RESPONSE

REDEFINING INNOVATION FOR PHARMACEUTICAL REGULATION[†]

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CONTENTS

[†] An invited response to Rachel E. Sachs, W. Nicholson Price II & Patricia J. Zettler, *Rethinking Innovation at FDA*, 104 B.U. L. REV. 513 (2024).

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INTRODUCTION

In *Rethinking Innovation at FDA*, Rachel Sachs, Nicholson Price, and Patricia Zettler critically analyze the institutional advantages and disadvantages of regulating innovation at the U.S. Food and Drug Administration ("FDA"). After demonstrating that FDA should not use broad innovation concerns to lower safety and efficacy standards or allow future product development to influence decisions about safety and efficacy of a specific drug currently before the Agency, they examine the advantages and disadvantages of an innovation-focused FDA.[1] Sachs, Price and Zettler describe the numerous ways the Agency considers pharmaceutical innovation and call for policymakers to thoughtfully consider both the opportunities and challenges of regulating pharmaceutical innovation at the FDA. These include internal agency choices, congressionally directed initiatives, ministerial judgments, and the inevitable impacts on innovation. Their nuanced analysis contributes to a growing interdisciplinary literature reexamining the role of innovation regulation in healthcare more broadly, including drugs, medical devices,[2] primary care,[3] health technologies[4] and much more.[5] In arguing against FDA's consideration of future innovation in specific drug approvals, *Rethinking Innovation at FDA* provides a regulatory

[1] Rachel E. Sachs, W. Nicholson Price II & Patricia J. Zettler, *Rethinking Innovation at FDA*, 104 B.U. L. REV. 101, 562.

[2] *See, e.g.*, Daniel B. Kramer, Yongtian T. Tan, Chiaki Sato & Aaron S. Kesselheim, *Ensuring Medical Device Effectiveness and Safety: A Cross National Comparison of Approaches to Regulation*, 69 FOOD & DRUG L.J. 1, 1-2 (2014); Ariel Dora Stern, *Innovation Under Regulatory Uncertainty: Evidence from Medical Technology*, 145 J. PUB. ECON. 181, 181 (2017).

[3] *See, e.g.*, Bruce E. Landon, Gabe Weinreb & Asaf Bitton, *Making Sense of New Approaches to Primary Care Delivery: A Typology of Innovations in Primary Care*, NEW ENG. J. MED. CATALYST, May 9, 2022, at 1, 1; JoAnn E. Kirchner, Jeffrey L. Smith, Byron J. Powell, Thomas J. Waltz & Enola K. Proctor, *Getting a Clinical Innovation into Practice: An Introduction to Implementation Strategies*, PSYCHIATRY RSCH., Jan., 2020, at 1, 1 (2020); Bruce Finke, Kathryn Davidson & Purva Rawal, *Addressing Challenges in Primary Care—Lessons To Guide Innovation*, JAMA HEALTH F., Aug. 19, 2022, at 1, 1.

[4] *See, e.g.*, Juan Carlos Rejon-Parilla, Jaime Espin & David Epstein, *How Innovation Can Be Defined, Evaluated and Rewarded in Health Technology Assessment*, HEALTH ECON. REV., Jan. 3, 2022, at 1, 1 (2022); Viknesh Sounderajah et al., *Are Disruptive Innovations Recognized in the Healthcare Literature? A Systematic Review*, 7 BMJ INNOVATIONS 208, 208 (2021); Robert S. Rudin, David W. Bates & Calum MacRae, *Accelerating Innovation in Health IT*, 375 NEW ENG. J. MED. 815, 817 (2016) ("The transformative potential of IT is no less powerful in health care than in other industries. The essential missing ingredient is a forum for innovation. Dedicated programs that facilitate collaboration among developers and users will help accelerate innovation so that health care can catch up with the modern world.").

[5] *See* Namita Seth Mohta, Edward Prewitt, Lisa Gordon & Thomas H. Lee, *Health Care Innovation, Locally and Globally*, NEJM CATALYST (July 19, 2023), https://catalyst.nejm.org/doi/full/10.1056/CAT.23.0216 ("Care delivery innovation is a goal and a necessity globally. Health care leaders and clinicians everywhere seek to provide better care at better value, improve the experience of patients, and — of increasing concern — [sic] protect the experience of health care workers.").

analysis in support of a growing reconceptualization of pharmaceutical innovation.

This Response explores their corollary question: If not FDA, who should regulate pharmaceutical innovation? As Sachs, Price, and Zettler astutely observe, "policymakers should actively consider [institutional advantage] tradeoffs both within and outside FDA as they make decisions about FDA's own innovation judgments."[6] They identify other agencies who may be better equipped to address innovation, including the National Institute of Health ("NIH"), the U.S. Patent and Trade Office ("PTO"), the Centers for Disease Control and Prevention, ("CDC"), the Centers for Medicare and Medicaid Services ("CMS"), or a new agency tasked with innovation regulation.[7] They lay out the institutional advantages and limitations of these agencies to regulate pharmaceutical innovation. I argue the answer to who should regulate innovation is predicated upon a consideration of what is pharmaceutical innovation. Part I illustrates the need for a new measurable definition of pharmaceutical innovation to match the broader paradigm shift redefining pharmaceutical innovation to mean assessment of therapeutic value. Part II considers the potentially conflicting dimensions of pharmaceutical innovation, and Part III explores how Medicare drug pricing negotiations after the Inflation Reduction Act ("IRA") may lay the foundation for value-based pharmaceutical innovation regulation and would also benefit from a measurable definition of pharmaceutical innovation.

I. CURRENT MEASURES OF PHARMACEUTICAL INNOVATION ARE INSUFFICIENT

Innovation is a much sought-after goal in the pharmaceutical context.[8] Interdisciplinary scholars agree that innovation benefits from optimized

[6] Sachs et al., *supra* note 1, at 574-75.

[7] *Id.* at 568, 574-76.

