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August 2, 2024

The Honorable Diana DeGette
2111 Rayburn House Office Building
Washington, DC 20515

The Honorable Larry Buschon
2313 Rayburn House Office Building
Washington, DC 20515

Submitted electronically via cures.rfi@mail.house.gov

RE: Next Steps in the 21st Century Cures Initiative

Dear Representative DeGette and Representative Buschon:

The National Pharmaceutical Council (NPC) appreciates the opportunity to provide feedback on next steps in the 21st Century Cures Initiative.

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.[1] Our research helps inform important healthcare policy debates and supports the achievement of the best patient outcomes in the most efficient way possible.

NPC supports the inclusion of additional elements related to expediting coverage for new medical products and removing barriers to drug development and coverage, utilizing of real-world evidence, and incorporating the patient and caregiver voice in the 21st Century Cures Initiative. Reforms under the broader 21st Century Cures Initiative should also include adjustment for passage of the Inflation Reduction Act. Focusing on these issues is vital in shaping a healthcare landscape that is innovative, responsive, and patient-focused.

We appreciate Congress' commitment to policies, which support biopharmaceutical innovation and access. There is robust evidence demonstrating the value of biopharmaceuticals on public health, including associated improvements in life expectancy[2], reductions in total healthcare costs,[3] and

[1] About the National Pharmaceutical Council. National Pharmaceutical Council. 2024. https://www.npcnow.org/about
[2] Buxbaum JD, Chernew ME, Fendrick AM, Cutler DM. Contributions Of Public Health, Pharmaceuticals, And Other Medical Care To US Life Expectancy Changes, 1990-2015. Health Aff (Millwood). 2020 Sep;39(9):1546-1556. doi: 10.1377/hlthaff.2020.00284. PMID: 32897792.
[3] Roebuck MC, Liberman JN, Gemmill-Toyama M, Brennan TA. Medication adherence leads to lower health care use and costs despite increased drug spending. Health Aff (Millwood). 2011 Jan;30(1):91-9. doi: 10.1377/hlthaff.2009.1087. PMID: 21209444.

reductions in other poor health outcomes.[4] We aim to support strategies within the Cures 2.0 Initiative that will sustain biopharmaceutical innovation and access to patients for years to come.

Our comments are as follows:

I. NPC Encourages the Adoption of Strategies that Support Access to Innovative Therapies

A. Access to Cell and Gene Therapies

Improving access to cell and gene therapies is one way in which Congress can move toward achieving the goals of the Cures Initiative. The cell and gene therapy market is poised to significantly increase in the coming years. It is projected that by 2030, there will be more than 60 cell and gene therapies and indications[5] approved in the United States, approximately 10-20 per year[6]. As these therapies become more widely available, we ask that any reports to Congress recognize that not every payment method may be suitable for all gene therapies or payers. The Centers for Medicare & Medicaid Services (CMS) has acknowledged the value of cell and gene therapies in its Cell and Gene Therapy Access Model, noting that these therapies "have the potential to reduce health care spending over time by addressing the underlying causes of disease, reducing the severity of illness, and reducing health care utilization."[7]

Given the complexities of these treatments and their potential value for improved patient outcomes, it is critical to design reimbursement policies that facilitate access to treatments for patients facing debilitating medical conditions. Furthermore, strategies that recognize the benefits of new innovative technologies can encourage future investment in these innovations, furthering patient access to cell and gene treatments. We also suggest that CMS monitor the accessibility of cell and gene therapies and treatment centers among patients across the United States. Cell and gene therapies are required to be administered at select treatment centers, and patients are often required to stay near a treatment center for up to 30 days after infusion.[8] Prior research has shown that there are significant geospatial disparities in distance to chimeric antigen receptor T-cell (CAR-T) treatment centers, particularly in Southeastern states.[9] Traveling far distances to treatment centers can pose significant barriers to access for patients living in rural areas with poor access to transportation. To promote equitable access to treatments, NPC suggests that the Cures Initiative consider monitoring the development of new payment policies that are aimed to improve access of innovative treatments to underserved populations.

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[4] Ho PM, Bryson CL, Rumsfeld JS. Medication adherence: its importance in cardiovascular outcomes. Circulation. 2009 Jun 16;119(23):3028-35. doi: 10.1161/CIRCULATIONAHA.108.768986. PMID: 19528344.

