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Program On Regulation, Therapeutics, And Law



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More Cures for More Patients: Overcoming Barriers

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Summary of major points

- Pharmaceutical innovation relies on academic and non-profit research centers as the source of much fundamental work. These insights are converted into practical applications for clinical care via translational research funded by large pharmaceutical companies as well as by academic institutions and academic spin-offs, or other small start-up companies with venture capital.
- Because it is good public policy, the US government invests substantial amounts of taxpayer dollars in basic and translational science that identifies potential new compounds and drug targets. In 2019, the NIH's budget was about \$39 billion, the largest investment by any government in scientific research in the world.
- Public funding by NIH and other public-sector organizations is key for promoting pharmaceutical innovation; from 2008-2017, 25% (62/248) of new drugs had patents or other late-stage intellectual contributions from or through publicly-supported research institutions.
- The US offers tax concessions and refunds to help pay for research and development spending by pharmaceutical companies. An additional credit can be earned by companies under the Orphan Drug Act to develop medications intended to treat patients with rare diseases.
- Despite the emergence of transformative new drugs from publicly-funded research, the disappointingly low pace of new drug developments with real clinical benefits for patients has led to concerns about misapplication of research and development tax credits. Lack of clarity over how companies define the 'base' amount of qualifying research has allowed the credit to apply to research that would have been done anyway or to activities unnecessary for taxpayers to fund.
- More NIH funding is key to identify treatments for unmet medical needs. Fairer royalty agreements with taxpayer-funded institutions, along with a reasonable pricing clause for products discovered with government-funded support, could help ensure that products with development costs largely underwritten by taxpayer dollars would be priced at levels commensurate with clinical value.
- Changes to the research and experimentation tax credit are unlikely to be as strong a driver of innovation as direct government funding. However, options for tax reform include narrowly defining the scope of qualifying research activities and raising the bar for the types of documentation needed to support the tax credit, including being more specific about the nature of the claimed costs. The Orphan Drug Act credit should be repayable for extremely high-revenue rare disease drugs.

Chairman Doggett, Ranking Member Nunes, and Members of the Health Subcommittee:

My name is Aaron Kesselheim, an internal medicine physician, lawyer, and health policy researcher and a Professor of Medicine at Harvard Medical School in the Division of Pharmacoepidemiology and Pharmacoeconomics at Brigham and Women's Hospital in Boston, one of the main Harvard teaching hospitals. I lead its Program On Regulation, Therapeutics, And Law (PORTAL), an interdisciplinary research group that studies the intersections between prescription drug affordability and use, laws and regulations related to medications, and the development and cost of drugs. We are here today to talk about pharmaceutical innovation and how the government can provide reasonable incentives for new drug discovery, while making sure that Americans can actually afford the medicines their doctors prescribe.

Sources of Pharmaceutical Innovation

The road to FDA approval of a new drug begins with basic science discoveries that may provide greater understanding of disease or a new potential target for therapy.¹ While drug companies do make important investments in product-development research, academic and non-profit research centers are the source of much of this fundamental early work, a great deal of it funded by taxpayer dollars through the National Institutes of Health (NIH) and other federal agencies. These basic science insights are converted into practical applications in clinical care via translational research funded by large pharmaceutical companies as well as by academic institutions and academic spin-offs or other small start-up companies funded by venture capital. Final product development research, including bioavailability studies and clinical trials to evaluate the efficacy and safety of a new drug, largely occurs in the private sector.

The process of pharmaceutical innovation is a long and expensive one. Estimates of the cost to develop a new drug range from the hundreds of millions to over a billion dollars,² and development time

¹ Kesselheim AS, Sinha MS, Avorn J, Sarpatwari A. Pharmaceutical policy in the United States in 2019: an overview of the landscape and avenues for improvement. *Stanford Law and Policy Review* 2019;30:421-480.

