

# Government Support of Meaningful Drug and Device Innovation: Pathways and Challenges

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**Abstract:** The US government supports drug innovation. It is therefore crucial that it distinguish between high-value and low-value innovation in purchasing expensive prescription drugs and medical devices and ensure the continued discovery of transformative drugs and that patient and taxpayer funds are not wasted.

The US government plays an essential role in pharmaceutical innovation. The goal of this piece is to review recent steps that the government has taken to incentivize meaningful drug innovation, while trying to ensure that vulnerable patients are not exposed to ineffective new drugs or devices sold for high prices.<sup>1</sup>

## Role of the US Government in Supporting Patients' Access to Transformative Drug Innovation

The greatest source of pharmaceutical innovation in the world is the National Institutes of Health (NIH). A new medication or biotechnology drug usually emerges from a long course of research that starts with pivotal

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basic science discoveries, followed by translational and applied studies, product development research, and clinical testing. While the contribution of industry-based research to drug development remains vital, NIH funding to academic medical centers and discoveries made in government laboratories provide extensive contributions to drug development. According to one review, every single drug approved by the Food and Drug Administration (FDA) from 2010 to 2016 could be traced back to funding from the NIH in some way.<sup>2</sup> In another review of 356 FDA-approved drugs from 2010 to 2019, investigators linked NIH funding to 354 (99.4%), calculating that on average public funding of basic or applied research contributed about \$1.44 billion per approval.<sup>3</sup>

Much NIH support is focused on drug discovery and the early stages of development, which is when private funding is least available because it is where the greatest risk lies. Activities at these stages include describing the pathophysiology of diseases, charting biochemical pathways that could be modulated, isolating druggable targets on proteins, and developing systems to allow for *in vitro* testing of potential lead compounds that could serve as therapeutics. For example, in the case of direct-acting antivirals that offer a nearly fully effective cure for chronic hepatitis C virus infection, there was at least \$60.9 million in NIH funding closely related to the development of sofosbuvir (Sovaldi), including developing hepatitis C virus cell culture systems and growing the virus *in vitro*.<sup>4</sup> Many large pharmaceutical companies have actively moved away from this sort of work in recent years, making the contributions of the NIH even more essential to the identification of new treatments.

In addition, public funding can also include substantial impact in later stages of drug development, including proof of concept testing and even the pivotal clinical trials leading to FDA approval. In a review of drugs approved from 2008 to 2017, 25% (62/248) were connected with patents or other late-stage intellectual contributions from publicly-supported research institutions.<sup>5</sup> Among 69 new biologic agents approved by the FDA during the same time period, 29 (42%) had late-stage contributions from public-sector institutions or originated from a public-sector spin-off company.<sup>6</sup> Drugs with links to late-stage public funding were more likely to receive expedited FDA approval or be designated first-in-class, two markers that often indicate therapeutic importance. A recent review of NIH records connected to use of the drug tenofovir disoproxil fumarate-emtricitabine (TDF-FTC, or Truvada) as HIV pre-exposure prophylaxis (PrEP) found that the key original work was based at the Centers for Disease Control and Prevention (CDC), and pivotal research evaluating use of the combination was supported by an estimated \$143 million of highly-related direct NIH funding, for example covering the key trials helped establish TDF-FTC's clinical efficacy for PrEP.<sup>7</sup> As yet another example, over the course of nearly four decades, the active ingredient in buprenorphine was synthesized by a pharmaceutical manufacturer, but it was developed for opioid use disorder primarily by investigators in government and academic centers, including a formal government-industry partnership for commercialization. Nearly \$40 million in highly related NIH went to institutions and investigators supported the development of buprenorphine as a treatment for opioid use disorder.<sup>8</sup>