[8] Robert M. Califf, Comm'r, FDA, Remarks by Commissioner Robert Califf to the 2023 Food and Drug Law Institute (FDLI) Annual Conference (May 17, 2023) (prepared remarks available at https://www.fda.gov/news-events/speeches-fda-officials/remarks-commissioner-robert-califf-2023-food-and-drug-law-institute-fdli-annual-conference-05172023) ("Make no mistake . . . the U.S. continues to be the number one innovator in medical products, producing drugs, biologics, tests, and devices that fuel health care around the world." (ellipses in original)); Steven Morgan, Ruth Lopert & Devon Greyson, *Toward a Definition of Pharmaceutical Innovation*, 2 OPEN MED. 4, 4 (2008) ("Ongoing debates in the pharmaceutical sector about intellectual property, pricing and reimbursement, and public research investments have a common denominator: the pursuit of innovation. However, there is little clarity about what constitutes a true pharmaceutical innovation, and as a result there is confusion about what kind of new products should be pursued, protected and encouraged through health policy and clinical practice. If the concept of pharmaceutical innovation can be clarified, then it may become easier for health policy-makers and practitioners to evaluate, adopt and procure products in ways that appropriately recognize, encourage and give priority to truly valuable pharmaceutical innovations." (footnotes omitted)). Christopher Buccafusco

regulation because "innovation governance involves risk-risk tradeoffs. . . . [E]xcessive regulation may deprive society of valuable new inventions, [but] insufficient regulation poses serious, even catastrophic risks to society."[9] There are widespread efforts to measure innovation,[10] as government agencies, industry professionals, and patient advocacy groups want to know if various policies will incentivize or hurt innovation.

Despite this widespread goal of incentivizing innovative drugs, there is still little clarity or agreement on what constitutes pharmaceutical innovation.[11] The term means different things to different groups.[12] Consequently, it is difficult to differentiate well-founded concerns about misaligned incentives from economically self-serving "innovation bulling."[13] A measurable, unified definition of pharmaceutical innovation[14] would facilitate optimal regulation; it

& Samuel N. Weinstein, *Antisocial Innovation*, 58 GA. L. REV. 573, 573 (2024) ("Innovation is a form of civic religion in the United States.").

[9] Buccafusco & Weinstein, *supra* note 8, at 586 (footnote omitted).

[10] *See, e.g.*, Naohiko Wakutsu, Emi Hirose, Naohiro Yonemoto & Sven Demiya, *Assessing Definitions and Incentives Adopted for Innovation for Pharmaceutical Products in Five High-Income Countries*: *A Systematic Literature Review*, 37 PHARM. MED. 53, 58 (2023).

[11] Some discoveries, like the discovery of insulin or amoxicillin, are unquestionably examples of pharmaceutical innovation. The precise boundaries of what is or is not innovative remain undefined. *See* Chris Morris, *10 Wonder Drugs That Changed Our Lives Forever*, CNBC (Apr. 1, 2016, 12:48 PM), https://www.cnbc.com/2016/03/28/10-wonder-drugs-that-changed-our-lives-forever.html [https://perma.cc/AUH3-QZAX]; Jeffrey K. Aronson, Robin E. Ferner & Dyfrig A. Hughes, *Defining Rewardable Innovation in Drug Therapy*, 11 NATURE REVS. DRUG DISCOVERY 253, 253 (2012) ("Not every medicine is innovative or, when innovative, to the same degree. We need to decide what is and what is not, to encourage innovation and to decide what is rewardable.").

[12] Morgan et al., *supra* note 8, at 4; *see also* Daniel G. Aaron, *The Fall of FDA Review*, 22 YALE J. HEALTH POL'Y L. & ETHICS 95, 108 (2023) ("What explains the lack of critical interrogation of what innovation *is*?"). A review of the definition of innovation across eleven high-income countries found:

> [I]n the regulatory guidelines and associated documents as well as there is no uniform usage of the term "innovation." In some countries, the term is used to explicitly refer to new drugs that fulfill certain criteria, with added therapeutic benefit generally being the most important criterion (France, Italy, and Japan). In England, on the contrary, the National Institute for Health and Care Excellence (NICE) seems to generally adopt a broader definition of innovation, stating that innovation can but "does not necessarily lead to better outcomes than the existing practice." Therefore, they define certain aspects of innovation that make it a rewardable innovation. The remaining countries do not use the term "innovative" or "innovation" in their guidelines or related documentation.

Sarah Hofmann, Jennifer Branner, Arpit Misra & Hannah Lintener, *A Review of Current Approaches to Defining and Valuing Innovation in Health Technology Assessment*, 24 VALUE HEALTH 1773, 1775 (2021) (citations omitted).

[13] Cynthia Ho & Liza Vertinsky, *"Innovation Bullying" in Drug Policy*, HEALTH AFFS. FOREFRONT (Sept. 11, 2023), https://www.healthaffairs.org/content/forefront/innovation-bullying-drug-policy.

[14] *See* Aronson et al., *supra* note 11, at 253 ("The need to define innovation in relation to medicinal products stems in part from a desire to stimulate innovation by recognizing it and

is a predicate to answering if a policy effectively incentivizes innovation and if the value generated by a policy is proportional to the cost.[15]

In its absence, concerned parties answer these questions with an assortment of easy to measure surrogate markers of innovation. In a 2013 taxonomy of publications addressing drug innovation across the medical, economic, and legal literature, 50% of the studies considered the marker of pharmaceutical innovation was the number of new drugs approved by FDA in a year.[16] Even the Congressional Budget Office utilized the annual number of new drugs coming to market as a measurement of innovation when estimating the impact of the IRA on drug development and innovation in 2022.[17] The second most common marker of innovation was assessment of therapeutic value (33%), followed distantly by patents (10%) and economic markers (7%).[18]

However, using FDA approvals as a marker of innovation may fail to capture important facets of innovation. Sachs, Price, and Zettler correctly point out FDA is statutorily authorized to make drug approvals determinations based on safety and efficacy rather than direct considerations of innovation.[19] FDA is not authorized to consider commercial success, patient access, value, or social need,

rewarding it appropriately. Indeed, innovativeness is increasingly becoming a major consideration in the valuation of new medicines . . . .").

[15] Stefan Larsson, Jennifer Clawson & Robert Howard, *Value-Based Health Care at an Inflection Point: A Global Agenda for the Next Decade*, NEW ENG. J. MED. CATALYST, Feb. 24, 2023, at 1, 1 ("A growing number of health care organizations around the world are using the systematic measurement of health outcomes that matter to patients — and the costs required to deliver those outcomes — as a catalyst for innovation and continuous improvement.").

[16] A.S. Kesselheim, B. Wang & J. Avorn, *Defining "Innovativeness" in Drug Development: A Systematic Review*, 94 CLINICAL PHARMACOLOGY & THERAPEUTICS 336, 338 (2013).

