Impacts of First-in-Class Drug Approvals on Future in-Class Innovation

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KEY TAKEAWAYS

- Some claim that FDA approval of drugs with uncertain efficacy today will slow future innovation. In fact, the relationship is much more complex.

- Five main factors determine the degree of innovation effort within a disease class: (1) probability of success, (2) size of the patient population, (3) expected post-launch market share of the drug given the possible or actual presence of competitor drugs, (4) expected cost of development and (5) innovator's cost of internal or external capital.

- Approval of the first drug in a disease area or drug class is likely to stimulate future innovation by sending a positive signal to innovators and expanding the patient population.

- However, approval of highly effective, breakthrough drugs can reduce clinical trial participation, leading to increased development costs for future drugs.

- Economic theory and empirical evidence do not support the broad conclusion that approvals of drugs with modest or uncertain efficacy harm innovation or make society worse off.

ABSTRACT

Some critics argue that the U.S. Food and Drug Administration (FDA) has relaxed its evidentiary standards by approving drugs with uncertain efficacy. A recent case in point is the investigational Alzheimer's disease (AD) drug under priority review at the FDA. If approved, aducanumab would be the first disease-modifying treatment for AD. But variation in its clinical trial results produced uncertainty about the precise clinical benefits of the treatment. These results have led some to raise concerns mirroring longstanding arguments about approvals for drugs of uncertain efficacy for diseases with high unmet need. Notably, the recent criticisms feature a new argument that approving drugs with uncertain efficacy today will slow the arrival of innovations tomorrow. We explore this argument by analyzing the underlying economic forces that shape the relationship between FDA approvals and future innovation. We identify multiple factors that together determine the outcomes in specific cases and show that both the relevant economic theory and empirical evidence suggest a complex relationship between FDA approval decisions and future innovations, including the possibility that aggressive approval decisions can stimulate, rather than deter, the arrival of effective future innovations.

A growing chorus of critics is charging that the U.S. Food and Drug Administration (FDA) has relaxed its evidentiary standards for drug approval.[1] Of particular focus have been FDA decisions in areas of acute unmet medical need, like Duchenne muscular dystrophy.[2, 3] Such clinical contexts pose a dilemma for regulators committed to protecting and improving patient health. When few or no clinical alternatives exist, patients and their physicians clamor for access to novel, first-in-class innovations, even when their precise clinical benefits may be uncertain.

A recent case in point is the investigational Alzheimer's disease (AD) drug aducanumab under priority review at the FDA.[4] If approved, aducanumab would be the first disease-modifying treatment for AD. At the same time, variation in its clinical trial results produced some uncertainty surrounding the precise clinical benefits of the treatment.[5] Some have raised concerns about the potential approval of aducanumab, mirroring some longstanding arguments about approvals for drugs of uncertain efficacy for diseases with high unmet need.[5, 6] Yet the recent criticisms also feature a new argument, namely concern that approving drugs with uncertain efficacy today will slow the arrival of innovations tomorrow.[7, 8] Somewhat ironically, this argument itself rests on an uncertain evidence base. Economic theory and empirical evidence suggest a more complicated relationship between FDA approval decisions and future innovations, including the possibility that aggressive approval decisions can stimulate the arrival of effective future innovation. In this paper, we set forth and analyze the underlying economic forces that shape the relationship between FDA approval policy and future innovation, illustrating the complex interplay of factors that in concert determine the outcomes in specific cases.

BACKGROUND

Unmet medical need is characterized by the lack of effective treatments or therapies to address a disease or medical condition.[9] In some cases, the need persists because the patient population is small and incentives to develop new treatments are correspondingly weak. However, data suggest that the Orphan Drug Act of 1983 encouraged innovation in these rare disease areas,[10] so many of today's diseases with high unmet medical need reflect the difficulty of treatment rather than simply weak incentives to innovate. Effective treatments for serious and highly prevalent conditions like acute heart failure,

AD and endometriosis have eluded drug makers for years, in spite of numerous attempts.[9, 11] In these contexts of high unmet need, the FDA faces difficult approval decisions in the presence of data suggesting modest efficacy because the cost of non-approval is higher when patients have fewer existing treatment options and because the expected value of waiting for the next drug candidate is lower in diseases with high rates of drug candidate failure.

For example, in 2016 the FDA faced a difficult decision over whether to approve a novel drug to treat Duchenne muscular dystrophy, a disease in young boys that causes progressive muscle weakness resulting in the inability to walk and in early death. The FDA's advisory committee voted that there was insufficient evidence of the drug's clinical efficacy to support approval. Debate within the medical community at the same time centered around possible health risks associated with the drug and whether approval was warranted. However, the FDA ultimately approved the drug, conditional on further testing in clinical trials.