The essential role of the government in supporting drug innovation is particularly notable in the development of transformative drugs — those that are both innovative and have had a groundbreaking effect on patient care.<sup>9</sup> A survey of clinical leaders in over a dozen different medical specialties from top academic medical centers in the US identified the most transformative drugs in their specialties to have been approved by the FDA from 1984 to 2009.<sup>10</sup> One key similarity among many of these transformative products was the centrality of publicly-funded government- and academic-based innovators and discoveries made by academic researchers supported by federal government funding, while others were jointly developed in both publicly funded and commercial institutions.<sup>11</sup> Perhaps the most highly visible example of public funding supporting transformative medical product development occurred earlier this decade with the mRNA COVID-19 vaccines. The US government invested

at least \$31.9 billion to develop, produce, and purchase mRNA COVID-19 vaccines, including sizeable investments in the three decades before the pandemic through March 2022 relating to development of lipid nanoparticles as a drug delivery system, synthesis and modification of mRNA and small interfering ribonucleic acid, definition of the prefusion “spike” protein structure of SARS-CoV-2, and development of RNA vaccine biotechnology for use in humans.<sup>12</sup> In this case, not only did the NIH and other federal agencies provide substantial support for the key discoveries and development of the mRNA vaccine technology, but they also provided a guaranteed market for the final stages of development through advanced market commitments. These highly effective vaccines have helped protect millions of people from the complications of COVID-19, and they would not have been discovered or disseminated as quickly in the first years of the pandemic without the key participation of the government.

Sofosbuvir, TDF-FTC as PrEP, buprenorphine for opioid use disorder, and COVID-19 vaccines are just a small number of the extremely important pharmaceutical innovations that have arisen directly from substantial government investment in the past few decades. For example, imatinib (Gleevec), developed in large part by researchers at the Dana-Farber Cancer Center in Boston, was approved in 1998 for chronic myelogenous leukemia.<sup>13</sup> It helped turn a rare disease with few effective treatments into one that many patients can now live with for years.<sup>14</sup> More recently, gene therapies like voretigene neparvovec (Luxturna) for a congenital form of blindness and tisagenlecleucel (Kymriah) for acute lymphoblastic leukemia now offer substantial improvements for patients.<sup>15,16</sup> To date, these gene therapies all have their origins in NIH funding to academic institutions or in spinoffs from such institutions, which developed indispensable know-how and underlying forms of technology.<sup>17,18</sup>

### **Role of the US Government in Steering Patients Away from Ineffective or Dangerous Innovation**

While the US government has had a substantial, consistent, and undeniable role in supporting the development of useful pharmaceutical innovation, it is also important to recognize that truly transformative drugs are unfortunately rare. Although the overall number of new drugs approved by the FDA has increased in the last few years, many new drugs do not offer important advances in efficacy or safety for patients despite generally being sold at high prices that make them quite profitable for manufacturers.<sup>19</sup> In a recent review of

FDA-approved drugs from 2007 to 2017, among 267 new drugs rated by five key international independent drug evaluation groups, fewer than one-third (31%) were rated as having high added therapeutic value by at least one organization.<sup>20</sup> Although these therapeutic benefit assessments are made without reference to the drugs' prices, all newly approved drugs are invariably expensive, particularly in the US. In fact, launch

other industrialized nation.<sup>25</sup> The federal government is also the largest single purchaser of prescription drugs in the US market; Medicare alone accounts for more than one-third of the country's total drug spending. Since too many of these products offer limited added therapeutic benefits over other existing products, it is essential for the solvency of the US health care system that the government ensure it does not

In fact, launch prices for new drugs increased by 20% per year from 2008 to 2021, such that by 2020 to 2021, 47% of new drugs were initially priced above \$150,000 per year. Thus, while some important new drugs are developed and marketed every year, many newly marketed drugs are very costly and may offer little clinical advantage over medications that are already available. Not only are low-additional-value drugs commonly approved by the FDA, they are also widely advertised: among 81 top-advertised drugs, 73 drugs had at least one therapeutic benefit rating and were associated with advertising spending of \$22.3 billion from 2015 to 2021 — but only 20 of these commonly marketed drugs (27%) were rated by any agency as having high added therapeutic value.

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It is widely recognized that the US spends more per capita on brand-name prescription drugs than any

pay extremely high prices for new drugs that do not actually offer meaningful added clinical benefits.

In recent years, various US government agencies have taken steps intended to ensure that there is fair reimbursement for meaningful innovation, but that the government does not pay excessively for drugs offering unclear or limited additional benefits.