[17] CONG. BUDGET OFF., ESTIMATED BUDGETARY EFFECTS OF SUBTITLE I OF RECONCILIATION RECOMMENDATIONS FOR PRESCRIPTION DRUG LEGISLATION 5 (2022) ("CBO estimates that under the bill, the number of drugs that would be introduced to the U.S. market would be reduced by about 2 over the 2023-2032 period . . . ."); *see also ICYMI: Biden's Drug Price Controls Kill Innovation and Drive-Up Long-Term Costs*, HOUSE BUDGET COMM. (June 1, 2023), https://budget.house.gov/press-release/icymi-bidens-drug-price-controls-kill-innovation-and-drive-up-long-term-costs ("Unfortunately, CBO's analysis appears to have significantly underestimated the impact and consequences from the IRA's price controls on drug development and innovation.").

[18] Kesselheim et al., *supra* note 16, at 338.

[19] *Cf.* Margaret A. Hamburg, *Innovation, Regulation, and the FDA*, 363 NEW ENG. J. MED. 2228, 2230-31 (2010). (Former FDA commissioner Dr. Margret Hamburg has argued FDA has an important role in innovation regulation, stating "the increasingly rigorous standards of the FDA created the conditions for innovation and progress in the pharmaceutical market, and together, American medicine and the FDA have accomplished an enormous amount" and that "[t]he FDA must work with its partners to promote innovation and creativity at various points throughout the development process." *Id.*; *What We Do*, FOOD & DRUG ADMIN. (NOV. 21, 2023), https://www.fda.gov/about-fda/what-we-do (noting FDA includes as part of its mission "helping to speed innovations that make medical products more effective, safer, and more affordable").

amongst other factors. Thus, measuring pharmaceutical innovation by the annual number of FDA approvals is an incomplete marker of innovation at best.

Over the last decade, interdisciplinary scholars have increasingly criticized reliance on the number of approvals as a marker of pharmaceutical innovation.[20] "[T]his criterion is no longer sufficient from the perspective of many stakeholders."[21] The growing perception that innovation is more than the number of new drugs approved underscores how *Rethinking Innovation at FDA* is part of a broader paradigm shift.[22] Sachs, Price and Zettler's descriptions of the legal limits of FDA and innovation provides a regulatory backing to this movement towards broader conceptualizations of pharmaceutical innovation.

Answering who should regulate pharmaceutical innovation requires an agreed-upon, measurable, shared understanding of what is pharmaceutical innovation and which goals should be perused, protected, and incentivized.[23] Currently, with conflicting criteria and lack of agreed upon measurements of innovation, almost any policy choice can be accused of hurting innovation. Policy tradeoffs cannot easily be compared or defended against such accusations without a clear delineation of what constitutes pharmaceutical innovation.[24] Moreover, without honest assessments of whether the innovation signals set by

[20] *E.g.*, Hofmann et al., *supra* note 12, at 1773. *Cf.* Naohiko Wakutsu et al., *supra* note 10, at 58 (2023) ("In the USA, an effective and safe treatment for a disease is defined as an innovative treatment, and innovation is defined in terms of new drugs that deliver substantial health benefits to patients and are approved by the FDA." (footnote omitted)).

[21] Hofmann et al., *supra* note 12, at 1773 ("[F]ormerly, denoting a new drug as innovative was based on the drug having received patent protection or being a new molecular entity . . . ."); *see also id.* at 1774 ("Formerly, the term [innovation] was mostly used to denote newly patented drugs or new molecular entities, thus, referring to the technological novelty of a drug. More recently, however, the central criterion to determine pharmaceutical innovation is the drug's value or benefit." (footnotes omitted)).

[22] *See generally* Sachs et al., *supra* note 1. Innovation may be conceptualized differently between disciplines. Engineers or bench scientists may view innovation differently than doctors running clinical trials or the Agency assessing safety and efficacy. Similarly, the drug patents can issue well over a decade before a single patient is prescribed the product. *See generally* Jeffrey Funk, *Beyond Patents: Scholars of Innovation Use Patenting as an Indicator of Both Innovativeness and the Value of Science. It Might Be Neither.*, ISSUES SCI. & TECH., Summer 2018, at 48, 48; Robin C. Feldman, David A. Hyman, W. Nicholson Price & Mark J. Ratain, *Negative Innovation: When Patents Are Bad for Patients*, 39 NATURE BIOTECH. 914, 914 (2021).

[23] Other scholars have recognized the tension between innovation and FDA. *See, e.g.*, Aaron, *supra* note 12, at 106 ("FDA's role is traditionally not 'innovation.' However, there are two ways in which FDA is increasingly being connected with innovation [including the] . . . pressure from industry to hurry products to market in order to expedite access to new products ('innovation') for patients . . . [and] the evidentiary bar new products must meet . . . [that] guard[s] against the sale of 'quack products,' [so that] FDA can protect market space for new products that are truly innovative." (footnotes omitted)).

[24] *See* Bernard Munos, *Lessons from 60 Years of Pharmaceutical Innovation*, 8 NATURE REVS. DRUG DISCOVERY 959, 960 (2009); Alexander Schuhmacher, Markus Hinder, Alexander Dodel, Oliver Gassman & Dominik Hartl, *Investigating the Origins of Recent Pharmaceutical Innovation*, 22 NATURE REVS. DRUG DISCOVERY 781, 781 (2023).

current policies are producing desired results, patients and families are at a higher risk for financial, emotional, and physical consequences from policies favoring numerous expensive less-impactful new drugs.[25] Transparency on which of the sometimes-conflicting aspects of innovation are being incentivized could benefit drug developers, regulators, and patient by improving public trust.[26] A quantifiable definition is overdue.

II. UNDERSTANDING PHARMACEUTICAL INNOVATION

What should pharmaceutical innovation mean? Oxford Advanced Learner's Dictionary defines innovation as "the introduction of new things, ideas or ways of doing something."[27] Newness (or perhaps novelty)[28] is similarly vital to pharmaceutical innovation. For example, the European Medical Agency defines innovation as "a medicine that contains an active substance or combination of active substances that has not been authorised before."[29] Historically, FDA conceptualized innovation as the discovery of a new molecular entity, defined as "an active ingredient that has never been marketed . . . in any form."[30] Yet new is not limited to new molecular entities. Policy makers and interdisciplinary scholars have long recognized that pharmaceutical innovation can be a new formulation, or a safer way to manufacture the product, or new way to slow drug absorption so that a product that works over a longer period and patients take

[25] Anjali D. Deshmukh, *Can We Get a Refund? Judicial Remedies for Drugs That Do Not Work*, TENN. L. REV. (forthcoming 2024) (on file with author); *see also* Buccafusco & Weinstein, *supra* note 8, at 581 (manuscript at 4) ("[M]any innovations have radically transformed human lives, prolonging and improving them. But we shouldn't let these breakthroughs distort our view of innovation as a whole. Vanishingly few innovations dramatically improve society, while many don't really affect it at all."); Michaela Tutone, Federico Villa, Antonio Addis, Francesco Trotta & Giovanni Tafuri, *How Do Drug Regulatory Bodies Deal with Potential Innovation Therapies?*, 54 THERAPEUTIC INNOVATION & REGUL. SCI. 195, 195 (2020) ("Harmonizing a definition and the criteria used to define pharmaceutical innovation would allow faster access to patients.").