While the two cases differ in several important respects, the current FDA review for aducanumab shares some similarities with the Duchenne example. In particular, both exhibit great unmet patient need, yet the efficacy data for both drugs failed to convince the majority of the advisory committee.[4, 6] However, the concerns voiced during and after the latest meeting to discuss aducanumab took on a new theme absent from the Duchenne discussion. Several committee members warned that a quick approval for an AD drug would harm future innovation and risk delaying the arrival of more effective treatments.[8] They argued that aducanumab's approval would cause companies to refocus development efforts into amyloid-based approaches to treating the disease despite the many drug failures with this approach in recent years. The fear, therefore, is that aducanumab's approval would distort the decisions of other innovators and draw too much investment into amyloid-based approaches, rather than focusing on alternative approaches to disease modification such as anti-tau therapies.[12] If true, other potentially more promising treatment approaches might be abandoned or delayed. Concerns have also been raised about the impact that an approved drug will have on current and future AD clinical trials.[i, 13] If patients can take aducanumab, they may be less motivated to enroll in new studies.[14] We study the economic evidence underlying these arguments.

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i Some have raised concern that the FDA will require current or future drug candidates to use aducanumab in their comparator arm. However, the FDA does not state this requirement in its guidelines, and a historical review of follow-on drugs' clinical trials suggests that it takes many years for a new drug to become standard of care and replace prior control arm therapies.

OVERVIEW OF DRUG INVESTMENT AND R&D DECISIONS

We analyze the potential impacts of FDA approval decisions on future drug development by first examining the economic theory of medical innovation and investment decisions. Potential investments are evaluated by comparing expected revenues and required capital investment. For drug development, investment decisions are complicated by uncertainty in obtaining FDA approval, which contributes to uncertainty over revenues. On average, only 10% to 14% of drugs that enter phase I clinical trials eventually go on to receive FDA approval.[15, 16] Additionally, approval rates can vary dramatically based upon the disease class or drug type. Vaccines for infectious diseases have an approval rate close to 33%, while only 3.4% of investigational cancer treatments are eventually approved.[15]

To formalize the theory of drug investment a bit, let R denote the cost of capital per dollar invested. Then the relevant condition for a potential drug to attract investment is:

(1)

where the expected net revenues for drug investments are a function of the potential market size for the drug, the market share the drug can expect to achieve if approved, and the likelihood of FDA approval.[ii] Thus, in this stylized model, five main factors determine the degree of innovation effort within a disease class: (1) the probability of success (i.e., FDA approval), (2) the market size (i.e., the total patient population), (3) the expected post-launch market share of the drug given the possible or actual presence of competitor drugs, (4) the expected cost of development and (5) the cost of capital, R. The first three factors impact expected net revenues, the fourth determines expected capital investment cost, and the fifth determines the cost of capital, R. In what follows, we explore the potential impacts of the FDA's approval decisions for first drugs in diseases with high unmet medical need, such as AD, on each factor in equation **(1)**.

THE PROBABILITY OF SUCCESS

FDA approval for the first drug in a disease area or drug class sets a precedent that informs expectations about the likelihood of future approvals. It provides information about

the minimum level of efficacy needed to obtain approval. As such, the approval of a first-in-class drug with modest efficacy sends a positive signal to innovators about the likelihood of future drug approvals within both the disease area and the drug class. In turn, this signal increases expected revenues from innovation investments in this area.

For example, hundreds of AD drugs failed to achieve FDA approval, including six high-profile, amyloid-based drugs across nine phase III trials, between 2016 and 2019 alone.[17] This history of failure led many to conclude that any new amyloid-based AD therapies would be similarly unsuccessful, likely causing companies to scale back their development efforts in this category.[18, 19] If the converse is also true, FDA approval of the first disease-modifying treatment for AD would lead drug developers to revise upward their expectations of approval likelihood for future AD drugs—both amyloid-based treatments and other approaches.