*Centers for Medicare and Medicaid Services (CMS)  
National Coverage Decision for Aducanumab  
(Aduhelm)*

Alzheimer's disease is the most common cause of memory impairment and dementia in older adults, and it is a progressive and often debilitating medical condition. It can have a major impact on quality of life and independence and is the seventh leading cause of death in the US.<sup>26</sup> Patients with Alzheimer's disease lack effective treatments that have meaningful long-term effects on thinking, behavior, or maintaining independent living.

Aducanumab (Aduhelm) was designed to reduce protein deposits called amyloid plaque in the brain. Excessive amyloid plaque is a main feature of Alzheimer's disease, but not everyone with amyloid plaque has or will get Alzheimer's disease. Unfortunately, the key trials studying aducanumab provided no clear evi-

dence that it worked. The drug was evaluated in two identical 18-month randomized trials involving over 3,000 patients with early Alzheimer's disease.<sup>27</sup> These trials were stopped before completion because they were found to be futile in a pre-specified analysis of the full dataset, even though aducanumab substantially reduced amyloid plaque in both trials. When reviewed individually, the key measure of the effect of the drug on the things that matter most to people with Alzheimer's and their families — remembering, learning, reasoning, and functioning<sup>28</sup> — was no different than placebo in one trial and only slightly better than placebo in the other, with people in the high-dose aducanumab group declining only slightly less than people randomized to placebo.<sup>29</sup> The absolute difference was small, 0.39 points on a 19-point scale, which is lower than the 1–2 point change cited as the smallest difference likely to be noticeable by physicians.<sup>30</sup> In addition, patients across both trials randomized to high-dose aducanumab frequently experienced problems including brain swelling (35% with the drug vs. 3% with placebo) and bleeding.

However, the FDA approved the drug anyway, under its accelerated approval program, agreeing with the manufacturer that the amyloid lowering was reasonably likely to lead to actual clinical benefits at some undetermined point in the future. This decision was made despite a “council of senior agency officials” concluding that “there wasn't enough evidence it worked” and one even noting that approval could “result in millions of patients taking aducanumab without any indication of actually receiving any benefit, or worse, cause harm.”<sup>31</sup> There were numerous related flaws in the decision. The FDA initially approved the drug for all patients with Alzheimer's disease, even though it was only tested in patients with mild disease (that approval language was amended a few weeks later). The manufacturer-written and FDA-approved labeling also called for less frequent monitoring than was performed in clinical trials,<sup>32</sup> which could heighten the risk for severe complications of the brain swelling and bleeding commonly associated with the drug and did not include contraindications for drugs that could further increase that risk. Although drugs approved via accelerated approval must conduct post-approval studies because they lack evidence that they affect real clinical outcomes, the manufacturer of aducanumab was given nine years for its trial. The FDA said that based on the results, “If the drug does not work as intended, we can take steps to remove it from the market.”<sup>33</sup>

The decision met with widespread disapproval by the medical community. Large academic centers like Cleveland Clinic, Mount Sinai, and the Veterans

Administration declined to put the drug on formularies, while regulators in Europe and Japan rejected it outright. Wanting to “establish ADULHELM [aducanumab brand name] as one of the top pharmaceutical launches of all time,”<sup>34</sup> aducanumab's manufacturer initially listed the drug at an average price of about \$56,000 per year (it was much later reduced by half). At that price, if only one-tenth of patients with Alzheimer's disease were prescribed it, Medicare's total annual spending would have exceeded \$28 billion (more than six times as much as Medicare spent to cover any other drug in 2019).<sup>35</sup> There would be substantial additional costs: considering charges for infusion services, repeated imaging and medical management (including hospitalization for severe symptoms), treatment costs could have exceeded \$100,000 per patient per year, of which Medicare covers a substantial portion but still leaves patients with large out-of-pocket costs.<sup>36</sup> In this way, US taxpayers were poised to spend as much as \$6 to \$29 billion per year (more than the total budgets of NASA or the CDC)<sup>37</sup> on a drug with unclear benefits that could have put thousands of patients' lives at risk. Reflecting this projection, CMS announced the largest-ever annual increase in Medicare premiums due to anticipated aducanumab spending with monthly Medicare Part B premiums increasing from \$148.50 to \$170.10 and Part B deductible increasing 15%, from \$203 to \$233.

