

July 7, 2023

Cathy McMorris Rodgers  
Chair, House Energy and Commerce Committee

Mike Crapo  
Ranking Member, Senate Finance Committee

Dear Chair Rodgers and Senator Crapo,

We are writing in response to your request for information about drug shortages and to inform policymaking. Please find answers to the questions below on which our group has expertise. Should you have any further questions, please do not hesitate to reach out to us.

Sincerely,

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## ***1. How would you define the scope and impact of the recent and ongoing U.S. drug shortages?***

Shortages of medications necessary to administer appropriate care to patients have been a persistent problem in the United States with more than 200 drugs reported in shortage each year over the past decade.<sup>1</sup> Recent studies suggest that despite this being a longstanding public health issue, shortages are once again on the rise and patients are currently experiencing a record high number of drug shortages. Between January 2022 and June 2023, the U.S. Food and Drug

Administration (FDA) reported 1119 new drug shortages for 283 unique products.<sup>2</sup> An overwhelming majority (97%) of these reported shortages were of generic medicines, including generic sterile injectables (GSIs), prescription drugs, and over-the-counter medications. Among originator (i.e., brand-name) drugs reported to be in shortage, most were attributable to business decisions and/or increases in demand. As ongoing and current shortages of drugs primarily impact generic medicines, which account for 90% of prescriptions filled in the United States, our responses to the questions posed within the RFI will be focused on the generic drug market.

Data on medicine shortages in the United States are collected from drug manufacturers and requires notification to the Secretary of Health and Human Services (HHS) of permanent discontinuation or short-term interruption in the manufacture of a finished pharmaceutical product (FPP) or active pharmaceutical ingredient (API).<sup>3</sup> These data are published by the FDA. Despite these requirements, to our knowledge there have been no sanctions against firms for non-reporting. For many shortages, no data are available on the cause of the shortage, and where reasons are given, they are rarely detailed. For example, ‘vendor supply interruption’, a frequently reported cause of drug shortage, could refer to a short-term disruption in a given contractual relationship, a global API shortage (for example, due to a natural disaster), or a quality issue that has required the factor to pause production.

At present, there is poor quality data to assess both the proximate and distal causes of drug shortages and their effects. Fifty-nine percent of current shortages do not have a declared cause. Of those with known causes, the majority (72%) are due to increased demand, followed by manufacturing delays or issues (10%), discontinuation (8%), issues with active pharmaceutical ingredient (API) (6%), quality issues (3%), shipping delays, (<1%), and regulatory delays (<1%) (Figure 1).<sup>4</sup>