[5] Young CM, Quinn C, Trusheim MR. Durable cell and gene therapy potential patient and financial impact: US projections of product approvals, patients treated, and product revenues. Drug Discov Today. Jan 2022;27(1):17-30. doi:10.1016/j.drudis.2021.09.001

[6] Gottlieb S. Statement from FDA Commissioner Scott Gottlieb, M.D. and Peter Marks, M.D., Ph.D., Director of the Center for Biologics Evaluation and Research on new policies to advance development of safe and effective cell and gene therapies. FDA. Updated January 19, 2019. https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-and-peter-marks-md-phd-director-center-biologics

[7] Cell and Gene Therapy Access Model. Centers for Medicare & Medicaid Services. Available at: https://www.cms.gov/priorities/innovation/innovation-models/cgt#:~:text=Cell%20and%20gene%20therapies%20have,and%20reducing%20health%20care%20utilization.

[8] Gustafson K, West M, Gillen EM, Nell A, Grady L. Socioeconomic Factors May Impact Patient Access to Cell Therapies. Avalere. April 2022. Available at: https://avalere.com/insights/socioeconomic-factors-may-impact-patient-access-to-cell-therapies.

[9] Kyei-Baffour B, West M, Coffelt J, Jackson J, Grady L. Advancements in Cell Therapies Require New Patient Support Solutions. Avalere. April 2021. Available at: https://avalere.com/insights/advancements-in-cell-therapies-require-new-patient-support-solutions

B. Sustained Innovation of RNA Therapies

The 21st Century Cures Act created section 529A of the Federal Food, Drug, and Cosmetic (FD&C) Act, provided tools to facilitate the development, review, and approval of drugs that incorporate or use genetically targeted therapies (GTTs). RNA-based therapies, a type of GTT, have complexities associated with product development, manufacturing, and resource investment comparable to other gene therapies, yet differences in regulatory classifications do not account for these challenges.

As such, some RNA-based therapies have been regulated as small molecule drugs, despite complexities associated with product development, manufacturing, and resource investment comparable to other gene therapies that FDA regulates as biologics.

The IRA requires that small molecule drugs be applicable to price setting in the Medicare DPNP seven years after FDA approval, which is four years earlier than a biologic drug becomes applicable to price setting in the Medicare DPNP. NPC suggests that Congress and other stakeholders continue to monitor the GTT pipeline among drugs classified as either small molecules or biologics. NPC suggests that Congress should consider evaluating the potential impact of creating parity in the timelines of potential selection in the Medicare DPNP among small molecules and biologics.

C. Payment Policies that Support Innovation

We also encourage the Cures Initiative to help ensure that CMS payment policies foster a robust, innovation environment for all treatments. For example, CMS established the multiple best price reporting option (MBPRO), where manufacturers may enter value-based contracts with commercial and Medicaid payers. However, more clarity is needed from CMS that the rebates and other concessions offered through VBPs will be exempt from average sales price calculations. Payment policies should be flexible enough to realize the full impacts of treatments to patients, without thwarting current reimbursement models. A one-size fits all approach to payment policies will not meet the needs of all stakeholders.

II. NPC Encourages Congress and Other Stakeholders to Monitor the Impacts of the Inflation Reduction Act

A. Post-Approval Indications for Orphan Drugs

A huge change impacting the goals of the 21st Century Cures Initiative is the passage of the Inflation Reduction Act (IRA). NPC has voiced its concerns with the IRA's impact on innovation and access to care in comments to CMS, supported by NPC research[10]. Of particular importance, orphan drug development

[10] National Pharmaceutical Council. Comments on Draft Guidance for the Medicare Drug Price Negotiation Program for 2027. July 2, 2024. Available at: https://www.npcnow.org/resources/npc-submits-comments-cms-draft-guidance-medicare-drug-price-negotiation-program-2027; Patterson J, Motyka J, O'Brien JM. Unintended Consequences of the Inflation Reduction Act: Clinical Development Toward Subsequent Indications *Am J Manag Care. 2024;30(2):82-86. https://doi.org/10.37765/ajmc.2024.89495*; Patterson J, Motyka J, O'Brien JM. How The IRA Could Delay Pharmaceutical Launches, Reduce Indications, And Chill Evidence Generation, Health Affairs Forefront, November 3, 2023. DOI: 10.1377/forefront.20231101.123865; Patterson JA, Wagner TD, O'Brien JM, Campbell JD. Medicare Part D Coverage of Drugs Selected for the

is at acute risk of being stymied by the IRA. This is because research shows that the structure of the Orphan Drug Exclusion (ODE) in the Medicare Drug Price Negotiation Program (DPNP) may undermine the incentives of the Orphan Drug Act (ODA). One analysis of orphan drug development predicts a 40 percent reduction in orphan FDA approvals between 2026 and 2035[11], and publicly available data from companies shows manufacturers have begun announcing decisions to rescind development based on the ODE.[12]

