VIEWPOINT

Accelerated Drug Approval and Health Inequality

Alex John London, PhD
Department of Philosophy and Center for Ethics and Policy, Carnegie Mellon University, Pittsburgh, Pennsylvania.

Jonathan Kimmelman, PhD
Studies of Translation, Ethics and Medicine (STREAM), Biomedical Ethics Unit, McGill University, Montréal, Quebec, Canada.

Corresponding Author: Jonathan Kimmelman, PhD, Studies of Translation, Ethics and Medicine (STREAM), Biomedical Ethics Unit, McGill University, 3647 Peel St, Montréal, QC H3A 1X1, Canada (jonathan.kimmelman@mcgill.ca).

In the United States, there is considerable political momentum for accelerating access to novel medications. Faster access is often portrayed as increasing fairness by providing treatment options to patients who currently lack them. There has been scant attention, however, to the broader effects such proposals would have on equity within health care and research.

The most important product of the drug development process is the evidence base about how to use potential new medications. This evidence base also informs further research.[1] This information includes which patients to treat, at what dose, and with what other treatments. It also includes estimates of the benefits and risks of appropriate use of the drug. Approving medications with data from fewer patients or patient-years of exposure diminishes this information base and increases the remaining uncertainty about benefits, risks, and use of a new medication. The costs and burdens of this additional uncertainty are unequally distributed in 4 ways.

First, earlier drug approval directs the burdens of medical uncertainty toward groups of people who are often disadvantaged. The amount of research conducted on a new medication determines how much information is available to guide its use. The United States already provides the fastest approval for new drugs in the world,[2] with almost a quarter of drugs approved in 2015 receiving approval through either breakthrough or accelerated pathways. Even under current laws and regulations, licensing approval is often based on trials of modest size, or single pivotal studies.[3] Patients enrolled in many studies are selected based on strict eligibility criteria; for instance, they are often healthier than the patients in whom the drug will typically be used. As a result, the evidence base available for guiding the use of novel drugs for other groups of patients is already thin.

Earlier approvals would amplify these inequalities. In early phase trials, the elderly, disabled, or ethnically diverse persons; women; and patients taking multiple medications are especially underrepresented,[4] in part because drug developers seek to minimize comorbidities or drug interactions that might derail research programs. Under proposals for accelerated approval, such patients will confront increased uncertainty and risk compared with men, people who are middle aged, or patients who may be healthier. Ironically, in some cases such "underrepresented populations" constitute the majority of the intended treatment population. In cancer, for example, roughly 60% of new cases occur among people aged 65 years or older.[5] Some previous efforts to accelerate drug approval have been associated with black-box warnings for groups of patients, such as rituximab for patients with hepatitis B exposure.[6,7]

Some legislation that aims to accelerate drug approvals, such as the 21st Century Cures Act, proposes to improve the evidence base for treating groups of people who have traditionally been underrepresented by promoting their inclusion in trials. Increasing diversity within trials is an important goal that the US Food and Drug Administration (FDA) is taking steps to advance.[8] However, the aspirations of accelerated approval and increased diversity in preapproval studies conflict. Permitting approval on the basis of data from fewer patients or from fewer patient-years of exposure, reduces the power of studies to detect differences in risks and benefits in relevant subgroups. Similarly, relying on trials that exclude patients who are elderly, who take multiple medications, or who have comorbidities leads to studies that have limited statistical power to detect differential effects in these groups. To accelerate approval, studies involving underrepresented groups would have to be conducted after drugs are approved, an approach that is problematic.

Second, earlier drug approvals strain the capacity of the health care system to distribute health care resources fairly. For pharmaceutical manufacturers, market approval represents a shift from spending money to conduct trials to earning money from product sales. Because incentives to conduct additional trials are vastly diminished after licensure and regulatory enforcement is lacking, the pace of drug company follow-through with postapproval trial obligations is often glacial. For example, 18 years after the accelerated approval of midodrine hydrochloride for symptomatic orthostatic hypotension, postapproval efficacy studies mandated by the FDA had yet to be completed.[9]

After marketing approval, the costs of reducing uncertainty about the benefits and risks of drugs are typically borne by health care organizations and research funded by government organizations. Health systems, however, are designed to deliver care, not to generate reliable medical evidence. Practices like blinding, randomization, or standardized-event recording are more difficult to implement in systems that are oriented toward care. Health care systems represent inefficient environments in which to learn about differential effects of novel drugs.

Disparities in health information for different patient groups could persist for long periods and be difficult to eliminate. Health systems could attempt to address them, but this would require a substantial shift of resources from delivering therapies toward evidence generation (eg, training physicians to record outcomes in a standardized fashion), further straining the resources available for care. Alternatively, publicly funded research systems like the National Institutes of Health could fund research to reduce residual uncertainties. Although this approach is more likely to produce reliable evidence efficiently, government agencies have limited resources and competing funding

priorities, including sponsorship of research not normally supported by drug companies.

Third, accelerating approval for new drugs socializes more of the costs of uncertainty, while private entities profit from new drug development. Many of the costs of uncertainty shift at the point of licensure from developers to those purchasing new drugs. Whether through out-of-pocket expenses, the costs of health insurance, or tax dollars, consumers bear both the cost of purchasing new medications and a larger share of the costs of generating the information needed to maximize the clinical benefit of these drugs.

It might be argued that this shift in the distribution of drug development costs is justifiable as a means of encouraging companies to research treatments for difficult-to-treat or rare diseases. However, there is no assurance that companies would invest in such efforts instead of focusing on other research areas or merely returning profits to shareholders.

Fourth, accelerating the drug approval process would shift the burdens of uncertainty away from study participants who are provided with a relatively rigorous and comprehensive process of informed consent. In research, institutional review boards and other oversight bodies ensure that uncertainty is explicitly communicated to study subjects. This respects the autonomy of participants by giving them the opportunity to accept or decline risks in light of an adequate understanding of relevant information. Consent procedures for trials prior to the licensure of drugs are often especially rigorous. Although informed consent should be an important component of all medical care, disclosure is often less demanding in care settings and is not subject to prior review. Indeed, some proponents of mechanisms that integrate care and research, like "learning health care systems," have advocated more lenient consent processes.[10]

The ability of health systems to safely and effectively treat diverse groups of people is an important issue of public policy. So too is the ability to contain health care expenditures and allocate them efficiently. Marketing approval for new medications represents a turning point in which costs and burdens associated with medical uncertainty shift from sponsors and research subjects to health systems and treatment populations. Accelerating the point at which approval takes place reduces the quality and relevance of medical information in a way that has substantial implications for the productivity and efficiency of the research and health systems.

Without corrective measures, accelerating market approval for new drugs may make the process of reducing health care disparities more costly, more burdensome to patients, and more protracted. Further evidence collection is likely to occur in settings where patients are less well protected by rigorous informed consent processes. Debates about accelerated access have inadequately addressed these broader effects on equity in health care and research.

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