² A frequently-cited study, from the industry-funded Tufts Center for the Study of Drug Development, estimated a cost of \$2.6 billion for a pharmaceutical manufacturer to develop a new drug, in addition to \$312 million for post-approval research. However, this projection was based on undisclosed, highly-selected group of drugs and represented a significant increase from the Center's previous estimated cost of \$802 million in 2003. Re-analyses of the 2003 figure place the real cost of new drug development at closer to \$240 million; if a non-highly-selected group of compounds was used, the number was \$161 million. In addition, approximately half of the \$2.6 billion estimate was obtained by compounding the cost of capital at 10.6% annually. *Id.* See, inter alia, Avorn J. The \$2.6 billion pill—methodologic and policy considerations. *New England Journal of Medicine* 2015;372(20):1877-1879; Tufts Center for Drug Development. Cost to develop and win marketing approval for a new drug is \$2.6 billion. 2014 Available at: http://csdd.tufts.edu/news/complete_story/pr_tufts_csdd_2014_cost_study; Public Citizen. Rx R&D Myths: The Case Against the Drug Industry's R&D "Scare Card". July 2001. Available at: <http://www.citizen.org/publications/publicationredirect.cfm?ID=7065>; Prasad V, Mailankody S. Research and Development Spending to Bring a Single Cancer Drug to Market and Revenues After Approval. *JAMA Internal Medicine* 2017;177(11):1569-1575.

can take years for product discovery and preclinical work and 6-7 additional years on average for clinical testing.³ Pharmaceutical innovation is crucial for patient care and the public health, because prescription drugs are among the most effective—and cost-effective—interventions that physicians can offer their patients. Many drugs save or extend patients’ lives, or markedly improve patients’ quality of life.

US Government Support of Pharmaceutical Innovation

Because it is good public policy, the US government supports investment in pharmaceutical innovation in numerous important ways. On the front end—so-called “push” incentives—the government invests substantial amounts of taxpayer dollars each year in basic and translational science that identifies potential new compounds and drug targets, and determines whether products that change molecular pathways can lead to health benefits. In 2019, the NIH’s budget was about \$39 billion, the largest investment by any government in scientific research in the world.

Such public funding by NIH and other public-sector organizations is key for promoting pharmaceutical innovation. One study found that all new drugs approved from 2010-2016 or their molecular targets could be linked back to government-funded research, mostly through the NIH.⁴ In addition to funding the fundamental work leading to all drug discovery, government-funded research also directly contributes to late-stage drug development. One review found government resources could be directly linked to over 150 drugs and vaccines marketed from 1990-2007, accounting for about 15% of new products approved during that time.⁵ We recently published in *BMJ* an updated review of drugs approved from 2008-2017, which found that 25% (62/248) had patents or other late-stage intellectual contributions from publicly-supported research institutions. This included 6% from private companies that were spun off from publicly-funded work done in academic settings.⁶

³ Darrow JJ, Avorn J, Kesselheim AS. FDA approval and regulation of pharmaceuticals, 1983-2018. *JAMA* 2020;323(2):164-176.

⁴ Galkina Cleary E, Beierlein JM, Khanuja NS, McNamee LM, Ledley FD. Contribution of NIH funding to new drug approvals 2010-2016. *Proceedings of the National Academy of Science of the USA* 2018;115(10):2329-2334. See also Sampat BN, Pincus HA. Citations in life science patents to publicly funded research at academic medical centers. *Clinical and Translational Science* 2015;8(6):759-763.

⁵ Stevens AJ, Jensen JJ, Wyller K, Kilgore PC, Chatterjee S, Rohrbaugh ML. The role of public-sector research in the discovery of drugs and vaccines. *New England Journal of Medicine* 2011;364(6):535-541. See also Sampat BN, Lichtenberg FR. What are the respective roles of the public and private sectors in pharmaceutical innovation? *Health Affairs* 2011;30:332-339.

⁶ Nayak RK, Avorn J, Kesselheim AS. Public sector financial support for late stage discovery of new drugs in the United States: cohort study. *BMJ*. 2019;367:15766.

The public sector's role in drug research is particularly important for transformative drugs.⁷ In an earlier study identifying the most transformative drugs approved in the US from 1984 to 2009, we found that much of the discovery and translational work occurred at academic medical centers.⁸ In our BMJ study, drugs with a late-stage link to publicly-funded institutions or their spin-offs were much more likely to receive expedited FDA approval (68% v 47%, P=0.005) or be designated first-in-class (45% v 26%, P=0.007), two indicators of their therapeutic importance.⁹