In this context, CMS made the reasonable decision to issue a national coverage determination — something it rarely does for FDA-approved drugs — to limit coverage of aducanumab and other potential anti-amyloid monoclonal antibodies approved under accelerated approval for patients enrolled in clinical trials only. Medicare is prohibited by law from paying for any medical products that are not “reasonable and necessary.” Since aducanumab was approved by the FDA despite a lack of any clear clinical benefit, CMS' proposal to restrict coverage of the drug to its use in clinical trials was the most reasonable pathway forward to help understand whether the drug actually works and whether any benefits it had outweighed its substantial risks. This decision was actually quite generous of CMS, since it is usually the financial responsibility of the manufacturer to supply the drug in the context of enrolling of patients in post-approval trials for patients receiving accelerated approval drugs. Ultimately, the manufacturer made the business decision to stop distribution of the drug rather than subject it to further clinical testing to tell if it actually worked to help patients.

CMS's aducanumab decision to live up to its Congressional mandate (even if the FDA did not, in

this case) to support effective, necessary care wisely avoided wasting the nation's health care resources on a drug with no proven efficacy and substantial risks. CMS' decision also served as a major incentive for any other manufacturer with anti-amyloid monoclonal antibodies targeting Alzheimer's disease to complete trials of the drug's clinical effects as expeditiously as possible. Patients with Alzheimer's disease deserve new treatments that have reliable evidence that their benefits outweigh their risks, and the CMS decision supported this goal by rejecting paying for a drug with no clear evidence of benefit unless patients were enrolled in trials designed to determine whether that benefit existed.

*The Center for Medicare and Medicaid Innovation's (CMMI) Demonstration Projects*

CMMI, situated within CMS, was created by Congress under the Affordable Care Act for numerous reasons, including the testing of innovative payment and ser-

ures can accurately predict clinical endpoints, but the accelerated approval program is designed for promising drugs based on changes to surrogates only reasonably likely to predict actual clinical benefits with the requirement that they conduct post-approval studies to show an effect on those clinical measures. Because it is difficult for the FDA to follow up on its requirement for post-approval trials, these trials can be delayed.<sup>40</sup> In many cases, post-approval studies continue to test surrogate measures, providing unclear insight into the usefulness of the drug for patients.<sup>41</sup> In some cases, those post-approval studies have been negative — in the last two years alone, about two dozen accelerated approval-based indications of approved drugs have been withdrawn based on negative confirmatory studies.<sup>42</sup>

Thus, by definition, accelerated approval drugs are approved based on uncertain clinical effects and without a clear pathway for if or when any clinical benefits will be demonstrated. They are also invariably expen-

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vice delivery models for Medicare and Medicaid beneficiaries. CMMI has launched numerous novel payment models in the last decade,<sup>38</sup> some of which have covered Medicare drug spending. CMMI's most recent drug pricing related pilot project was a set of three proposals affecting the way Medicare patients pay for certain generic drugs, expensive cell and gene therapies, and accelerated approval drugs lacking proven clinical benefit to patients. In these potential pilot projects, CMMI sought to ensure that CMS paid for treatments in ways that are related to the benefits they provide to patients.

For example, one model involves paying less for drugs that receive accelerated approval from the FDA than for drugs granted traditional approvals. Accelerated approval, as described in the aducanumab case, is a special pathway through which the FDA can approve drugs based on changes to surrogate measures — laboratory testing, radiologic studies, or biomarkers like amyloid level — rather than changes to clinical outcomes that are of actual importance to patients (how they feel, function, or survive).<sup>39</sup> Some surrogate mea-

sive, costing hundreds of thousands of dollars per year or more, because the US allows manufacturers to set their own prices for newly-approved drugs.<sup>43</sup> Yet, aducanumab aside, nearly all FDA-approved drugs have been covered by Medicare Part B at the average sales price (plus a small additional amount), and accelerated approval drugs distributed through retail pharmacies generally must be covered by Medicare Part D plans, particularly if they fall in one of six protected classes, which includes cancer treatments. For Medicare and Medicaid, accelerated approval therefore often becomes a pathway for a new product to enter the market, but also a mandate for government payers to cover high prices for unproven therapies.<sup>43</sup>