[26] Morgan et al., *supra* note 8, at 4 ("If the concept of pharmaceutical innovation can be clarified, then it may become easier for health policy-makers and practitioners to evaluate, adopt and procure products in ways that appropriately recognize, encourage and give priority to truly valuable pharmaceutical innovations.").

[27] *Innovation*, OXFORD LEARNER'S DICTIONARIES, https://www.oxfordlearnersdictionaries.com/us/definition/english/innovation# [https://perma.cc/B5GN-UPQH] (last visited Feb. 14, 2023).

[28] Morgan et al., *supra* note 8, at 4 (comparing definitions of pharmaceutical innovation addressing newness and novelty).

[29] *Innovative Medicine*, EUR. MEDS. AGENCY, https://www.ema.europa.eu/en/ glossary/innovative-medicine# [https://perma.cc/9YKY-TCFA] (last visited Feb. 14, 2023).

[30] Derek J. Ward, Angharad Slade, Tracey Genus, Orsolina I. Martino & Andrew J. Stevens, *How Innovative Are New Drugs Launched in the UK? A Retrospective Study of New Drugs Listed in the British National Formulary (BNF) 2001-2012*, BMJ OPEN, Oct. 24, 2014, at 1, 1 (quoting 2014 FDA glossary of terms).

fewer pills in a day, amongst many other advantages.[31] "An important objective of modern pharmaceutical research is the discovery of new medical uses for known molecules,"[32] but "[d]eciding when newness constitutes true novelty may require value judgement."[33]

There is also a notion of "better" implied by the term pharmaceutical innovation.[34] Patients ultimately want to take a drug that produces more benefit or fewer side effects than its predecessors;[35] a new molecule that fails to improve the risk-benefit balance may not be innovation worth incentivizing.[36] As Rebecca Eisenberg noted over fifteen years ago, pharmaceutical innovation requires "the development of credible information about the effects of drugs."[37] Many think "innovative pharmaceutical" implies improved, increased value, or otherwise "healthier" compared to the status quo. That said, policies to spur development of truly "better" or "groundbreaking" drugs may reduce the overall number of drugs approved in a year, increase costs to patients, or impact access.

Other definitions of pharmaceutical innovation include newness, proven comparative effectiveness, cost, commercial value, and the gravity of the unmet social needs addressed.[38] Scholars disagree on the importance of commercial success as not all new drug approvals are valuable to society, even if they are a commercial success.[39] In contrast, IDEA Pharma's Pharmaceutical Innovation

[31] While each of these potential advances can be new and innovative, they may not bring value to patient outcomes in proportion with cost. *See* Aaron S. Kesselheim & Jerry Avorn, *Using Patent Data To Assess the Value of Pharmaceutical Innovation*, 37 J.L. MED. & ETHICS 176, 176 (2009); Hofmann et al., *supra* note 12, at 1774 ("Although the requirements for receiving a patent in pharmaceutical research are precisely defined and globally aligned, notions on what constitutes a rewardable aspect of innovation differ.").

[32] Warner-Lambert Co. v. Generics (UK) Ltd. [2018] UKSC 56 [1].

[33] Aronson et al., *supra* note 11, at 253.

[34] *Id.* ("There may be a fine line between drugs that are truly innovative and so-called 'me too' drugs, which are new but not novel. Indeed, small pharmacological differences between successive drugs may eventually lead to a major difference that can be regarded as being innovative in some respect . . . ."); *id.* at 254 ("The innovativeness of a medicinal product can arise from one or more of several properties: chemical structure; method of synthesis; drug class; method of formulation; and pharmacodynamic, pharmacokinetic, pharmacogenetic or therapeutic properties." (citing Jeffrey K. Aronson, *Something New Every Day: Defining Innovation and Innovativeness in Drug Therapy*, 31 J. AMBULATORY CARE MGMT. 65 (2008))).

[35] Sarah Hofmann et al., *supra* note 12, at 1773 ("More recently, however, the central criterion to determine pharmaceutical innovation is the drug's value or benefit. . . . A major challenge though remains to define what offers a value and, therefore, deserves reward.").

[36] Ho & Vertinsky, *supra* note 13 ("And not all innovation is good. Indeed, some new drugs may create more harm than benefit.").

[37] Rebecca S. Eisenberg, *The Role of the FDA in Innovation Policy*, 13 MICH. TELECOMM. & TECH. L. REV. 345, 347 (2007).

[38] Aronson et al., *supra* note 11, at tbl.S1 (Supp. 2012).

[39] *See* Daniel J. Hemel & Lisa Larrimore Ouellette, *Innovation Institutions and the Opioid Crisis*, J.L. & BIOSCIENCES, Jan.-June, 2020, at 1, 4 (2020). The opposite is also true; not all valuable drugs are commercially successful. This especially true with novel antibiotics, which

and Invention Index defines innovation as "[r]eturn on invention; creation of meaningful value from invention."[40] As opposed to primarily reflecting social needs[41] or commercial value,[42] others consider innovation as a multi-dimensional spectrum that includes the extent to which a new product addresses unmet or under met healthcare needs and the extent to which it improves healthcare outcomes (comparative effectiveness).[43] There is no universal definition of innovation.

Lastly, what is innovation is tied to questions of *when* innovation occurs.[44] For drugs, this is deceptively complicated. "Competition and technological change mean that the standard by which the unique value of a pharmaceutical innovation is measured" will change over time.[45] Government protections and policies aim to reward the initial innovative leap.[46] However, an innovative invention ten years ago may no longer be innovative today. Drugs are developed over an average of ten to fifteen years,[47] so it is not obvious when innovation

are most valuable to society when not used widely in order to limit the development of antibiotic resistance.