Another "push" incentive that the US government offers to drug companies is various tax concessions and refunds directed at research and development spending by private firms. According to the industry trade organization PhRMA, spending by member companies exceeded \$90 billion in 2017,¹⁰ although that generally accounts for less than 20% of the revenues received by these pharmaceutical manufacturers.¹¹ Most such investment by large pharmaceutical manufacturers occurs at a relatively late stage in development, since clinical trials account for approximately two-thirds of industry research and development expenditures,¹² or on further development and testing of already-approved drugs.¹³

Some of these investments benefit from research and experimentation tax deductions and tax credits. The deduction encourages investment in qualifying research and development activities by taxing the returns to such investment at a marginal effective rate of zero.¹⁴ The non-refundable credit is intended to stimulate more research and development investment.¹⁵ It allows up to 20% of a manufacturer's "qualified research expenses" above a base amount to be credited. This is defined as the sum of in-house research expenses and contract research expenses, and is supposed to involve technologically complex and societally useful experimentation, and must be performed in the US. Excluded from qualified research expenses is research after commercial production and market research. A Government Accountability Office

⁷ Kesselheim AS. The Role of Public Funding in the Development of Transformative Drugs. U.S. House of Representatives, Committee on Oversight and Government Reform. 2015.

⁸ Kesselheim AS, Avorn J. The most transformative drugs of the past 25 years: a survey of physicians. *Nature Reviews Drug Discovery* 2013;12(6):425-431.

⁹ Nayak RK, Avorn J, Kesselheim AS. Public sector financial support for late stage discovery of new drugs in the United States: cohort study. *BMJ*. 2019;367:15766.

¹⁰ Pharmaceutical Research and Manufacturers of America. Industry Profile 2019. Washington, D.C.: PhRMA. Available at: https://www.phrma.org/-/media/Project/PhRMA/PhRMA-Org/PhRMA-Org/PDF/2019-Profile-Booklet_FINAL_NoBleeds.pdf

¹¹ Kesselheim AS, Avorn J, Sarpatwari A. The high cost of prescription drugs in the United States: origins and prospects for reform. *JAMA* 2016;316(8):858-871.

¹² Berndt ER, Cockburn IM. Price indexes for clinical trial research: a feasibility study. June 2014; <https://www.bls.gov/opub/mlr/2014/article/price-indexes-for-clinical-trial-research-a-feasibility-study.htm>.

¹³ Light DW, Lexchin J. Foreign free riders and the high price of US medicines. *BMJ*. 2005;331(7522):958-960.

¹⁴ Guenther G. Research tax credit: current law and policy issues for the 114th Congress. Congressional Research Service. Mar 13, 2015.

¹⁵ *Id.*

report from 2017 found that research and experimentation credit claims by pharmaceutical manufacturers remained relatively stable between 2005-2014, amounting to between \$1.2 and \$1.5 billion per year, while annual reported qualified research expenses for pharmaceutical corporations stayed steady at \$20-25 billion since 2007.¹⁶ The difference between this number and the amount of research and development spending claimed by PhRMA in part reflects investment in follow-on innovation related to marketed products, which would not count as a qualified research expense.

An additional research and development tax credit can be earned by companies for investigational drugs certified by the FDA as designed to treat patients with rare diseases, defined as affecting fewer than 200,000 people per year in the US. This tax credit was created as part of the 1983 Orphan Drug Act to enhance private investment in research for treatments for rare diseases. In 2016, it was estimated to account for \$1.76 billion in tax incentives paid to drug companies in 2016.¹⁷ The credit was reduced from 50% to 25% of qualified research expenses—which in this case include human clinical testing—in the Tax Cuts and Jobs Act of 2017.

The government also provides substantial “pull” incentives—incentives offered after a drug is approved—for pharmaceutical research and development investment. This includes the granting of 20-year patents for innovative products, which gives the patent holder the ability to prevent competitors from making their products. By preventing competition, this can reward innovation but also delays the entry of more affordable generic versions of a drug. The key patent on a drug may be issued when it is first discovered or synthesized, but pharmaceutical manufacturers often seek dozens—or even hundreds—of additional patents to protect their products covering everything from their formulations and uses to the devices that patients use to administer them.¹⁸ The government also provides about 6-7 years of guaranteed generic-free marketing periods for new brand-name drugs via the Hatch-Waxman Act of 1984. (This has been expanded to about 12 years for qualified antibiotics or biologic drugs.) Together, these incentives provide an average of about 12.5 years of market exclusivity for new brand-name small-molecule drugs, and about 14.5 years for more innovative first-in-class products.¹⁹ During that time, brand-name manufacturers