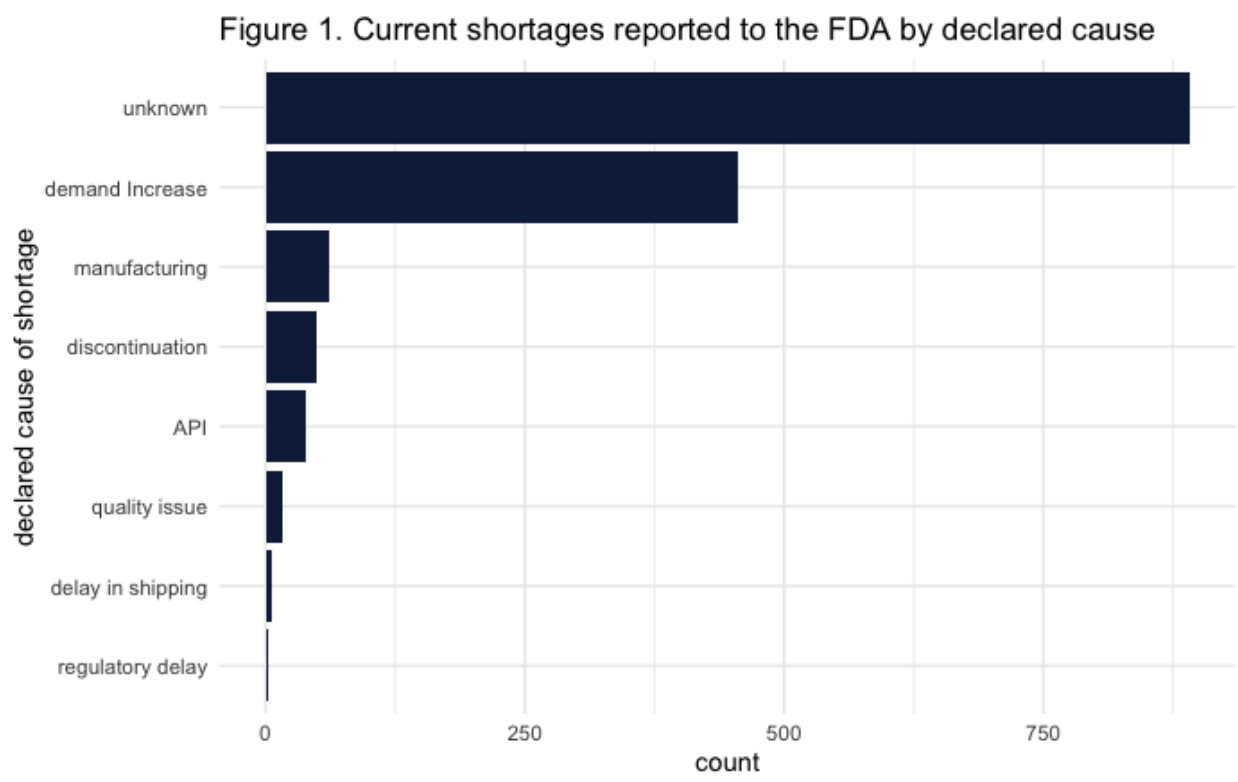
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<sup>1</sup> U.S. Government Accountability. (2016, July 7). *Drug shortages: Certain factors are strongly associated with this persistent Public Health Challenge*. Retrieved July 3, 2023, from, <https://www.gao.gov/products/gao-16-595>

<sup>2</sup> Center for Drug Evaluation and Research. (n.d.). *Current Drug Shortages*. U.S. Food and Drug Administration. Retrieved July 6, 2023, from <https://www.fda.gov/drugs/drug-safety-and-availability/drug-shortages>

<sup>3</sup> Data is collected pursuant to [21 U.S. Code § 356c](#)

<sup>4</sup> Center for Drug Evaluation and Research. (n.d.). *Current Drug Shortages*. U.S. Food and Drug Administration. Shortages data retrieved July 3, 2023, from <https://www.fda.gov/drugs/drug-safety-and-availability/drug-shortages>. There are no standardized codes for shortages; data were manually recoded using any information provided in the record. Shortages were filtered to include unique company, generic name, and presentation (formulation) combinations.



**a. For drugs currently in shortage, what percentage of their market is reimbursed through public payers, such as Medicare and Medicaid?**

Currently, there is no published research providing a breakdown of payers for drugs in shortage. In general, market size data are considered commercially confidential and are not publicly available. Some data are available from commercial claims databases, but these include only a subset of prescriptions. Firms selling data targeting investors like IQVIA may sell some data, but these sources are unaudited and of indeterminate quality. Such commercial data has been the subject of FDA’s complaints about “serious concerns about systemic issues with IQVIA’s data and quality control procedures.”<sup>5</sup>

