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Comments of the Biotechnology Innovation Organization (BIO) to the July 31, 2023 NIH Workshop on Transforming Discoveries into Products: Maximizing NIH's Levers to Catalyze Technology Transfer

Vial email to SciencePolicy@od.nih.gov

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On behalf of its member organizations, the Biotechnology Innovation Organization ("BIO") is pleased to submit this Comment in preparation for the NIH July 31 Workshop on Technology Transfer.[1] BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers, and related organizations across the United States and in more than 30 other nations. BIO members range from startup companies developing their first commercial products to multi-national Fortune 500 pharmaceutical corporations. BIO's members routinely collaborate and interact with researchers in NIH's intra- and extramural programs, and have long supported the NIH in its critically important role of funding and advancing biomedical science in the United States and throughout the world.

As an initial matter, we are pleased to participate in the NIH's upcoming workshop, and we look forward to learning more about any specific interests or concerns the NIH may have identified with how it currently "approaches the patenting and licensing of biomedical inventions," and with its role "in the broader biomedical research enterprise in promoting the application of knowledge to enhance human health." Articulating those interests or concerns will help enable informative and focused comments in ongoing dialogue between the NIH and its stakeholder community. We appreciate the NIH's outreach and look forward to learning more at the workshop.

Biomedical research productivity in the United States is the highest in the world, with 62% of new drugs first approved by the FDA having their origins in the U.S., more than the rest of the world combined.[2] This high biomedical research productivity depends on a fluid system of technology transfer, licensing, and partnering that was first perfected in the United States, and in which both the private and the public sector participate. For example, in a cohort of 223 new U.S. drug approvals from 2011-2020, thirty drugs (13.5%) originated in public sector institutions and all were licensed to biopharmaceutical firms for development and regulatory submission.[3] In another study of 248 small molecule drugs approved by the FDA between 2008-2017, thirty-five (14%) had evidence of U.S. academic or public research institution involvement in their creation (about half of which were specifically found to have a US government

[1] See https://osp.od.nih.gov/events/workshop-on-transforming-discoveries-into-products-maximizing-nihs-levers-to-catalyze-technology-transfer/

[2] The US Ecosystem for Medicines. How New Drug Innovations Get to Patients. White paper available at: https://vitaltransformation.com/2022/12/the-us-ecosystem-for-medicines-how-new-drug-innovations-get-to-patients/

[3] See id. Another 33 drugs (15%) were first conceived in large biopharmaceutical firms and transferred to small- or medium-sized firms during development; and 20 drugs (9%) were first conceived by small or medium-sized enterprises and transferred to large ones prior to FDA approval.

contribution);[4] and another 13 drugs (5%) involved inventive contributions from *foreign* public research institutions; all of which were licensed to the private sector for development and commercialization. These studies are consistent with earlier reports that found the U.S. public sector to have contributed *directly* to the invention of about 10-15% of new drugs over the past several decades.[5]

In addition to direct contributions to the invention of at least some new drugs, public sector research also plays an important enabling role by funding basic research and generating new insights into biology and disease. For example, NIH-supported published research was found to be relevant to each of 210 new medicines first approved by the FDA from 2010-2016. Over 90% of this research related to the underlying mechanism of disease and the drug targets (not the drugs themselves), and thus represents an indirect, but important, contribution to the generation of new therapies.[6] This in itself should be unsurprising, as all new drugs are built on a solid foundation of earlier research, which itself built on yet earlier research, much of which was publicly-funded.

In fact, our system is very effective in funding basic research that the private sector is not in a position to conduct. The results of this publicly-funded research in the vast majority of cases enters the public domain through scientific publications, scholarly exchange, generally-accessible databases and other mechanisms that are accessible to anyone. At times, publicly funded research also results in technology that is suitable for patenting (either by the government or by the academic institutions it funds), and is then offered for licensing to suitable private firms better able to translate those early discoveries into FDA approved therapies. This collaboration between the public and private sectors forms the foundation for US leadership in this field. In evaluating our tech transfer system, BIO urges NIH to examine what has made this partnership so successful so that we can build on that success.

Because taxpayers support a great amount of basic biomedical research, many people believe that the public pays twice for drugs; once by funding underlying research and once when payors and patients buy drugs for personal use. This has led to calls for measures that tie medicine prices to public science funding, such as an (renewed) implementation of “reasonable pricing clauses” in government research grants and contracts. Explicit in such proposals is a belief that taxpayers are being insufficiently rewarded for their contributions to the creation of new drugs and therapies.

U.S. investment from all sources in both basic and applied biomedical R&D in 2020 was estimated to amount to approximately $245 billion, of which $61.5 billion was attributable to the federal government; $16.8 billion to academic and research institutions; $3 billion to foundations, philanthropies, and professional societies; and $161.8 billion (66% of the total) to the private sector.[7]

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[4] Nayak, Avorn, and Kesselheim, Public Sector Support for Late-Stage Discovery of New Drugs in the United States: Cohort Study, *BMJ* 2019;367:l5766; available at: https://doi.org/10.1136/bmj.l5766 . A US government contribution was defined as the drug originating in a federal laboratory, or a patent assignment to a federal agency, or a patent declaring US government funding of the invention.