Congress passed the ODA in 1983, because patients living with rare diseases were being left out due to the barrier to investment in the research and development for new therapies. The ODA's incentives have accelerated rare disease research over the last 40 years, including 20 new FDA approvals for rare diseases in 2022 alone.[13] Without the needed tax credits for rare disease research in the ODA, it is estimated that 67 fewer orphan drugs would be on the market today.[14]

Much of the rare disease development pipeline and the progress over the last 40 years has relied on identifying new applications for existing drugs that could address unmet needs for patients living with rare diseases. For example, an analysis by Tufts' Center for the Evaluation of Value and Risk in Health found that from 2003 to 2022, the FDA approved 282 novel orphan-designated drugs; after initial approval, the FDA approved 152 separate follow-on indications.[15] Nearly two-thirds (61%) of these follow-on indications were for orphan conditions. NPC analyzed 30 small-molecule medicines with multiple indications and high gross spending in Medicare Part D (2020). The study showed that six (20%) of the included medicines were originally approved for an orphan drug designation, and all six of these medicines received at least one or more subsequent orphan drug indications. These additional indications resulted in expanding the use of these six medicines to at least 18 additional orphan disease populations. [16] CMS has taken the position that it lacks statutory authority to implement a change to the orphan definition, and a change in legislation may be the path forward.
As Congress evaluates potential policies in the Cures Initiative, we ask that Congress consider protecting the spirit of original intent of the bipartisan, bicameral ODA through fueling research on the impacts of the structure of the IRA's ODE and incentives for developing orphan treatments.

Drug Price Negotiation Program. JAMA Health Forum. 2024;5(2):e235237. doi:10.1001/jamahealthforum.2023.5237; O'Brien JM, Hansen JE. Section 50 of the Inflation Reduction Act Drug Price Negotiation Program: Considerations for the Centers for Medicare Medicaid Services, Manufacturers, and the Health Economics and Outcomes Research Community [Editor's Choice]. Value in Health. December 2023. Available at: https://www.ispor.org/publications/journals/value-in-health/issue/Volume-26--Issue-12. National Pharmaceutical Council. NPC IRA Negotiation Guidance Comment Letter. April 14, 2023. Available at: https://www.npcnow.org/sites/default/files/2023-04/04-14-2023%20NPC%20IRA%20NEG%20GUIDANCE%20CMT%20LTR.pdf

[11] Gassull, D., Bowen, H., & Schulthess, D. (2023, Jun 1). *IRA's Impact on the US Biopharma Ecosystem*. Vital Transformation. https://vitaltransformation.com/wp-content/uploads/2023/10/VT-BIO_IRA_v14.pdf.

[12] Masia, N. (2023). *Rare Disease Companies in the Public Markets: Challenging Performance Against a Backdrop of Policy Uncertainty*. Health Capital Group. https://www.rarecoalition.com/wp-content/uploads/Health-Capital-Group-White-Paper-FINAL-1.pdf

[13] Food and Drug Administration. New Drug Therapy Approvals 2022. January 10, 2023. Available at: https://www.fda.gov/drugs/novel-drug-approvals-fda/new-drug-therapy-approvals-2022

[14] National Organization for Rare Disorders (NORD), Biotechnology Industry Organization (BIO), and Ernst & Young. Impact of the Orphan Drug Tax Credit on Treatments for Rare Diseases. June 2015. Available at: https://rarediseases.org/assets/files/white-papers/2015-06-17.nord-bio-ey-odtc.pdf

[15] Chambers JD, Clifford KA, Enright DE, Neumann PJ. Follow-On Indications for Orphan Drugs Related to the Inflation Reduction Act. *JAMA Netw Open.* 2023;6(8):e2329006. doi:10.1001/jamanetworkopen.2023.29006

[16] Patterson J and Motyka J. Unintended Consequences of the Inflation Reduction Act: Clinical Development Toward Subsequent Indications. AMJC. 2024; 30 (2):82-86. Available at: https://www.ajmc.com/view/unintended-consequences-of-the-inflation-reduction-act-clinical-development-toward-subsequent-indications

B. Small Molecule Pipelines and Access to Part D Therapies

Under the IRA, small molecule drugs can be selected for price setting in the Medicare DPNP seven years after FDA approval, which is significantly less time than the potential selection of biologic therapies (i.e., eleven years post-FDA approval).[17] As shown in our prior research, the IRA's DPNP may have unintended consequences on the economic incentives surrounding the launch of medicines, including small molecules, in the US.[18] Small molecule therapies represent many drugs used to treat cardiovascular, mental health, and oncology conditions. We recommend that Congress continue to promote and monitor the small molecule pipeline, under the Cures Initiative.