MARKET SIZE

Innovation efforts increase with the expansion of total market size, which depends not only on the patient population but also on a patient's (or their insurer's derived) willingness to pay.[20] AD exhibits high prevalence and significant unmet treatment need, along with strong demand for new and effective drugs. In other words, the potential market size for AD therapies is substantial. According to the Alzheimer's Association, 5.8 million Americans over age 65 are living with AD, and another 15% to 20% of that population lives with mild cognitive impairment. In 2020, AD and other dementias in patients 65 and older were estimated to cost the U.S. $305 billion, a figure consistent with previous estimates over a similar patient population.[21] Despite the huge unmet medical need in AD, as of yet no approved treatments prevent or slow its progression.[22]

Additionally, market size may increase following the first drug's approval. The arrival of a disease-modifying therapy will strengthen incentives for patients with mild symptoms to seek a diagnosis and thus enter the market for treatment. HIV serves as a useful example in that the arrival of highly active antiretroviral therapies led to greater demand for HIV testing.[23, 24] Additionally, the manufacturer of a newly approved drug is likely to promote it through direct-to-physician and direct-to-consumer advertising, further expanding the market.

Moreover, empirical research shows that new drug introductions themselves may expand the number of patients

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ii *We abstract from costs of production and distribution, as these are unlikely to vary with the factors we study.*

treated within a disease class, because new drugs may expand the number of patients who respond to or can tolerate the therapy. Prior analysis shows that new drug launches for top-selling drugs increase the number of treated patients by an average of 20%.[25]

MARKET SHARE OF FUTURE DRUGS

The net impact of an FDA approval decision on the potential market share for future drugs is less clear and depends on how directly future drugs will compete for patients with the approved drug, the incremental efficacy improvements brought by future drugs, and the elasticity of patients' and physicians' demands with respect to drug quality. These factors can vary greatly across diseases and drug classes.

For example, some researchers fear that the first AD drug approved will capture a large share of the market and dramatically shrink the market share available for subsequent AD drugs. Certainly, we would expect the first drug approved for AD to have strong uptake among indicated patients. But there are countervailing effects to consider. The first AD drugs to market will likely focus on narrow patient populations, at least initially, as they attempt to halt or reverse disease progression. To date, the focus has been largely on early-stage AD patients who are already symptomatic, because they are easier to identify and eager to obtain treatment.[5] These patients represent only a fraction of the AD population, and exclude the large prodromal or asymptomatic patient population that will likely be identified at higher rates as AD biomarker testing becomes faster and less expensive.[26] Thus, future AD drugs may serve different market segments than those in late-stage development today.

Even follow-on AD drugs that would compete for the same patients as a first-approved drug are unlikely to be deterred by the prior approval, because a drug that can establish greater efficacy than the first-approved drug may quickly supplant it as the drug of choice. The responsiveness of patients and their physicians to introduction of a new drug with superior efficacy depends on the risks associated with medication switching. For example, physicians are often reluctant to switch antidepressants when patients are stabilized because the risks of nonresponse to the new medication could be dangerous, and patients may experience withdrawal symptoms during the switch.[27]

Indeed, concerns about the innovation effects of aducanumab approval rest principally on the notion that more effective drugs will be stymied in the development pipeline by the current approval. However, AD patients and their physicians may be quite sensitive or elastic in their response to drug quality in this space, meaning that they will switch to new drugs with superior efficacy or better toxicity profiles as they become available. Thus, an initial drug approval need not imply that future drugs will earn less revenue as a consequence, particularly if the future drugs serve broader patient populations or demonstrate greater efficacy.

THE COSTS OF CAPITAL

The capital investment required to develop a drug depends on the costs of research and development, undertaking clinical trials, marketing and distribution, and the risk-adjusted interest rate or cost of capital. The empirical evidence suggests that pharmaceutical innovators face imperfect capital markets in which the costs of external capital exceed the costs of internal capital. That is, capital borrowed from lenders or raised from investors comes at greater cost than capital generated internally via the cash flows of an existing business. For instance, several studies have shown that the most important determinant of R&D spending is current cash flow, which likely implies that firms regard internal capital as less costly than securing external capital. Defining R_I and R_E as the costs of internal and external capital, respectively, this implies that $R_I < R_E$.[27, 28] As a result, innovators with limited access to internal capital may face higher capital costs and thus require higher expected returns to go forward with a potential investment than those with greater access.[29] Because of constraints on internal capital, it is at least theoretically possible that the pursuit of one new drug candidate exhausts internal capital and thus makes it costlier to pursue another, as some have suggested.[30]

Although companies' internal capital is limited, we are not aware of evidence suggesting that capital constraints are limiting pursuit of promising treatments in areas of high unmet clinical need. Companies that exhaust internal capital can and will turn to more expensive external capital as long as the expected return on their marginal research projects exceeds the cost of that external capital. All projects with sufficiently high expected returns will find capital investment either using internal or external sources. In fact, in 2019 the pharmaceutical industry spent $186 billion on R&D, and that investment is expected to grow to $230 billion by 2026.[31] The top 10 companies alone spent $82 billion collectively in 2019.[32] Similarly, startup biotech companies without deep pockets have demonstrated tremendous success in accessing venture capital, including from wealthy entrepreneurs like Jeff Bezos and Bill Gates.[33, 34] Thus, one project crowds out another only in the limited case where both projects satisfy equation (1) for R_I, but neither satisfies it for R_E.