¹⁶ Government Accountability Office. Drug industry: profits, research and development spending, and merger and acquisition deals. Nov 2017. Available at: <https://www.gao.gov/assets/690/688472.pdf>

¹⁷ <https://www.treasury.gov/resource-center/tax-policy/Documents/Tax-Expenditures-FY2017.pdf>

¹⁸ See, e.g., Kesselheim AS, Sinha MS, Avorn J. Determinants of market exclusivity for prescription drugs in the United States. *JAMA Internal Medicine* 2017;177(11):1658-1664; Amin T, Kesselheim AS. Secondary patenting of branded pharmaceuticals: a case study of how patents on two HIV drugs could be extended for decades. *Health Affairs* 2012;31:2286-2294; Beall RF, Kesselheim AS. Tertiary patenting on drug-device combination products in the United States. *Nature Biotechnology* 2018;36(2):142-145.

¹⁹ Wang B, Liu J, Kesselheim AS. Variations in time of market exclusivity among top-selling prescription drugs in the United States. *JAMA Internal Medicine* 2015;175(4):635-637.

can charge in the US whatever they want—a condition not seen in any other developed nation. Numerous laws and rules require coverage of many high-priced drugs by the lattice of government or private payors that provide prescription drug insurance coverage to patients, or otherwise undermine their negotiating power. As a result, brand-name prescription drug prices in the US far exceed prices for the same drugs made by the same companies for use in other high-income countries around the world; these drug prices have been rising much faster than the rate of inflation.²⁰ Manufacturers also take numerous steps to extend their market exclusivity periods as long as possible by delaying generic entry.²¹ As a result, the pharmaceutical industry has been one of the most profitable of all US industries over the past two decades.

Outcomes of Investment in Pharmaceutical Innovation

Government and private investment in pharmaceutical development have led to extremely important innovations 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. It helped turn a rare disease with few effective treatments into one that many patients can now live with for years. In the mid-2010s, sofosbuvir (Sovaldi) was approved, based in large part on NIH-funded work at Emory University and elsewhere. This class of drugs actually cures hepatitis C virus infection, a chronic and transmissible infectious disease affecting 3-5 million people in the US that can cause liver failure and cancer. More recently, CAR-T therapy made it possible to bring about remission of certain types of cancers that previously had to be treated with risky bone marrow transplants that caused horrendous side effects. Gene therapies like voretigene neparvovec (Luxturna) now offer substantial improvements for patients with a congenital form of blindness.

Reflecting the importance of NIH investment in development of transformative medical treatments, each of these emerged from substantial investment by the National Institutes of Health and years of publicly funded work done at academic medical centers and their spin-off small companies being transferred to larger pharmaceutical manufacturers for the final costly steps of development. The NIH funding level grew substantially in the 1990s but remained stagnant for many years after that in inflation-adjusted numbers; in fact, a 2018 study from the Congressional Research Service suggested that, after accounting for inflation,

²⁰ Kesselheim AS, Avorn J, Sarpatwari A. The high cost of prescription drugs in the United States: origins and prospects for reform. *JAMA* 2016;316(8):858-871.

²¹ Vokinger KN, Kesselheim AS, Avorn J, Sarpatwari A. Strategies that delay market entry of generic drugs. *JAMA Internal Medicine* 2017;177(11):1665-1669

estimated NIH funding for 2019 was to remain nearly ten percent below 2003 funding levels.²² The 21st Century Cures Act of 2016 promised to add \$4.8 billion to this total over 10 years, but this funding depends on annual appropriation by Congress.

By several metrics, pharmaceutical innovation in the US has been disappointing. Although the overall number of new drugs approved by the FDA has increased in the last few years, many new drugs—despite generally sold at high prices and often quite profitable—do not offer important advances in efficacy or safety for patients. To provide more insight this question, my colleagues Richard Frank and Jerry Avorn and I reviewed the all new drugs that FDA approved in one recent year. We examined how these drugs were reviewed by expert health care technology assessment organizations in other countries that evaluate the clinical benefit of new medical products, without reference to their prices. (This is a useful function that has no governmental equivalent in the US.) We found that among the drugs that had been reviewed in our study countries to date, 20 were found by at least one of the three assessing agencies to offer no or just minor additional benefits over existing treatments. By contrast, in a recent published study, my colleagues and I reviewed the 25 brand-name drugs with the highest Medicare Part D spending in 2017, and we found that 41% (11/27) of the active ingredients had previously been approved by the FDA in other formulations or products. In addition, 22% (6/27) were approved before 2000—that is, over 20 years ago.²³ Yes, important new drugs are developed and marketed every year. But at the same time, many newly marketed drugs are very costly and may offer little clinical advantage over medications that are already available.²⁴ As a result, a disturbingly high proportion of the pharmaceutical industry’s revenues seems to be coming from high prices on drugs discovered many decades ago or reformulations of them.

