National Pharmaceutical Council®

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February 6, 2024

The Honorable Laurie E. Locascio
Under Secretary of Commerce for Standards and Technology
Director, National Institute of Standards and Technology
Department of Commerce
Washington, DC 20230

Submitted electronically via: www.regulations.gov

RE: Request for Information Regarding the Draft Interagency Guidance Framework for Considering the Exercise of March-In Rights [NIST-2023-0008]

Dear Under Secretary Locascio,

The National Pharmaceutical Council (NPC) appreciates the opportunity to submit comments regarding the National Institute of Standards and Technology *Request for Information Regarding the Draft Interagency Guidance Framework for Considering the Exercise of March-In Rights.*

NPC is a health policy research organization dedicated to the advancement of good evidence and science and to fostering an environment in the United States that supports medical innovation. We have rich experience conducting research and disseminating information about the critical issues of evidence, innovation and the value of medicines for patients. Our research helps inform important healthcare policy debates and supports the achievement of best patient outcomes.

The draft interagency guidance framework (the draft guidance) notes two main themes informing the priorities of the Bay-Dole Act: "promoting the development of new products in the U.S. and their availability to end-users or consumers in the U.S.", and states that when considering march-in, agencies must prioritize U.S. innovation as well as access. NPC agrees that in considering the exercise of march-in rights, considering how they would affect innovation is paramount.

NPC has recently supported two pieces of research that examine the pharmaceutical industry's investment in drug development compared to the government's investment and can inform the potential impact of the draft guidance on innovation: *Spending on Phased Clinical Development of Approved Drugs by the US National Institutes of Health Compared With Industry*[1] and *March-in rights under the Bayh-Dole Act & NIH Contributions to pharmaceutical patents*[2]. Based on findings from these studies, **NPC is concerned that using price as a factor when determining whether to exercise march-in rights runs counter to the Bayh-Dole Act policy objectives of incentivizing and promoting innovation. We expect using price as a factor to have an overarching chilling effect on private and public partnership across the industry, reducing drug research and development and the industry's willingness to partner with the National Institutes of Health (NIH). This will ultimately reduce patient access to innovative new drugs and negatively impact competition in the marketplace by**

[1] Zhou EW, Jackson MJ, Ledley FD. Spending on Phased Clinical Development of Approved Drugs by the US National Institutes of Health Compared With Industry. JAMA Health Forum. 2023;4(7):e231921. doi:10.1001/jamahealthforum.2023.1921
[2] O'Loughlin G, Schultess D. VitalTransformation. March-in rights under the Bayh-Dole Act & NIH contributions to pharmaceutical patents. November 30, 2023. Available at: https://vitaltransformation.com/wp-content/uploads/2023/11/march-in_v11_BIO-approved-30Nov2023.pdf

disincentivizing the development of new drugs. We ask that NIST consider these research findings, as outlined below, and remove price as a factor in determining whether to exercise march-in rights from the draft guidance framework.

The Bayh-Dole Act authorizes four circumstances under which march-in rights may be applied. NIST's draft guidance framework provides guidance on the prerequisites for exercising march-in and the factors to consider when determining whether to march-in. In this draft guidance, for the first time, NIST specifies that price can be a factor. **NPC opposes the use of price as a factor in determining whether to exercise march-in rights and asks that NIST remove price as a factor in determining whether to exercise march-in rights from the draft guidance framework. Our comments and recommendations, which we provide more detail on below, are as follows:**

1. Using price as factor in determining whether to exercise march-in rights would create additional uncertainty and risk for investors, which we expect to meaningfully decrease investment into research and development for new drugs.
2. We expect the number of partnerships between the pharmaceutical industry and NIH will be reduced if price is used as a factor in determining whether to exercise march-in rights, leading to a decrease in innovation.
3. NIH's investment into new therapies focuses on basic and applied research, rather than clinical development funding needed to bring a new drug to market. It already requires a licensing fee, meaning it is additionally funded by industry.
4. As march-in rights apply to patents rather than products, march-in rights would not serve their intended purpose unless every invention and every patent covering a drug is subject to Bayh-Dole. As these types of drugs are rare, exercising march-in rights to control costs would be ineffective and has the potential to chill innovation with minimal gain.
5. Price should not be used as a factor in determining whether to exercise march-in rights because of the challenge posed by the inability of this guidance to adequately articulate a framework for evaluating how value impacts prices and associate a specific patent with the full value of a drug, including its treatment costs, the cost offsets it may produce, and its benefits to patients.