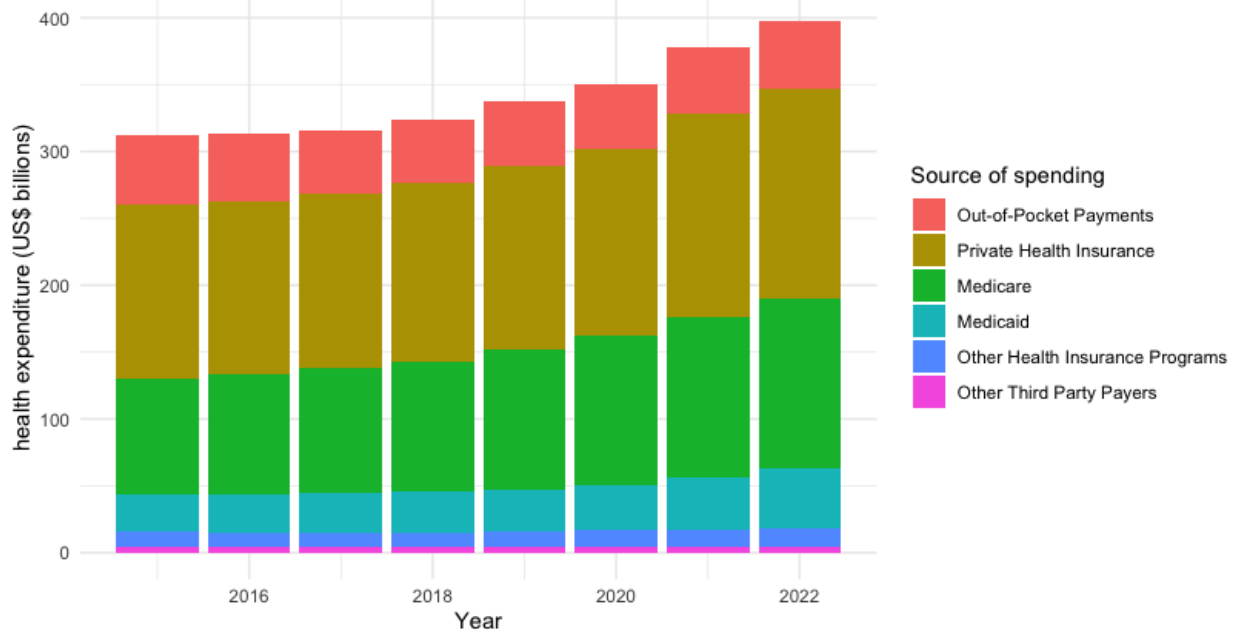
In general, the share of prescription drug spending represented by Medicare and Medicaid has grown in recent years, from 37% of total health expenditures in 2015 to 50% in 2022 (Figure 2).<sup>6</sup> Several drugs in shortage are frequently prescribed to Medicare and Medicaid beneficiaries, including common chronic disease medications to treat heart disease, diabetes mellitus, asthma, and cancer. Thus, it is likely that drug shortages have a significant impact on Medicare and Medicaid beneficiaries. CMS holds claims data, which could be

<sup>5</sup> US Food and Drug Administration. FDA reports quality problems for data provided by the firm IQVIA that were used to inform estimates for some controlled substances; 2018. Available from: <https://www.fda.gov/drugs/drug-safety-and-availability/fda-reports-quality-problems-data-provided-firm-iqvia-were-used-inform-estimates-some-controlled>

<sup>6</sup> National Health Expenditure Data. Available from: <https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/NationalHealthExpendData>

used or made available to investigators to better characterize the clinical impact of drug shortages, including their impact on the health outcomes of specific beneficiary populations.

Figure 2. Prescription drug health expenditure by source



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Access to claims data from public payers could enable analysis of the duration of shortages and variability of their impact across patient populations. Additionally, claims data would enable analyses to determine for which drugs targeted interventions to enhance supply chain resiliency should be prioritized to mitigate the undue impacts of drug shortages.