Congress and the public should also be concerned about misapplication of the research and development tax credit. The goal is to incentivize new research, but lack of clarity over what companies are allowed to define as the base amount of qualifying research may have allowed the credit to be applied to research that would have been done anyway.²⁵ Another component of the problem appears to be insufficient ability of the IRS to obtain records about the nature of research and experimentation costs,

²² Johnson JA, Sekar K. NIH Funding: FY1994-FY2019. Congressional Research Service, 2018.

²³ Jung EH, Sarpatwari A, Kesselheim AS. Novelty of active ingredients in high-cost Brand-name drugs. *Journal of General Internal Medicine* 2020 Jan 2.

²⁴ Notably, some of these new drugs are effective, but are just second- or third-in-class products. Such products may offer some utility to patients, such as those who cannot tolerate the first-in-class product, and so we could offer incentives for their production. However, available tax credits are currently designed in ways that do not distinguish effectively between more innovative and follow-on products.

²⁵ Sullivan MA. Economic analysis: time to scrap the research credit. *Tax Notes*. Feb 22, 2010.

making it hard to judge if the credit is being appropriately applied.²⁶ Most worrisome, the credit can apply to activities that are unnecessary for taxpayers to fund and are unlikely to directly contribute to important new innovation. In one advertisement intended for pharmaceutical manufacturers, the accounting firm KPMG describes its capacity to advise on qualifying activities including “developing technology for compliance with various regulatory agencies” and “developing improvements to existing products.”²⁷ When these tax credits are used for activities other than drug research and development activities aimed at creating important new treatments, it can reduce the intended public health impact of the credit.

Issues with the tax credit and disappointing levels of innovation should lead to calls to re-examine the research and experimentation and Orphan Drug Act tax credits, as well as other incentives the government provides to the pharmaceutical industry. If they are not working optimally, we need to better understand how they can be improved and offer better incentives to create drugs that will address key public health issues facing US patients. I will address this topic in the final section.

Policy Solutions

This committee is well-placed to take on specific remedies that can better incentivize important pharmaceutical innovation and at the same time ensure that the resulting products are available to the patients who would benefit from it. I am pleased to offer some suggestions for policy solutions, and am happy to talk further in more detail about any of these ideas.

As the committee considers interventions intended to promote pharmaceutical innovation, we need to come back to the fact that federal funding of research and development through the NIH has proven to be a very effective way of generating breakthrough drugs. More such funding would therefore be extremely valuable in the push to identify treatments for unmet medical needs. But at present, when government-funded innovations are transferred to a private company for commercialization, these contracts rarely provide for reasonable royalties to be returned to the government for reinvestment in research and development, or to be used to lower drug prices for patients and payors. Further, these contracts never have restrictions on the price that manufacturers can charge for these taxpayer-funded discoveries. The subcommittee could further study how to arrange such royalty agreements and how a reasonable pricing clause associated with government-funded work could be structured. This could ensure that any product

²⁶ Government Accountability Office. Tax policy: the research tax credit’s design and administration can be improved. November 2009.

²⁷ KPMG. R&D tax credits for the pharmaceutical industry: accounting methods and credit services. 2018.

with development costs that were largely underwritten by taxpayer dollars would be priced at a level that patients could afford, and commensurate with its clinical value.