[40] Sy Mukherjee & IDEA Pharma, *The Most Innovative and Inventive Drug Companies of 2022 Set the Foundation for Success Before the Pandemic*, FORTUNE (Apr. 21, 2022), https://fortune.com/2022/04/20/top-pharmaceutical-companies-innovation-invention-2022/ [https://perma.cc/G268-LX7V].

[41] *See* Morgan et al., *supra* note 8, at 4-5 ("It is the uniqueness of such health improvements that defines pharmaceutical innovations. A drug can be considered a pharmaceutical innovation only if it meets otherwise unmet or inadequately met health care needs.").

[42] Hofmann et al., *supra* note 12, at 1773 ("[I]ncreasing focus on the value of new drugs in turn has also lead to a more differentiated notion of innovation in the context of pharmaceutical products.").

[43] Wakutsu et al., *supra* note 10, at 61 tbl.5 (The different dimensions of innovation identified were therapeutic benefit (forty-six studies), newness (thirty-two), novelty (twenty), cost (thirteen), unmet need (twelve), administration (five), availability of existing treatment (three), clinical evidence (three), and access (one)).

[44] *See* Stuart Minor Benjamin & Arti K. Rai, *Fixing Innovation Policy: A Structural Perspective*, 77 GEO. WASH. L. REV. 1, 11 (2008) ("[A]nother salient reason for the importance of innovation relates to timing. Because innovation is highly cumulative[,] . . . small changes in initial innovation conditions can have huge future impacts. . . . [T]he failure to sufficiently encourage an innovation at time T1 may mean that innovators at time T2 lack a crucial building block and thus that the course of innovation is significantly retarded."); *see also* Sachs et al., *supra* note 1, at 542 ("FDA may be well suited to making innovation-related judgments [because], unlike other biopharmaceutical innovation actors, FDA oversees a drug's entire lifecycle . . . ." (footnote omitted)).

[45] Morgan et al., *supra* note 8, at 5 ("[T]he notion of pharmaceutical innovation is time-dependant.").

[46] Olivier J. Wouters, Martin McKee & Jeroen Luyten, *Estimated Research and Development Investment Needed To Bring a New Medicine to Market, 2009-2018*, 323 JAMA 844, 844 (2020).

[47] Industry groups generally estimate that it takes ten to fifteen years on average to develop one new medicine from initial discovery to regulatory approval. Many rewards and incentives for innovation are given early in the drug development process, years before a drug is ever tested in patients. Maxime Derep, *What's the Average Time To Bring a Drug to Market in*

occurs. Is it defined at a single point or as a multidecade process? Innovation could be evaluated early, marked by NIH grant or patents. Alternatively, innovation could be evaluated later in a drug's life, marked by market entry, commercial value, or patient impact. It could also be defined as all five. Sachs, Price, and Zettler argue "[i]nnovation incentives should be dynamic, reflecting developments in the market and in science,"[48] suggesting a combination of early and late markers.

Taken together, these competing definitions illustrate that pharmaceutical innovation is not a monolithic idea, but a careful balance between potentially conflicting goals. Patients, payers, pharmaceutical manufactures, prescribers, scientists, and international interdisciplinary scholars passionately disagree about the appropriate balance between these dimensions of innovation. For example, the controversies analyzed in *Rethinking Innovation at FDA* can be conceptualized as disagreements about how to weigh concerns of effectiveness, medical need, and commercialization. The case studies of aducanumab (Aduhelm) and eteplirsen (Exondys 51) can be characterized as approvals that place inappropriate weight on the unmet need for Alzheimer's,[49] Duchenne's Muscular Dystrophy,[50] and yet to be developed future therapies, over the safety, efficacy, and social-value dimensions of innovation such as patient outcomes, access, and cost effectiveness.[51] The right balance is debatable. Therefore, the

2022?, N-SIDE (Nov. 5, 2022), https://lifesciences.n-side.com/blog/what-is-the-average-time-to-bring-a-drug-to-market-in-2022 [https://perma.cc/TD9V-C8AR]; Gaurav Agrawal, Felix Bader, Jan Günthner & Stephan Wurzer, *Fast to First-in-Human: Getting New Medicines to Patients More Quickly*, MCKINSEY & CO. (Feb. 10, 2023), https://www.mckinsey.com/industries/life-sciences/our-insights/fast-to-first-in-human-getting-new-medicines-to-patients-more-quickly. Some claim, however, it can be as high as thirty years. Fred D. Ledley, *30 Years Is Too Long To Wait for New Medicines. There Are Ways To Speed Up Drug Development*, STAT (June 6, 2018), https://www.statnews.com/2018/06/06/drug-development-speed-new-medicines/ [https://perma.cc/3WFY-FF26].

[48] Sachs et al., *supra* note 1, at 563.

[49] Patrizia Cavazzoni, *FDA's Decision To Approve New Treatment for Alzheimer's Disease*, FOOD & DRUG ADMIN (June 7, 2021), https://www.fda.gov/drugs/our-perspective/fdas-decision-approve-new-treatment-alzheimers-disease (Dr. Patrizia Cavazzoni, Director of FDA's Center for Drug Evaluation and Research, stating "Aduhelm is the first novel therapy approved for Alzheimer's disease since 2003" and "[t]he need for treatments is urgent"); *see also* Sachs et al., *supra* note 1, at 544-49.

[50] News Release, FDA, FDA Grants Accelerated Approval to First Drug for Duchenne Muscular Dystrophy (Sept. 29, 2016), https://www.fda.gov/news-events/press-announcements/fda-grants-accelerated-approval-first-drug-duchenne-muscular-dystrophy (Dr. Patrizia Cavazzoni, Director of FDA's Center for Drug Evaluation and Research, stating "Patients with a particular type of Duchenne muscular dystrophy will now have access to an approved treatment for this rare and devastating disease."); *see also* Sachs et al., *supra* note 1, at 544-49.

[51] There may be benefits to patients that are not captured by traditional metrics of therapeutic benefit. Many scholars' debate what counts as a clinically meaningful difference and if the tradeoff is worthwhile. Putting several compounds commonly taken together into one pill will improve the lives of patients who no longer require multiple pills per day. That

underlying policy question of how to best incentivize innovation (and whether is it better to incentivize *potential for* innovation or reward the *actual* pharmaceutical innovation itself) can be better answered with a measurable definition of pharmaceutical innovation.