I. Using Price as a Factor in Determining Whether to Exercise March-in Rights Will Decrease Investment into Research and Development for New Drugs

Using price as a factor in determining whether to march in would create additional uncertainty and risk for investors, which we expect to lead to decreased industry and venture capital investment into drug commercialization. Research and development investments represent significant risks to pharmaceutical manufacturers and their investors, as a significant number of investments do not result in the development of an approved and marketed product. Investors recognize that clinical drug development fails more than 90 percent of the time.[3] Even for drugs that do not receive FDA approval, there is substantial financial investment from private companies that far surpasses NIH investment. In a review of funding for 23 drugs that did not receive FDA approval, the total private contribution towards these therapies was four times larger than the contributions of the NIH.[4]

NPC values the contribution of federal funding from agencies such as the NIH to drug development and recognizes that funding from the federal government contributes to pharmaceutical innovation

[3] O'Loughlin G, Schultess D. VitalTransformation. March-in rights under the Bayh-Dole Act & NIH contributions to pharmaceutical patents. November 30, 2023. Available at: https://vitaltransformation.com/wp-content/uploads/2023/11/march-in_v11_BIO-approved-30Nov2023.pdf
[4] O'Loughlin G, Schultess D. VitalTransformation. March-in rights under the Bayh-Dole Act & NIH contributions to pharmaceutical patents. November 30, 2023. Available at: https://vitaltransformation.com/wp-content/uploads/2023/11/march-in_v11_BIO-approved-30Nov2023.pdf

but is concerned that the draft guidance does not adequately consider the significant contributions from and risks taken by the pharmaceutical industry. In the study, *Spending on Phased Clinical Development of Approved Drugs by the US National Institutes of Health Compared With Industry,* researchers examined NIH funding for 387 drugs approved between 2010 and 2019. Researchers found that NIH spending represents a significantly smaller portion of investment into drug development compared to industry spending. For every dollar spent by the NIH, the private sector spends $10 on research necessary to turn scientific advances into innovative treatments for patients.[5] Even with partnerships between the pharmaceutical industry and the government, the contributions of the pharmaceutical industry and private funding outweigh government funding across therapeutic areas, including in oncology, neurology, rheumatology, radiology, anti-microbial, and virology. For 26 unexpired patents with a Government Interest Statement, which cover 15 approved novel therapies, spending by the industry totaled $44.32 billion, compared to $276 million, from 2011-2020.[6] If investors are dissuaded from contributing to the development of drugs that also receive government funding, the development landscape will be impacted enormously.

II. Partnerships Between the Pharmaceutical Industry and NIH Will be Reduced if Price is Used as a Factor in Determining Whether to Exercise March-in Rights

We expect the number of partnerships between the pharmaceutical industry and NIH will be reduced if price is used as a factor in determining whether to exercise march-in rights, leading to a decrease in innovation. NIH has previously experienced this drop in partnerships following the fair pricing requirements for NIH Cooperation Research and Development Agreements (CRADAs). After the removal of the fair pricing clause from the agreement, former NIH director Dr. Harold Varmus stated: "An extensive review of this matter over the past year indicated that the pricing clause has driven industry away from potentially beneficial scientific collaborations with [Public Health Service] scientists without providing an offsetting benefit to the public."[7] In the five years following the removal of the fair pricing clause, new NIH CRADAs per year significantly increased, with a four-fold increase over the previous five years in the number of CRADAs overall, and a doubling of individual collaborating companies.[8,9]

III. NIH's Investment into New Therapies Focuses on Basic and Applied Research, Rather Than the Clinical Development Funding Needed to Bring a New Drug to Market, and Already Requires a Licensing Fee

The nature of industry investment as well as its volume contribute significantly to drug development. NIH's investments have a strong focus on basic and applied research, rather than the targeted clinical development needed to bring a new drug to patients. **In a review of research funding for drugs approved between 2010-2019, only 3.3 percent of NIH spending on approved drugs was related to phased clinical development. Clinical developments account for approximately 70 percent of the total expenditures needed to bring new therapies to patients, but NIH investment into this area is far lower**

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[5] Zhou EW, Jackson MJ, Ledley FD. Spending on Phased Clinical Development of Approved Drugs by the US National Institutes of Health Compared With Industry. JAMA Health Forum. 2023;4(7):e231921. doi:10.1001/jamahealthforum.2023.1921

[6] O'Loughlin G, Schultess D. VitalTransformation. March-in rights under the Bayh-Dole Act & NIH contributions to pharmaceutical patents. November 30, 2023. Available at: https://vitaltransformation.com/wp-content/uploads/2023/11/march-in_v11_BIO-approved-30Nov2023.pdf