Changes to the research and experimentation tax credit are unlikely to be as strong a driver of innovation as direct government funding. However, if the committee is considering such changes, options include more narrowly defining the scope of qualifying research activities and raising the bar for what documentation is required to support the tax credit, such as being more specific about the nature of the claimed costs. The committee could also consider whether a “payback” provision could be added to the tax code for drugs that benefitted from tax breaks during their development and then became a blockbuster product that earns over \$1 billion in annual sales. One field of medicine that has seen unexpected blockbusters in recent years has been rare disease drugs. The Orphan Drug Act was passed by Congress 36 years ago to encourage investment in treatments that would otherwise not have been profitable, so a highly profitable ‘rare disease’ drug seems inconsistent with the goals of the legislation. Thus, Orphan Drug Act tax credits could be made to be repayable for extremely profitable rare disease drugs, and the subcommittee should consider whether the statute should be revised to narrow the definition of qualifying diseases to its original form: those rare diseases for which the manufacturer is not expected to be able to make a profit. This would include, for example, infectious diseases prevalent in resource-poor settings around the world.

There are also ways that the tax system could be leveraged to better promote the availability of high-priced drugs to patients. One change could be to increase taxes on drugs when manufacturers impose price increases well beyond the rate of inflation, unless new evidence of their effectiveness has emerged. Additional tax burdens could also be used to disincentivize pharmaceutical industry practices that undermine the public health, such as failing to complete FDA-mandated post-approval studies to clarify a drug’s effectiveness or safety. For example, the FDA’s Accelerated Approval pathway allows promising new drugs to be approved based on preliminary evidence from changes in lab tests of imaging studies—so-called surrogate measures—rather than real clinical endpoints. In exchange for the FDA allowing drugs on the market without clear evidence that they actually make patients better, and with only a very limited safety record, pharmaceutical manufacturers must agree with the FDA to conduct post-approval confirmatory trials. However, we have shown that such trials may be delayed and when they are done, a surprising number are tested using the very same surrogate measures as the preliminary trials.²⁸ For example, the muscular dystrophy drug eteplirsen (Exondys 51) was approved in 2016 based on very small changes to a

²⁸ See Naci H, Smalley KR, Kesselheim AS. Characteristics of preapproval and postapproval studies for drugs granted accelerated approval by the US Food and Drug Administration. *JAMA* 2017;318(7):626-636; Gyawali B, Hey SP, Kesselheim AS. Assessment of the clinical benefit of cancer drugs receiving accelerated approval. *JAMA Internal Medicine* 2019;179(7):906-913.

protein in the muscle (a surrogate measure). But an FDA letter in August 2019 noted that the post-approval confirmatory trials that the company promised to complete by May 2021 had not yet even been started.²⁹ Nonetheless, such Accelerated Approval drugs are often sold at extremely high prices during the post-approval period: eteplirsen was reported to initially cost \$300,000 or more per year for each patient. The tax code could be changed to tax a company's profits after a certain reasonable period of time at a much higher rate if a manufacturer fails to complete its agreed-upon FDA-mandated post-approval trials.

Conclusion

The government provides substantial support for pharmaceutical research and development through direct investment in biomedical research and favorable tax treatment, as well as protections for brand-name manufacturers to sell their drugs at their chosen prices post-approval. While funding of innovation through NIH has directly contributed to important drug development, tax breaks such as the research and experimentation credit have been less meaningful because they have often been misapplied to a variety of activities and have not been tailored to preferentially encourage development of important new products. With limited direct federal funding and misguided tax benefits offered to pharmaceutical manufacturers, important diseases remain without treatments, while many new drugs come onto the market that offer small or no clinical improvements over already-available products.

To encourage research and development with the greatest impact on patient health outcomes, Congress should work to enhance NIH funding and ensure that the products that emerge from it are made available at an affordable price that accords with their value and cost of development. This committee could also consider changes to the tax code that reduce the chance of misapplication of the research and exemption tax credit, including cases when it does not appear to have been useful in the first place.

We all want to encourage continuing drug innovation, but a new drug that patients cannot pay for will do them no good. We need to move beyond the idea that any changes to policy that are opposed by the pharmaceutical industry will cripple the discovery of future new products; that threat simply is not valid. Congress can, and should, develop more thoughtful ways of using its many policy tools to encourage discovery of important new drugs in both the public and private sectors, but also make sure to do so in way that will make these medicines more affordable to the patients who need them.

²⁹ FDA. Complete Response Letter: Sarepta Therapeutics. August 19, 2019. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/211970Orig1s000OtherActionLtrs.pdf. (The FDA wrote: "Please understand that your failure to initiate eteplirsen's confirmatory study with due diligence is very concerning to FDA and is of concern to the public.")