This commentary is not intended to provide a comprehensive list of the dimensions of pharmaceutical innovation, nor to provide a solution to the timing of innovation.[52] Rather, it seeks only to illustrate that defining pharmaceutical innovation requires difficult ethical judgments balancing competing aspects of innovation. These include social value in addressing an unmet need, monetary value in commercialization, comparative effectiveness, timeliness, newness, novelty, and others.[53] With competing and conflicting ideas of what makes a drug innovative, pharmaceutical innovation is a contentious, fragmented concept. Without agreement on which competing aspects of innovation should be prioritized, it is not clear what is pharmaceutical innovation or which agency can best regulate it.

III. THE IRA AND PHARMACEUTICAL INNOVATION

The question of who should regulate innovation is, in fact, asking which agency or agencies should regulate which of the potentially conflicting fragments of pharmaceutical innovation. Innovation regulation in the United States is fragmented such that different agencies manage innovation in different ways for different types of science.[54] Simply put, the singular "office of innovation" Arti Rai and Stuart Benjamin called for in 2008 has yet to be developed.[55] Illustrating how regulation of pharmaceutical innovation is

advantage also delays generic competition, costing consumers billions of dollars. For example, delaying generic competition of one drug for two years was associated with $4.3-6.5 billion in additional spending for a single drug. Benjamin N. Rome, Frazer A. Tessema & Aaron S. Kesselheim, *US Spending Associated with Transition from Daily to 3-Times-Weekly Glatiramer Acetate*, 180 JAMA INTERNAL MED. 1165, 1165 (2020). Promoting competition and fair prices without deterring innovation is a complex antitrust legal challenge. *See generally* Michael A. Carrier & Steve D. Shadowen, *Product Hopping: A New Framework*, 92 NOTRE DAME L. REV. 167 (2017).

[52] Scholars disagree on what is pharmaceutical innovation. Different elements are used to assess the value of new drugs around the world. *See, e.g.*, ORG. FOR ECON. COOP. & DEV., PHARMACEUTICAL INNOVATION AND ACCESS TO MEDICINES 1 (2018); Aris Angelis, Ansgar Lange & Panos Kanavos, *Using Health Technology Assessment To Assess the Value of New Medicines: Results of a Systematic Review and Expert Consultation Across Eight European Countries*, 19 EUR. J. HEALTH ECON. 123, 123 (2018); Oriol de Solà-Morales et al., *Defining Innovation with Respect to New Medicines: A Systematic Review from a Payer Perspective*, 34 INT'L J. TECH. ASSESSMENT HEALTH CARE 224, 224 (2018); Tutone et al., *supra* note 25, at 195.

[53] *See* Aronson et al., *supra* note 11, at 254 ("Interpretation of 'significantly and substantially' requires value judgements.").

[54] *See* Benjamin & Rai, *supra* note 44, at 25 (2008).

[55] *Id.* at 56.

similarly disjointed,[56] Sachs, Price, and Zettler point to five potential who play a "limited" role in innovation regulation "at particular points in a drug's lifecycle."[57] This includes the NIH's "pull incentives" in small prizes for biomedical innovations and grants for basic or translational research, the PTO's role for issuing patents as the "Agency generally tasked with 'driv[ing] innovation,'"[58] and FDA's role in identifying drugs worthy of expedited approval pathways, issue guidance, and exclusivities.[59] The CDC identifies unmet needs and categorizes orphan and topical diseases.[60] Fifth, CMS can regulate pharmaceutical innovation in its role in helping to pay for drugs used by Medicaid and Medicare patients after FDA approval.[61] Who regulates innovation is particularly important in light of diminishing trust in public health agencies.[62]

Congress may have recently provided a partial answer to who should regulate an additional fragment of pharmaceutical innovation.[63] The 2022 IRA authorized CMS to negotiate the price Medicare pays for pharmaceuticals and to receive rebates when drug prices increase at a rate that exceeds inflation, amongst other measures.[64] Heralded as "the first major piece of legislation with

[56] *Id.* at 20-21.

[57] Sachs et al., *supra* note 1, at 543.

[58] *Id.* at 540 (quoting *U.S. Patent and Trademark Office*, U.S. DEPT. OF COM., https://www.commerce.gov/bureaus-and-offices/uspto [https://perma.cc/MV6G-KZLB] (last visited Feb. 14, 2024))); *see also* Rebecca E. Wolitz, *States, Preemption, and Patented Drug Prices*, 52 SETON HALL L. REV. 385, 392 (2021) ("[T]he federal patent system is best understood as being charged with *sufficiently* incentivizing innovation." (emphasis added)).

[59] Sachs et al., *supra* note 1, at 534-40, 542-43.

[60] *Id.* at 569-70.

[61] *Id.* at 558-59.

[62] Selena Simmons-Duffin, *Poll Finds Public Health Has a Trust Problem*, NPR (May 13, 2021, 12:01 AM), https://www.npr.org/2021/05/13/996331692/poll-finds-public-health-has-a-trust-problem [https://perma.cc/2LWE-5P2M]; Sachs et al., *supra* note 1, at 560-61.

[63] Rachel Sachs, Loren Adler & Richard Frank, *A Holistic View of Innovation Incentives and Pharmaceutical Policy Reform*, HEALTH AFFS. SCHOLAR, July, 2023, at 1, 1 ("The IRA's negotiation program centers innovation in three main ways, which we categorize as preserving innovation *as a whole,* innovation in *certain classes of products*, and innovation specifically delivering *high value for patients*." (emphasis in original)).

[64] In addition to price negotiation, the IRA requires CMS to justify formulary placement of selected drugs on non-preferred tiers, justify if utilization management applies to the selected drugs, and expand coverage to selected drugs. Inflation Reduction Act of 2022, Pub. L. No. 117-169, 136 Stat. 1818, 1833-34, 66, § 1191, 11101(A)(i)(2)(B) (codified at 42 USC 1320f). Juliette Cubanski, Anthony Damico & Tricia Neuman, *How Medicare's New Drug Price Negotiation Program Could Expand Access to Selected Drugs*, KFF (Sept. 26, 2023), https://www.kff.org/medicare/issue-brief/how-medicares-new-drug-price-negotiation-program-could-expand-access-to-selected-drugs/ [https://perma.cc/2F9U-TQRH]; *see also Medicare Drug Price Negotiation*, U.S. CTRS. FOR MEDICARE & MEDICAID SERVS., https://www.cms.gov/inflation-reduction-act-and-medicare/medicare-drug-price-negotiation [https://perma.cc/4LX7-6FU4] (last modified Dec. 8, 2023).

an explicit focus on drug price regulation,"[65] CMS can potentially "improve access to lifesaving drugs for millions of people with Medicare while driving market competition and scientific innovation."[66]

Under the IRA, the Secretary for the Department of Health and Human Services negotiates drug prices with participating manufacturers on certain drugs. CMS selects ten drugs that meet specific cost-criteria, and determines a "maximum fair price"[67] after balancing a list of factors. Several of the factors that CMS must consider in negotiating prices are also dimensions of pharmaceutical innovation value. For example, both the effectiveness of the selected drug and its therapeutic alternatives and the extent to which the selected drug and its therapeutic alternatives address unmet needs are aspects of value-based innovation.[68] Thus, the IRA aligns with the interdisciplinary paradigm shift redefining pharmaceutical innovation as assessment of therapeutic value.