[5] See, e.g. Sampat and Lichtenberg, What are the Respective Roles of the Public and Private Sectors in Pharmaceutical Innovation? Health Aff. 30 (2011), 332-339; Stevens et al., The Role of Public-Sector Research in the Discovery of Drugs and Vaccines, N. Engl. J. Med. 364 (2011) 535-541.

[6] Cleary et al., Contribution of NIH Funding to New Drug Approvals 2010-2016, Proc. Natl. Acad. Sci. USA 115 (2018) 2329-2334.

[7] Research!America, U.S. Investments in Medical and Health Research and Development 2016-2020; available at: https://www.researchamerica.org/wp-content/uploads/2022/09/ResearchAmerica-Investment-Report.Final_.January-2022-1.pdf

By this measure, the federal government does indeed contribute a significant chunk of the total national biomedical R&D spend – about 25% of the total. Great difficulties arise, however, when trying to quantify the public contribution to new drug development in the context of ongoing debates over drug prices. For example, in an effort to quantify the NIH contribution to the creation of remdesivir, one of the first COVID antiviral compounds, study authors added up decades of NIH-supported basic research publications in the general fields of nucleoside analogue chemistry (the drug molecule's chemical class) and RNA-dependent RNA polymerase (the enzyme on which remdesivir acts), to arrive at an eye-popping public contribution of $6.5 billion in basic research funding that, they propose, "led to" the drug and should be counted when considering its pricing.[8] A subsequent GAO study, however, found only a much smaller public contribution of $161 million to preclinical and clinical investigations of remdesivir itself (a 40-fold difference) and no inventive government contribution to the drug product at all. Meanwhile, the manufacturer of remdesivir estimates its financial outlays for the drug's preclinical and clinical development at approximately $1.3 billion.[9]

This example illustrates some of the many conceptual and practical problems with comparing the public funding of research in the field to which a drug pertains against the cost of subsequent R&D on the drug itself. Government funding makes vast and critical contributions to the advancement of medicine by furthering our understanding of human disease and pointing in promising directions for applied drug research, but the weight of the evidence shows that in most cases the private sector invents the drugs that are based on that research and assumes the cost and risk of translating new scientific insights into practical new products.[10]

It is true that direct returns to the government from licensing, in monetary terms, constitute only a small fraction of the NIH budget,[11] but criticisms of insufficient returns do not account for the vast indirect benefits and externalities that accrue to the public in the United States (and in foreign countries around the world) in the form of improved health outcomes, job creation, research productivity, education, economic development, and tax revenues. When the government's *direct* financial contribution to drug development is assessed (i.e. not counting basic research in the general field to which the drug pertains), the picture is quite different. For example, a prospective study of >23,000 NIH grants in FY 2000, representing $7.1 billion in public funding, showed that only a small fraction could be linked to only 18 new drug approvals over the subsequent two decades. And for these 18 drugs, the government's contribution to their creation constituted $640 million whereas the private sector firms that developed

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[8] Cleary et at., Foundational Research and NIH Funding Enabling Emergency Use Authorization of Remdesivir for COVID-19, available at: https://www.bentley.edu/news/65-billion-nih-funding-foundational-research-enabled-emergency-use-authorization-remdesivir

[9] US Government Accountability Office Report GAO-21-272, Information on Federal Contributions to Remdesivir, available at: https://www.gao.gov/assets/gao-21-272.pdf

[10] Developing a new drug through clinical trials and regulatory approval has been estimated to consume about 10 years and require an investment ranging from 0.7-2.5 billion dollars at an approximately 90% chance of development failure. These risks and costs are borne almost entirely by the private sector.

[11] NIH Technology Transfer Report FY 2021, available at: https://www.techtransfer.nih.gov/sites/default/files/documents/pdfs/FY2021%20NIH%20Technology%20Transfer%20Annual%20Report.pdf . NIH licensing revenue for FY 2021 was reported at approximately $127 million.

these drugs to approval contributed $44.3 billion.[12] This study, as well as other accumulated evidence, indicates that the government's direct monetary returns may be small in relative terms, but generally commensurate with its proportionally small direct investment in drug development.

Conversely, the lion's share of public research funding does not go towards new product development, but towards advancing science and enriching the public domain with new knowledge, thus creating opportunity, and stimulating commercial risk-taking and vast amounts of private follow-on investment. Seen this way, most public research funding is properly viewed as an infrastructure investment where the resulting body of scientific knowledge becomes available to anyone, anywhere – it is non-excludable - and where one entity's use of that knowledge does not diminish another entity's ability to use it too – it is non-rivalrous. In this sense the NIH helps fund a public good whose importance cannot be overstated. If entrepreneurial businesses, inspired by scientific knowledge that was funded by the public and made available to anyone, decide to invest capital and take on business risk, they are doing exactly what the system intends. In addition to the direct public health benefits derived from the invention of new therapies, this private follow-on investment then generates even more jobs, and fuels economic development.