NPC is also concerned with the growing research suggesting that the IRA's changes to Part D redesign could lead to increased utilization management and narrower formularies among Part D plans. In a recent survey of managed care professionals, representing 310 million US lives, 24% of payers said that they expect significantly narrower formularies as a result of the IRA's Part D changes. In addition, greater than one-third (42%) of payers expect greater utilization management among Part D plans.[19] Our prior research demonstrates that pre-implementation of the Medicare Part D redesign, access to the first 10 selected drugs for the Medicare DPNP was common without step therapy. However, access to certain biologics and oncological drugs without prior authorization was rare.[20]

We encourage Congress and CMS to continue to monitor Part D formularies. We also urge Congress to continue to monitor patient access to the six protected classes of medicines in Medicare.

III. NPC Encourages Better Use of Real-World Evidence (RWE)

Real-world evidence (RWE) can provide valuable insights about the benefit innovations provide to patients and providers. RWE is a key component of a value-based health care system and should be transparently incorporated into coverage and payment decisions for CMS programs, including the DPNP.

The U.S. Food and Drug Administration (FDA) has made progress in its use of RWE[21]. For example, in October of 2022 the FDA announced they would conduct an Advancing Real-World Evidence (RWE) Program with the goal of improving the quality and acceptability of RWE-based approaches. NPC is pleased to see that FDA has developed a centralized repository of its regulations, guidance, and other documents related to RWE, as NPC recommended in its 2019 comment letter on Cures 2.0.[22] Despite

[17] H.R. 5376 – The Inflation Reduction Act (2022). Congress.gov.
[18] O'Brien JM, Motyka J, Patterson J. How The IRA Could Delay Pharmaceutical Launches, Reduce Indications, And Chill Evidence Generation. HealthAffairs Forefront. November 2023. Available at: https://www.healthaffairs.org/content/forefront/ira-could-delay-pharmaceutical-launches-reduce-indications-and-chill-evidence
[19] McCormick B. How Payers Expect the IRA to Financially Impact Medicare Part D Plans. AJMC. Oct. 2023. Available at: https://www.ajmc.com/view/payers-expect-the-inflation-reduction-act-to-financially-impact-medicare-part-d-plans
[20] Patterson JA, Wagner TD, O'Brien JM, Campbell JD. Medicare Part D Coverage of Drugs Selected for the Drug Price Negotiation Program. JAMA Health Forum. 2024;5(2):e235237. doi:10.1001/jamahealthforum.2023.5237
[21] Food and Drug Administration. Real-World Evidence. Available at: https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence
[22] National Pharmaceutical Council. Comments on Request for Public Input on Cures 2.0. December 16, 2019. Available at: https://www.npcnow.org/resources/npc-comments-public-request-input-cures-20

progress by FDA, CMS has been more limited in its incorporation of RWE into coverage and reimbursement decisions.

While RWE has been considered for specific applications in some CMS programs, such as the New Technology Add-on Payment (NTAP) and Transitional Add-on Payment Adjustment for New and Innovative Equipment and Supplies (TPNIES), CMS can go further in incorporating RWE in its policymaking. NPC believes that the incorporation of RWE is appropriate for inclusion in payment policies. For example, "Substantial clinical improvement criteria" for NTAP and TPNIES applications note several evidence types that will be considered, but do not specifically note the use of RWE[23]. Additional clarity and guidance surrounding how RWE is considered in these applications and a framework to foster the use of RWE will further CMS's goal of facilitating patient access to technologies.

When considering evidence about therapeutic alternatives for selected drugs and to inform adjustment of the starting point based on Section 1194(e)(2) factors under the Medicare DPNP, CMS notes that it will review existing literature and real-world evidence. Specifically, CMS will consider "real-world evidence relating to Medicare populations, including on individuals with disabilities, patients with end-stage renal disease (ESRD), and Medicare-aged populations, as particularly important." [24] NPC has continued to voice concerns about the lack of transparency surrounding the DPNP and encourages the use of transparent and reproducible methods and results. NPC reiterates that CMS should create and publish its decision-making framework – both generally and for selected drugs – including the source(s) of evidence considered, how each benefit and impact considered influenced the final Maximum Fair Price (MFP), and the limitations of data collected and uncertainties in CMS's decision-making. While the use of RWE in this process may be beneficial, stakeholders currently have limited visibility into how specifically RWE is used and weighed within the negotiation process.