In this context, CMMI's demonstration project makes logical sense. If a drug is not yet shown to have clinical benefit, payment for it should be consistent with that state of the evidence. If new data come out, a fair pricing level can be reconsidered. But while the drug is FDA-approved based on limited evidence, patients and taxpayers should not be expected to pay whatever excessively high price the manufacturer

decides it wants to set. As a secondary benefit, CMMI's model pricing structure could provide incentives for manufacturers to complete their post-approval studies in a timely fashion, helping garner needed evidence of the drug's actual clinical benefits to better inform clinical decision-making.

CMMI's proposal to pay for cell and gene therapies involves helping coordinate and administer multi-state agreements that would be dependent on outcomes. This model is useful because multiple cell and gene therapy treatments have been approved in recent years and priced at eye-popping levels.<sup>17</sup> Most recently, etranacogene dezaparvovec (Hemgenix) for hemophilia B (factor IX deficiency) was made available at \$3.5 million.<sup>44</sup> In addition, not all cell and gene therapies are fully curative; rather, some still require additional expensive treatments, and the effects may wane over time.<sup>45,46</sup> Since evidence for the efficacy and durability of response is unknown at the time of approval, for gene therapies, payers are faced with the risk of paying too much upfront for unrealized benefits. For example, some patients initially respond to chimeric antigen receptor (CAR) T-cell therapy but then rapidly progress, requiring stem cell transplants or leading to death.<sup>47</sup> Current payment approaches in the US for these products largely do not take outcomes into account, which is why CMMI's proposal is useful. It can help ensure that patients receive the potentially life-changing benefits of gene therapies when those benefits are meaningful and try to ensure that payments for them are more closely linked to the clinical benefits they provide.

Finally, CMMI's third proposal to encourage Medicare prescription drug insurers to offer certain key generic drugs for a flat two dollar copay can help promote medication adherence to essential medications for common, chronic conditions such as high blood pressure and diabetes. Medication non-adherence is common among patients with high out-of-pocket costs, and well-designed studies have shown that reducing patient out-of-pocket costs can improve adherence and important clinical outcomes.<sup>48</sup> Unfortunately, in recent years, some generic drugs have been subject to price increases for a variety of reasons, which can lead to changes in out-of-pocket costs.<sup>49</sup> Here again, as with the other two proposals, CMMI attempted to ensure that patients have access to meaningful innovation — in this case, essential generic medicines.

#### *Ending the CMS MCIT Pathway Rule*

In January 2021, CMS finalized a rule called Medicare Coverage of Innovative Technology (MCIT) that would guarantee up to four years of federal coverage

for devices authorized by the FDA under the Breakthrough Devices Program. The breakthrough program for medical devices has been available in pilot form since 2014 to expedite development and approval of certain high-risk medical devices for serious or life-threatening conditions.<sup>50</sup> As codified by Congress in 2016, the FDA was directed to grant breakthrough device designation for devices (1) that provide for more effective treatment or diagnosis of life-threatening conditions and (2) which are either in the best interest of the patient, for which no alternatives exist, or that offer substantial advantages over alternatives. But in its subsequent guidance, the FDA announced its intention to apply these criteria broadly, for example, defining providing “for more effective treatment” as covering the manufacturer’s “*reasonable expectation* that the device *could* provide for more effective treatment or diagnosis of the disease or condition” (emphasis added).<sup>51</sup> Guidance documents for other criteria also set low bars.