And in instances where publicly-funded institutions *do* make direct contributions to the invention and development of new products, direct benefits can flow back through profit sharing, royalty payments, repayment of the initial investment, or some other bargained-for mechanism. Indeed, publicly-funded institutions around the country routinely, in appropriate circumstances, acquire proprietary rights in their inventions which they use for partnering, licensing, or other valorization of their institutions' research, in keeping with federal technology transfer statutes and their institutions' policies.

Nonetheless, some members of Congress, advocacy groups, and opinion journalists persist in wanting to link public research spending to the price of downstream products, regardless of the investments made and risks taken by the biopharmaceutical businesses that develop these products. In instances where companies benefited from decades of prior basic research that has long been in the public domain, these companies are said, effectively, to owe a scientific debt to the public, and they should price their products accordingly. And in instances where companies licensed publicly-funded proprietary technology, met their due diligence obligations, and paid milestones and royalties, the licensing institution is nonetheless said to have struck a bad bargain and should have insisted on lower consumer prices of the licensed product. Either way, the narrative goes, taxpayers have generously funded biomedical research and are therefore "owed" more "reasonable" prices for medicines.

Such pseudo-transactional notions[13] - that the current system of public biomedical research funding justifies a form of drug price control – not only misstate the realities of our public-private R&D ecosystem; they are also profoundly infeasible. For example, if public research funding entitles taxpayers to a discounted price for a successful drug, how much of a discount would be justified? Should that price reduction be commensurate with how much public funding was involved, relative to how much private funding went into commercializing the drug? In the much-publicized march-in petition for Xtandi®, the US government's contribution has been stated as approx. $500,000 in the form of initial research funding,

[12] Schulthess *et al.* The Relative Contributions of NIH and Private Sector Funding to the Approval of New Biopharmaceuticals. *Ther Innov Regul Sci* **57**, 160–169 (2023). https://doi.org/10.1007/s43441-022-00451-8

[13] See, for example, the statement made by Rep. Ocasio-Cortez in a January 2019 hearing of the House Committee on Oversight and Reform: "[T]he public is acting as early investor, putting tons of money into the development of drugs that then become privatized, and then they receive no return on the investment that they have made."

whereas the manufacturer of the drug and its commercial partners estimate their subsequent investment at approx. $2.2 billion[14] – how much of a lower price could the public be deemed to have "earned" by virtue of a federal research grant in such situations?

In general, arguments that the public is owed lower prices ignore the fact that the public and the private sectors, for the most part, fund research that is different but complementary, that the private sector spends significantly more than the public sector in monetary terms, and that the private sector assumes basically the entire risk that an experimental product will fail on the path of drug development.

Most important, proponents of so-called "reasonable pricing" fail to understand that their concept cannot work in the absence of a framework where *ex ante* bargaining can occur. At the time when a typical biomedical research grant is awarded, or a license to untested technology is offered, the parties will generally not know if the funded research will ever contribute to a drug product, when that drug product will come into existence, or who will bring it into existence. It will not be known how much it will cost to develop that drug, which conditions it will treat, or how it will be used in clinical practice. In such situations it is impossible to bind future parties to an agreement under which, if a drug is eventually developed against all odds, they could lose their investment and their rights if the government doesn't deem the drug's price reasonable. Businesses would simply walk away and invest their time and capital elsewhere.

Our current tech transfer system has been enormously successful. In 1980, prior to the enactment of the Bayh-Dole Act, less than 5% of the federal government's nearly 30,000 patents had been licensed for commercial development.[15] By empowering federally-supported universities and small businesses to hold and license patents, the Bayh-Dole Act fueled a vibrant innovation sector that, between 1996 and 2017, contributed to the development of more than 200 new drugs and vaccines, $865 billion in added GDP, 5.9 million jobs, and more than 13,000 startups.[16] It is hard to see how the American public could be said to have been "ripped off," as some critics now argue.

It may be superficially appealing to argue that U.S. payors should pay less for a new drug that was developed on the basis of seminal publicly-funded research. But it would be neither feasible nor rational to control a drug's price based on relative appraisals of the value and amount of underlying public research. Doing so would only put brakes on the pace of biomedical innovation and distract from other, more rational efforts to lower the cost of healthcare in the United States.

BIO looks forward to engaging further with the NIH on these important questions and thanks the agency for the opportunity to submit these comments.

Respectfully submitted,

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[14] https://newsroom.astellas.us/Astellas-Quote-and-Statement-on-the-Bayh-Dole-Act-and-XTANDI-June-14,-2022

[15] Government Accountability Office, Administration of the Bayh-Dole Act by Research Universities, GAO/RCED-98-126 at 3 (May 1998).

[16] AUTM, Driving the Innovation Economy (2018). Available at: https://autm.net/AUTM/media/Surveys-Tools/Documents/AUTM_FY2018_Infographic.pdf