IV. To Continue to Build Towards a Patient-Centered Healthcare System, the Beneficiary and Caregiver Voice Should be Incorporated Into Healthcare Decision-Making Whenever Possible

Decisions made by both public and private payers can critically impact patients and their caregivers, with the power to impact a patient's overall quality of life. We have seen CMS make efforts to include the patient perspective in both the DPNP and in other areas such as Pharmacy and Therapeutic (P&T) Committees[25]; however, more must be done to ensure that the patient voice is prioritized at all stages of

[23] Centers for Medicare and Medicaid Services. Substantial Clinical Improvement Criteria for the Transitional Add-on Payment Adjustment for New and Innovative Equipment and Supplies (TPNIES) under the ESRD PPS. Available at: https://www.cms.gov/files/document/cy-2021-tpnies-substantial-clinical-improvement-criterion.pdf; Centers for Medicare and Medicaid Services. Appendix B: Substantial Clinical Improvement. Available at: https://mearis.cms.gov/assets/pdfs/NTAP%20Appendix%20B%20Substantial%20Clinical%20Improvement.pdf

[24] Centers for Medicare and Medicaid Services. Draft Guidance on the Medicare Drug Price Negotiation Program. May 3, 2024. Available at: https://www.cms.gov/files/document/medicare-drug-price-negotiation-draft-guidance-ipay-2027-and-manufacturer-effectuation-mfp-2026-2027.pdf

[25] Department of Health and Human Services. Contract Year 2025 Notice of Benefit and Payment Parameters Final Rule. April 15, 2024. Available at: https://www.federalregister.gov/documents/2024/04/15/2024-07274/patient-protection-and-affordable-care-act-hhs-notice-of-benefit-and-payment-parameters-for-2025

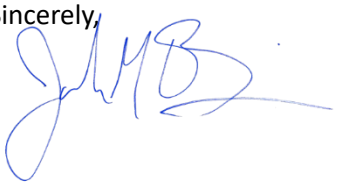
healthcare decision-making. Documented heterogeneity in treatment preferences[26] and effects[27], as well as disparities in health status and access to care, further underscore the need for diverse patient voices.

Cures 2.0 included additional opportunities for the patient voice, including through the implementation of a Real-World Evidence Task Force that would "coordinate the programs and activities of the Department of Health and Human Services with regard to the collection and use of real world evidence" and be required to have "private sector representatives, including patient group representatives, to be appointed by the Secretary.[28]" For any efforts related to this initiative, as well as other efforts to include the patient voice in government programs, we recommend Congress consider relevant recommendations from NPC's *Guiding Practices for Patient-Centered Value Assessment*, which includes 33 specific elements surrounding six key aspects of value assessment, including the assessment process, scientific methodology, benefits, costs, evidence, and dissemination and utilization, when proposing policies that facilitate the inclusion of the patient voice in healthcare decision-making.[29] The patient voice is vital to the development of these policies, particularly when they impact drug coverage and access.[30]

Conclusion

The National Pharmaceutical Council appreciates the opportunity to submit comments in response to this Request for Information. Please contact me at john.obrien@npcnow.org or (202) 827-2080 if we may provide any additional information.

Sincerely,



John Michael O'Brien PharmD, MPH

President & Chief Executive Officer

[26] Hollin IL, González JM, Buelt L, Ciarametaro M, Dubois RW. Do Patient Preferences Align With Value Frameworks? A Discrete-Choice Experiment of Patients With Breast Cancer. MDM Policy Pract. 2020;5:238146832092801; Groothuis-Oudshoorn CGM, Flynn TN, Yoo H Il, Magidson J, Oppe M. Key Issues and Potential Solutions for Understanding Healthcare Preference Heterogeneity Free from Patient-Level Scale Confounds. The Patient - Patient-Centered Outcomes Research. 2018;11:463–6.; Whitty JA, Fraenkel L, Saigal CS, Groothuis-Oudshoorn CGM, Regier DA, Marshall DA. Assessment of Individual Patient Preferences to Inform Clinical Practice. The Patient - Patient-Centered Outcomes Research. 2017;10:519–21.

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

[28] H.R. 6000. Congress.gov. Available at: https://www.congress.gov/bill/117th-congress/house-bill/6000/text

[29] 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%20PatientCentered%20Value%20Assessment%20January.pdf

[30] 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%20PatientCentered%20Value%20Assessment%20January.pdf