The proper balance between these competing dimensions of pharmaceutical innovation inspires considerable debate and criticism. CMS is already facing accusations of stifling pharmaceutical innovation.[69] Although some U.S. government departments[70] and peer countries engage in price negotiations to

[65] Karl Stark, *Medicare's New Price-Setting Powers Are Historic but Could Harm Innovation, an LDI Fellow Warns*, PENN LDI (May 1, 2023), https://ldi.upenn.edu/our-work/research-updates/medicares-new-price-setting-powers-are-historic-but-could-harm-innovation-an-ldi-fellow-warns/ [https://perma.cc/698C-SJCE].

[66] Press Release, CMS, CMS Releases Revised Guidance for Historic Medicare Drug Price Negotiation Program, U.S. CTRS. FOR MEDICARE & MEDICAID SERVS. (June 30, 2023) [hereinafter *CMS Press Release*], https://www.cms.gov/newsroom/press-releases/cms-releases-revised-guidance-historic-medicare-drug-price-negotiation-program [https://perma.cc/A99F-9FP4].

[67] Inflation Reduction Act § 1191. CMS must select eligible drugs with the highest gross Medicare spending in the year prior to selection. *Id.* § 1192(b); *see also* Ho & Vertinsky, *supra* note 13; CMS Press Release, *supra* note 66 ("CMS will consider the selected drug's clinical benefit, the extent to which it fulfills an unmet medical need, and its impact on people who rely on Medicare, among other considerations, such as costs associated with research and development and production and distribution for selected drugs.").

[68] Inflation Reduction Act, §1192(e) of 2022, Pub. L. No. 117-169, 136 Stat. 1818 (2022); *see also* Juliette Cubanski, *FAQs About the Inflation Reduction Act's Medicare Drug Price Negotiation Program*, KFF (Aug. 8, 2023), https://www.kff.org/medicare/issue-brief/faqs-about-the-inflation-reduction-acts-medicare-drug-price-negotiation-program/ [https://perma.cc/K6E3-KXF3]; Sachs et al., *supra* note 63, at 2 ("[T]he IRA aims to limit adverse impacts on innovation that delivers high clinical value for patients, particularly in cases when new products provide only marginal or no clinical benefits when compared with existing treatments. As part of the negotiation process, Medicare must consider a drug's 'comparative effectiveness' and 'therapeutic alternatives,' as well as whether the drug 'address[es] unmet medical needs' for patients.").

[69] Asher Mullard, *Pushing Both Sides of the Drug Pricing Aisle*, 22 NATURE REVS. DRUG DISCOVERY 779, 779 (2023).

[70] Other government entities negotiate drug prices, including the Veterans Administration, Department of Defense, Coast Guard, Public Health Service, and Medicaid. *Determining the Cost of Pharmaceuticals for a Cost-Effectiveness Analysis*, U.S. Dep't of Veteran Affs.,

limit spending on healthcare without deleterious effects on the supply of innovative new drugs,[71] opponents claim the IRA "would kill innovation."[72] While these claims are prevalent,[73] multiple scholars have questioned their accuracy. "Claims of innovation harm are almost always made without any independent, substantiated evidence linking proposed measures to actual social welfare harm, let alone evidence of harm that would exceed the benefits associated with the proposed measure."[74]

Unfortunately, the IRA does not provide a measurable definition of innovation against which policy outcomes can be measured. Without clarity on what "counts" as pharmaceutical innovation, it is not possible to objectively evaluate the successes, failures, and unintended consequences of the IRA or any other policy proposals to incentivize pharmaceutical innovation. An agreed upon easily measurable definition of pharmaceutical innovation can increase transparency and public trust in agencies tasked with innovation regulation.[75]

https://www.herc.research.va.gov/include/page.asp?id=pharmaceutical-costs (last updated Feb. 15, 2022); *Medicaid Price Negotiation*, CMS.GOV, https://www.cms.gov/ inflation-reduction-act-and-medicare/medicare-drug-price-negotiation [https://perma.cc/596P-Y7N2] (last visited Feb. 14, 2024).

[71] *See, e.g.*, Ward et al., *supra* note 30, at 1; Rejon-Parilla et al., *supra* note 4, at 1; Aronson et al., *supra* note 11, at 254 ("Whether pharmaceutical innovation should be rewarded is a social value judgement that must take into account the opportunity costs of doing so. The acceptance of such costs implies that innovation needs to be defined in terms of what an innovation is and what it should do. The level of reward will depend on the degree of innovativeness and the rewarder's willingness to pay. Defining rewardable innovation, as we have done here [for the UK], should facilitate such judgements.").

[72] Ho & Vertinsky, *supra* note 13 (quoting *Senate Passes Drug Price Controls; Legislation Would Kill Innovation, Access*, BIO.NEWS (Aug. 8, 2022), https://bio.news/federal-policy/senate-passes-drug-price-controls-legislation-would-kill-innovation-access/ [https://perma.cc/4YV4-CHFR]); *see also* Joe Grogan, Opinion, *The Inflation Reduction Act Is Already Killing Potential Cures*, WALL ST. J. (Nov. 3, 2022, 6:20 PM), https://www.wsj.com/articles/the-inflation-reduction-act-killing-potential-cures-pharmaceutical-companies-treatment-patients-drugs-prescriptions-ira-manufacturers-11667508291. Pharmaceutical companies have launched multiple legal challenges to this program, including allegations of violations of free speech, taking property without fair compensation, deprivation of due process, and excessive fines. Lawrence O. Gostin, James G. Hodge, Jr. & Andrew J. Twinamatsiko, *Medicare's Historic Prescription Drug Price Negotiations*, 330 JAMA 1621, 1621 (2023).