[7] National Institutes of Health News. April 11, 1995. Available at: https://www.techtransfer.nih.gov/sites/default/files/documents/pdfs/NIH-Notice-Rescinding-Reasonable-Pricing-Clause.pdf

[8] National Institutes of Health. The NIH Experience with the Reasonable Pricing Clause in CRADAs FY 1990-1995. November 15, 2021. Available at: https://www.techtransfer.nih.gov/sites/default/files/CRADA%20Q&A%20Nov%202021%20FINAL.pdf

[9] O'Loughlin G, Schultess D. VitalTransformation. March-in rights under the Bayh-Dole Act & NIH contributions to pharmaceutical patents. November 30, 2023. Available at: https://vitaltransformation.com/wp-content/uploads/2023/11/march-in_v11_BIO-approved-30Nov2023.pdf

than the pharmaceutical industry's contribution, with spending by NIH on phased development representing 9.8 to 10.7 percent of estimated industry spending.[10,11] Moreover, NIH sponsored research work is licensed for a fee after an arms-length negotiation with the university (government grant recipient) and is based on the value of the research at the time. Research that is further along will receive a higher royalty than earlier stage research. If final price is used as a factor in determining whether to exercise march-in rights, it is not based upon the NIH funded work exclusively but also leverages privately funded work and is therefore asking for an additional royalty many years after the agreement was made.

IV. Exercising March-in Rights Will Stifle Innovation with Limited Benefit

Research has shown that exercising march-in rights to control costs would be ineffective and has the potential to chill innovation with minimal gain. As march-in rights apply to patents rather than products, march-in rights would not serve their intended purpose unless every invention and every patent covering a drug is subject to Bayh-Dole. Drugs of this kind are very rare.[12] In the report, *March-in rights under the Bayh-Dole Act & NIH Contributions to pharmaceutical patents*, researchers found that only 5 of 361 therapies reviewed had a Government Interest Statement for all mechanism of action and composition of action patents covering the inventions in the drug. This represents approximately 1.4 percent of the drugs in the research cohort.

V. Price Should Not Be Used as a Factor in Determining Whether to Exercise March-in Rights Because of the Challenge Posed by the Inability of this Guidance to Adequately Articulate a Framework for Evaluating how Value Impacts Prices and Associate a Specific Patent with the Full Value of a Drug, Including its Treatment Costs, the Cost Offsets it May Produce, and its Benefits to Patients

A transparent decision-making process for exercising march-in rights is vital to investment and innovation. The definitions and standards in the draft guidance fall short. The draft guidance notes that when evaluating criteria for march-in, "the initial price may also be considered if it appears that the price is extreme, unjustified, and exploitative of a health or safety need," and "whether action may be needed to meet the needs of the Government or protect the public against nonuse or unreasonable use of the subject invention may include consideration of factors that unreasonably limit availability of the invention to the public, including the reasonableness of the price and other terms at which the product is made available to end-users." The draft guidance does not outline specifically how the agency would determine whether a price is "extreme, unjustified, and exploitative of a health or safety need," and how "reasonableness of the price" would be evaluated.

A pivotal challenge with including pricing considerations is the inability to adequately associate a specific patent with the full value of a drug, including its treatment costs, the cost offsets it may produce, and its benefits to patients. It is not feasible for a guidance document relevant to multiple agencies to put forward a meaningful value framework given the highly specialized capabilities, personnel and experience needed to assess pricing appropriately across the many innovations that the guidance will

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[10] DiMasi JA, Grabowski HG, Hansen RW. Innovation in the pharmaceutical industry: New estimates of R&D costs. J Health Econ. 2016 May;47:20-33. doi: 10.1016/j.jhealeco.2016.01.012. Epub 2016 Feb 12. PMID: 26928437.

[11] Zhou EW, Jackson MJ, Ledley FD. Spending on Phased Clinical Development of Approved Drugs by the US National Institutes of Health Compared With Industry. JAMA Health Forum. 2023;4(7):e231921. doi:10.1001/jamahealthforum.2023.1921

[12] O'Loughlin G, Schultess D. VitalTransformation. March-in rights under the Bayh-Dole Act & NIH contributions to pharmaceutical patents. November 30, 2023. Available at: https://vitaltransformation.com/wp-content/uploads/2023/11/march-in_v11_BIO-approved-30Nov2023.pdf

cover. NPC has numerous resources on appropriate tools for value assessment that incorporate specific practices for evidence evaluation such as treatment costs, the cost offsets it may produce, and its benefit to patients that apply specifically to drugs (see below). Including price as a factor is overbroad, will chill innovation, and will not meaningfully address value in Agencies' investments.

