authority over study design and execution including the ability to deny an Investigational New Drug (IND) application, place a clinical hold on human trials that were initially approved, censor what clinical trial investigators can convey to study participants, the media, and the public, and to reject findings from clinical trials that were approved by the same body. These regulatory mandates served to identify safety issues and/or lack of efficacy prior to a new drug being marketed. Despite the good intent to ensure safety, there could be insidious downsides with increased regulatory authority of the FDA.

As the U.S. Congress granted the FDA more arbitrary power, the agency enacted bureaucratic mandates that impede the ability of Americans to gain access to lifesaving medications. This is underscored by succinct descriptions of how America missed averting the thalidomide health disaster largely because of internal FDA delays [5]. Largely because of the thalidomide debacle, Congress granted the FDA more regulatory authority. Although this was progress, it resulted in lifesaving drugs being delayed, rejected, or in most cases, drugs that might be effective not making it through the FDA's approval labyrinth. The latter is mostly due to the high costs of complying with increasingly stringent regulations. A widely cited example is beta-blocker drugs that save significant numbers of American lives each year. However, such approval was delayed by the FDA even though years of use showed beta-blockers to be safe in other countries [6–8].

If the FDA approves a drug with unanticipated dangerous side effects, the victims of their mistake will be highly visible. There may be congressional hearings, embarrassment to the agency, and officials fired. On the flip-side, if the FDA errs on the side of over-caution and either disapproves or delays a drug that is safe and effective, the victims are invisible. The victims of overregulation will have no idea that their suffering could have been eliminated, or in the case of death, the public will have little idea why they died. Their suffering and/or death will be considered incurable rather than the result of a delayed or rejected FDA drug application. Doctors will say that nothing could have been done, without accountability. The aforementioned

discussion underscores how the policy could delay/deny multi-interventional clinical trials in the aged. The FDA requires safety data to protect those whose life expectancy may be measured in months or less [9]. There are decades of discussions to elucidate how to accelerate lifesaving innovations. The latter should ensure protecting study participants from what the FDA considers to be potentially dangerous compounds, but should give careful consideration to combinations of relatively safe compounds that may already be used in clinical practices, but without meticulous human study evidence to substantiate safety/efficacy of these combinations.

It is the opinion of this author that it may be possible to address the issues discussed. It is widely known that the leading causes of death among the citizens of advanced nations relate to what has been considered normal aging. In those who do not die from a degenerative illness or other cause, the aging process itself results in termination of life in 100% of humans, since there is no survival with advanced aging. Experimental therapies exist today that may delay or reverse certain normal aging processes. Volunteer study participants and various organizations would like to initiate experimental interventions with fully informed patient consent and Institutional Review Board (IRB) approval. These agencies have opted out of the FDA's clinical trial approval process that increases research costs while delaying implementation of multi-modal experimental interventions. Study participants will be fully informed that these regenerative medicine experimental or non-medical nutritional studies have not been reviewed by the FDA for safety, and therefore may pose significant health risks. Publication of the findings from these clinical trials will clearly state that the design, execution, analyses, and all other aspects of these IRB-approved, Informed Consent-granted clinical trials have not been reviewed by, nor approved by the FDA for safety or efficacy. Some trials will deal with one or more repurposed drugs that are already FDA- approved, or with experimental compounds that have not been extensively studied in humans.

There are compelling research studies with the potential for treating the aged. This could be combined drug, gene, and cell therapies [10, 11]. Such therapies could be accommodated by regulatory bodies such as the FDA. In the 1980s, HIV activists advocated for the FDA to think differently about the way it assessed drug efficacy. AIDS activists wanted the FDA to formally authorize the use of surrogate data markers, data points that indicate patients are benefiting, without definitive proof they are surviving longer. The agency agreed and in 1992, initiated the Accelerated Approval Program that allowed for faster approval of drugs for HIV and other life-threatening

conditions [12]. AIDS was a universally fatal disease in the 1980s–1990s. Beyond formal acceleration of AIDS research, the FDA compromised and allowed AIDS patients to try any intervention that might be effective. The result was rapid development of effective therapies and almost immediate recognition of worthless treatments. A similar approach can easily be taken today whereby the FDA could agree to have similar regulatory oversight for aging studies.

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