THE COST OF DRUG DEVELOPMENT

While FDA approval of a new drug does not directly impact the costs of developing future drugs, if that approval impacts companies' abilities to enroll patients in future clinical trials for experimental drugs, it could increase those costs. This may be a salient issue in AD, where innovators have faced trial recruitment challenges in the past.[35-37] The disease impacts elderly patients who have a high rate of comorbidities and other medication usage, and thus many are disqualified from participating in trials. Trials also frequently require patients to have a partner (caretaker) who can accompany them to visits, further raising the costs of participation and shrinking the pool of those eligible. Detection has also been a barrier to enrollment. Without approved therapies to modify the disease process, patients have weaker incentives to seek a formal AD diagnosis. This challenge only increases as the industry moves toward earlier interventions in the disease process when disease detection is most difficult.

More generally, it is not clear that a modestly effective drug approval would meaningfully reduce trial participation incentives. The existing literature demonstrates that the approval of highly effective, breakthrough drugs did reduce clinical trial participation in the cases of HIV and hepatitis C.[14] However, we are not aware of evidence applicable to drugs of modest incremental efficacy. Clearly, drugs with more limited efficacy will have correspondingly weaker effects on incentives to participate in clinical trials.

Finally, improvements in diagnostic technology may also mitigate trial recruitment challenges in AD specifically. To date, expensive PET scans have been used to identify beta-amyloid plaques in patients' brains, along with other biomarkers indicative of the disease and sometimes required as a condition of trial participation. Fortunately, in fall 2020 a new blood-based test was introduced that can identify the state of amyloid plaque in the brain.[38] This new technology may reduce the costs of clinical trial enrollment.

EVIDENCE FROM OTHER DISEASE CLASSES

Lastly, although there are examples of first-in-class therapies that have gone on to become blockbuster drugs that achieve significant market share (e.g., Gleevec to treat leukemia), it is relatively common for follow-on drugs to become industry leaders. An analysis of recent drug launches revealed that follow-on drugs (i.e., not the first drug in the class) earn the largest market share in more than 50% of the drug classes studied.[39] This is consistent with suggestions that a first drug approval may pave the way for more effective drugs in the future. For example, the top-selling drug in 2019, Humira, was actually the third drug approved for treatment of rheumatoid arthritis, introduced four years after drugs by Johnson & Johnson (infliximab) and Amgen (etanercept).[40, 41] Lipitor (atorvastatin) is another frequently cited example of superior efficacy winning over the market.[43] It was the fifth statin brought to market, introduced more than nine years after the first statin, Mevacor (lovastatin), was approved, but it remains, after more than 20 years, the most prescribed anti-cholesterol medication in the world.[42] In sum, it is difficult to find specific evidence that first-in-class drugs, particularly ones with modest efficacy, inhibit innovation or that first-in-class drugs tend to crowd out subsequent discoveries.

CONCLUSION

To date, data limitations have resulted in little empirical evidence about the effects of drug approvals and failures on future in-class innovation. Considerable uncertainty remains about the effects of modestly efficacious first-in-class drug approvals on future innovation. We have shown that economic theory and empirical evidence do not support the broad conclusion that approvals of modestly efficacious drugs harm the innovation process or make society worse off. Rather, a case-by-case evaluation is needed wherein the various factors set forth here can be quantified and weighed.

In small disease markets like that of Duchenne muscular dystrophy, the crowd-out impact of initial drug approvals could be a serious concern, because first-in-class drugs may find it easier to garner a large market share. Even in these markets, however, decisions to continue to invest in new drugs may depend heavily on the elasticity of patient and physician demand to drug quality. More generally, the relationship between current drug approvals and future innovation is complex. There are many reasons to believe that first-in-class approvals stimulate future innovation rather than suppressing it. While mitigating factors do exist, like the possibility of dampening clinical trial recruitment, existing evidence does not justify the contention that the approval of marginal drugs today systematically harms incentives for future innovation. The opposite effect may be at least as likely.

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