[73] Larry Levitt, *The 4 Arguments You Will Hear Against Drug Price Negotiation*, N.Y. TIMES (Sept. 6, 2023), https://www.nytimes.com/2023/09/06/opinion/medicare-drug-price-negotiation.html ("The idea that curbs on drug pricing will stifle innovation has long been the pharmaceutical industry's go-to argument."); *see also* Press Release, PhRMA, *PhRMA Statement on First List of Medicines Subject to Government Price-Setting* (Aug. 29, 2023), https://phrma.org/resource-center/Topics/Access-to-Medicines/PhRMA-Statement-on-First-List-of-Medicines-Subject-to-Government-Price-Setting [https://perma.cc/9ZFH-2WDD].

[74] Ho & Vertinsky, *supra* note 13 (defining "innovation bullying" as "[t]he threat that any intervention not designed purely to preserve or increase private sector incentives will chill innovation is used as a hammer on policymakers to deter even modest regulatory initiatives.").

[75] *Id.*; Aronson et al., *supra* note 11.

Ultimately, the IRA further fragments an already fragmented innovation regulatory system.[76] While some fragmentation may be optimal, the IRA still leaves many aspects of pharmaceutical innovation relatively unregulated. For example, the IRA directs the CMS to negotiate the price of a small number of drugs at one point in a drug's lifecycle after approval.[77] The vast majority of FDA-approved drugs do not quality. Even for qualifying drugs, the negotiated price does not apply across the drug's full lifespan. However, with "the potential to transform the ways in which Medicare pays for drugs, and to provide financial benefits to millions of seniors who have difficulty affording their medications," the IRA may "be just the beginning, rather than the end, of developments over Medicare drug price negotiation."[78] For now, CMS regulates another small piece of pharmaceutical innovation after the IRA. Congress has yet to answer who should regulate all aspects of pharmaceutical innovation or even what innovation means. Optimal pharmaceutical innovation regulation deserves further consideration.

CONCLUSION

Innovative drugs are potentially many things: they are new, novel, timely, commercially successful products; proven to be better, safer, or more effective beyond prior therapies; they address important unmet social needs and so much more. The historically relied-upon measure of the number of new drug approvals in a year is poor proxy for all the dimensions of innovation. The ongoing interdisciplinary paradigm shift reexamining FDA's relationship to pharmaceutical innovation underscores conflicting views of what is innovation. Sachs, Price, and Zettler, in *Rethinking Innovation at FDA* provide a legal analysis to this shift, demonstrating FDA should not consider innovation in determining an individual drug's safety and efficacy, in part, due to the

[76] CMS is not tasked with regulating pharmaceutical innovation directly across all drugs, or to engage in comparative effectiveness of all pharmaceutical products broadly. Rather, CMS is tasked with considering some aspects of innovation at a specific point in a drugs' lifecycle of an extremely limited number of drugs. *See* Rachel E. Sachs, *Administering Health Innovation*, 39 CARDOZO L. REV. 1991, 2012-15 (2018).

[77] Cubanski, *supra* note 68 ("Drugs qualify for price negotiation for 2026 if they are covered under Medicare Part D, Medicare's outpatient prescription drug benefit program, and are single source brand-name drugs or biological products without therapeutically-equivalent generic or biosimilar alternatives that are approved or licensed and marketed on a 'bona fide' basis. . . . In addition, a drug product must be at least 7 years (for small-molecule drugs) or 11 years (for biologics) past its FDA approval or licensure date, as of the date that the list of drugs selected for negotiation is published.").

[78] Rachel Sachs, *Understanding the Democrats' Drug Pricing Package*, HEALTH AFF. FOREFRONT (Aug. 10, 2022), https://www.healthaffairs.org/content/forefront/understanding-democrats-drug-pricing-package; *see also* Mullard, *supra* note 69, at 780 ("I have deep empathy for the folks at CMS. It's almost impossible to get it perfectly right the first time.").

"stickiness" of FDA's regulations and the risk of adding inflexibility to an continuously evolving issue.[79]

I echo the call for a coherent policy towards U.S. pharmaceutical innovation regulation. It starts with a measurable definition of innovation. While the IRA is groundbreaking, it does not answer which agency could best regulate each dimension of pharmaceutical innovation. Further regulatory analysis and economic models are needed to determine if it is better to regulate all the competing aspects of innovation together within a single newly created innovation agency, as previously suggested by Rai and Benjamin, or to regulate different dimensions of innovation across the CDC, NIH, FDA, PTO, and CMS over a drug's life cycle, with some degree of cooperation between these agencies.[80] In designing a reasoned regulatory approach to support pharmaceutical innovation, the relative institutional advantages outlined by Sachs, Price, and Zettler should be considered for each potentially conflicting aspect of pharmaceutical innovation. Yet without clarity about what constitutes pharmaceutical innovation, disputes about what ought to be incentivized through regulation will continue. Perhaps the time has arrived for a real conversation about how regulators can best support pharmaceutical innovation, starting with finally agreeing upon what that means.[81] It will not be easy, as regulation of pharmaceutical innovation can save or destroy patients' lives and companies' financial fortunes, but "the merit in all things consists . . . in the difficult[y]."[82]

[79] Sachs et al., *supra* note 1, at 563 ("[A]pproval decisions are sticky, with long-lasting impacts."); *see also* Peter Barton Hutt, *Historical Themes and Developments at FDA over the Past Fifty Years*, *in* FDA IN THE TWENTY-FIRST CENTURY: THE CHALLENGES OF REGULATING DRUGS AND NEW TECHNOLOGIES 17 (Holly Fernandez Lynch & I. Glenn Cohen eds. 2015) ("FDA . . . must continually change . . . to provide a reasonable balance between fostering innovation and protecting the public health."); *cf.* Press Release, President Donald J. Trump Announces the White House Office of American Innovation (OAI) (Mar. 27, 2017), https://trumpwhitehouse.archives.gov/briefings-statements/president-donald-j-trump-announces-white-house-office-american-innovation-oai/ ("The OAI will make recommendations to the President on policies and plans that improve Government operations and services, improve the quality of life for Americans now and in the future, and spur job creation.").

[80] This is exemplary and not a comprehensive list of relevant agencies.

[81] Ho & Vertinsky, *supra* note 13.

[82] ALEXANDRE DUMAS, THE THREE MUSKETEERS 300 (Eleanor Hochman trans., 1991).