- NPC's *Guiding Practices for Patient-Centered Value Assessment* includes 33 specific elements surrounding six key aspects of value assessment, including the assessment process, scientific methodology, benefits, costs, evidence, and dissemination and utilization.[13]
- *Principles for planning and conducting comparative effectiveness research*, published by NPC researchers alongside a team of international collaborators, highlights thirteen principles for planning and conducting comparative effectiveness research.[14]
- *The Myth of Average: Why Individual Patient Difference Matter*, published by NPC, provides recommendations for ways improving the patient-centeredness of value assessment.[15]
- ISPOR and the International Society for Pharmacoepidemiology (ISPE) have published good practices for real-word data studies of comparative effectiveness with the goal of providing a trustworthy foundation for use of real world evidence (RWE) in decision-making.[16]
- *Key principles for the improved conduct of health technology assessments for resource allocation decisions*, published by a leading team of value assessment experts, offers a set of 15 principles for health technology assessments.[17]
- The Innovation and Value Initiative provides recommendations applying the tools of value assessment, with an emphasis on consensus among stakeholder communities.[18]
- PhRMA's *Principles for Value Assessment Frameworks* offers 15 principles tailored to meeting patient needs and improving healthcare decision-making.[19]
- *Domains of Patient Centeredness in Value Assessment*, authored by the National Health Council (NHC), highlights the key areas for healthcare stakeholders to focus on when implementing patient perspectives in value assessments.[20]
- The NHC also created a Patient-Centered Value Model Rubric for healthcare stakeholders to assess the use of patient centeredness in value model development and to guide model developers on how to implement patient engagement throughout the value modeling process.[21]

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[13] National Pharmaceutical Council. Guiding Practices for Patient-Centered Value Assessment. 2024. Washington, DC. Available at: https://www.npcnow.org/sites/default/files/2024-01/2024%20Guiding%20Practices%20for%20Patient-Centered%20Value%20Assessment%20January.pdf

[14] Luce BR, Drummond MF, Dubois RW, Neumann PJ, Jönsson B, Siebert U, Schwartz JS. Principles for planning and conducting comparative effectiveness research. J Comp Eff Res. 2012 Sep;1(5):431-40.

[15] National Pharmaceutical Council. The Myth of Average: Why Individual Patient Differences Matter. 2022. Washington, DC. Available at: https://www.npcnow.org/sites/default/files/2022-01/The_Myth_of_Average_01.2022.pdf

[16] Berger ML, Sox H, Willke RJ, Brixner DL, Eichler HG, Goettsch W, Madigan D, Makady A, Schneeweiss S, Tarricone R, Wang SV, Watkins J, Mullins CD. Good Practices for Real-World Data Studies of Treatment and/or Comparative Effectiveness: Recommendations from the Joint ISPOR-ISPE Special Task Force on Real-World Evidence in Health Care Decision Making. Value Health. 2017 Sep;20(8):1003-1008.

[17] Drummond M, Schwartz JS, Jansson B, Luce BR, Neumann BR, Seibert U, Sullivan SD. Principle 10. Key Principles for the Improved Conduct of Health Technology Assessments for Resource Allocation Decisions. International Journal of Technology Assessment in Health Care. 2008. 24:3:250.

[18] Innovation and Value Initiative. Principles for Value assessment in the US. https://thevalueinitiative.org/principles-for-valueassessment-in-the-us/

[19] PhRMA. (2016). Principles for Value Assessment Frameworks. Available at: https://phrma.org/resource-center/Topics/Costand-Value/Principles-for-Value-Assessment-Frameworks

[20] National Health Council. Domains of Patient Centeredness in Value Assessment. 2020. Available at: https://nationalhealthcouncil.org/wp-content/uploads/2020/03/NHC-One-Pagers_Domains.pdf

[21] National Health Council. (2016). The Patient Voice in Value: The National Health Council Patient-Centered Value Model Rubric. Available at: https://nationalhealthcouncil.org/wp-content/uploads/2020/11/20160328-NHC-Value-Model-Rubricfinal.pdf; National Health Council. (2021). Value Classroom. https://nationalhealthcouncil.org/education/value-classroom/

Conclusion

The National Pharmaceutical Council asks the agency to consider our comments in response to the RFI and to remove price as a factor in determining whether to exercise march-in rights from the draft guidance framework. We would be happy to meet to expand upon our comments and share this research. Please contact me at john.obrien@npcnow.org or (202) 827-2080 if we may provide any additional information.

Sincerely,

John M. O'Brien, PharmD, MPH
President and Chief Executive Officer