Perhaps not surprisingly given these lax criteria, large numbers of medical devices have qualified for this designation (222 in the program's first three years alone), with some that do not actually offer real clinical benefits to patients. In one review of breakthrough devices first made available from 2016 to 2019, investigators found breakthrough-designated devices were FDA-authorized primarily via studies that used short-term, surrogate measures of effectiveness — which may not translate into clinical benefits, as with aducanumab — using safety data alone (without supporting evidence of effectiveness), and despite well-described serious safety risks.<sup>52</sup> The MCIT rule also included no requirement that additional post-approval studies of these devices be conducted as a condition of Medicare coverage.<sup>53</sup>

Ending the implementation of this rule was therefore consistent with the other moves described above, albeit in the context of medical devices. The MCIT rule was a wrongly conceived approach that would have forced Medicare to pay for ineffective or potentially dangerous device “innovation.” By stepping back from the rule, CMS returned to its baseline requirement of covering new technologies that are reasonable and necessary, rather than being forced to cover potentially non-useful new medical devices merely because they were given the FDA breakthrough device designation, which is not a consistent indicator of truly meaningful innovation for patients.

#### **Future Steps**

As these examples show, not only does the US government fund some of the most transformative drugs we

have, but it can also take steps to ensure that patients and taxpayers avoid wasting resources on drugs that are not meaningful innovation. This latter role is extremely important in providing the necessary incentives for the private market to invest its resources in generating optimally useful innovation that offers the greatest benefit to patients. The current system in which Medicare and Medicaid — as large payers in the market — too often end up reimbursing at unnecessarily high prices for low-value new products is one reason why there are so many unimpressive new prescription drugs and medical devices and so few truly transformative therapies.

There is also more that the government should be doing in this area to support the development of and payment for meaningful drug (and device) innovation for patients' benefit. First, under no circumstances should Congress be looking to reduce the NIH's budget. A bill that recently passed the House of Representatives would cut the NIH's funding by \$10 billion in fiscal year 2024, or about 20% of its annual budget.<sup>54</sup> This would devastate the prospect of future transformative drug development and doom prospects of future useful treatments in many areas of unmet medical need. Instead, the NIH budget should be expanded considerably — even doubled in size — and more funding dedicated to supporting pivotal clinical trials of NIH-funded products that could be used to bring more such products through the final stages of the development process, as well as to post-approval comparative effectiveness studies in which drugs are tested against each other to determine which drugs are better for which patients.

Second, Congress should give the government more authority and leverage to reduce unnecessary spending on excessively priced pharmaceutical products that do not provide meaningful benefits to patients. For example, the Inflation Reduction Act (IRA) of 2022 for the first time vested in CMS the authority to negotiate prices for certain drugs based on their clinical value and other important factors. This is an important step to ensuring that the government pays fair prices for these products, but the bill is limited in that it only applies to a small number of products and has numerous exclusions, including drugs for which Medicare spends less than \$200 million per year, drugs approved within the last 9 years (13 years for biologics), and drugs with one rare disease approval. Congress should build on this legislation to give CMS the authority to negotiate fair prices for all new drugs shortly after approval, as is done in all other industrialized countries.

Finally, the US should look for more ways to help ensure that patients and taxpayers only pay for meaningful innovation. For example, there is no national body right now in the US designed to help patients identify drugs with limited clinical value so that they can make informed clinical decisions about them. Congress should establish and fund a new expert panel to provide rapid-turnaround evidence-based reports on new drugs' added clinical value, pricing, and any potential disparities in access. Its recommendations could be non-binding, but the body would be tasked with issuing high-profile data-driven pronouncements on these issues regularly. Everyone who believes that marketplaces function best with more information should support such an organization.

#### Disclosures

This article is adapted from testimony that Dr. Kesselheim gave to the United States House of Representatives Ways and Means Subcommittee on Health on May 10, 2023, in Washington, DC on May 10, 2023. Dr. Kesselheim reports serving as an expert witness on behalf of a class of individual plaintiffs in a case against Gilead related to its tenofovir-containing products, and on behalf of the Federal Trade Commission (FTC) in a merger case and a licensing case (both now resolved).

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22. Some of these new drugs are effective but are just second- or later-in-class products. Such products may offer some utility to patients, such as those who cannot tolerate the first-in-class product, and can have pro-competitive benefits even without being direct competitors, so we could offer more tailored incentives for their production.
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