**b. What are the impacts of recent and recurring shortages of generics and other critical medicines on patient care?**

Drug shortages have been linked to adverse health and economic outcomes for patients. One scoping review found that during times of drug shortage, patients more often reported having higher rates of adverse drug reactions, morbidity and mortality, and increased out of pocket costs.<sup>8</sup> In addition to nearly all hospitals experiencing shortages of medicines required to provide adequate care for patients, physicians often report having to use alternative products and potentially, even suboptimal treatments.<sup>9</sup>

<sup>7</sup> National Health Expenditure Data. CMS.gov. (n.d.). <https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/NationalHealthExpendData>

<sup>8</sup> Phuong, J. M., Penm, J., Chaar, B., Oldfield, L. D., & Moles, R. (2019, May 3). The impacts of medication shortages on patient outcomes: A scoping review. *PLOS ONE*, 14(5). <https://doi.org/10.1371/journal.pone.0215837>

<sup>9</sup> id

Of particular concern are generic sterile injectable (GSI) drugs, which comprise most of the generic drugs (and thus, all drugs) that are in shortage.<sup>10</sup> Of 138 generic medicines currently recorded as being in shortage by the FDA, 68% are injectables, 16% are tablets or capsules, and 16% are other formulations (oral, topical, suppositories).<sup>11</sup> GSIs play a critical role in the management and treatment of patients across healthcare facilities including outpatient cancer clinics, emergency departments, hospital floors, intensive care units, and operating rooms. Commonly used GSIs such as normal saline, morphine, and other diluting agents as well as lifesaving or life-prolonging cancer treatments are currently in shortage, significantly compromising patient care. For example, shortages of norepinephrine, a first-line vasopressor GSI for septic shock, was associated with greater hospital mortality.<sup>12</sup>

As a result of recent and recurring cancer drug shortages, hospitals and physicians have been forced to ration treatments and thus, withhold treatments from patients with conditions for which there are effective cures. In a recent survey by the National Comprehensive Cancer Network of academic medical centers, over 90% reported having shortages of carboplatin and cisplatin, two of the most widely used cancer chemotherapy medications.<sup>13</sup> Several centers also reported the use of dose reductions when appropriate or the use of alternative treatment.<sup>14</sup>

Nevertheless, the FDA has stated that comprehensive data of the impact of drug shortages on health outcomes are also lacking, believing that studies may have underestimated such impacts.<sup>15</sup> As FDA also notes, more accurate information may be beneficial to payers in making more informed purchasing decisions and in determining which strategies to employ to address this issue.

## **2. *What market and economic conditions undermine pharmaceutical supply chains or the availability of drugs? Please discuss any specific barriers in public payment programs.***

As noted above, most drugs in shortage are generics. Although generics comprise 90% of drugs sold in the United States, they only comprise 18% of all prescription drug costs. Negotiation by pharmacies and providers for the “lowest” acquisition cost of generics generates a so called “race to the bottom” among generic manufacturers to obtain and retain market share. Healthcare providers’ and pharmacies are not incentivized to consider quality and reliability of manufacturing in generic selection, as the reimbursement rate is the same for all generic versions of a given product. These reimbursement dynamics in turn disincentivize the entry and retention of manufacturers into the market. A recent study found that approximately one-third of generic

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<sup>10</sup> Center for Drug Evaluation and Research. (n.d.). *Current Drug Shortages*. U.S. Food and Drug Administration. Retrieved July 6, 2023, from <https://www.fda.gov/drugs/drug-safety-and-availability/drug-shortages>

<sup>11</sup> Shortages data downloaded from <https://www.fda.gov/drugs/drug-safety-and-availability/drug-shortages> on 3 July 2023. There are no standardized codes for formulation type; data were manually recoded using any information provided in the record. Shortages were filtered to include generic name.

<sup>12</sup> Vail, E., Gershengom, H. B., Hua, M., Walkey, A. J., Rubinfeld, G., & Wunsch, H. (2017). Association between US norepinephrine shortage and mortality among patients with septic shock. *JAMA*, 317(14), 1433. <https://doi.org/10.1001/jama.2017.2841>

<sup>13</sup> National Comprehensive Cancer Network. (2023, June 7). *NCCN Best Practices Committee Carboplatin & Cisplatin Shortage Survey Results*. NCCN. Retrieved July 1, 2023, from <https://www.nccn.org/docs/default-source/oncology-policy-program/NCCN-Drug-Shortage-Survey.pdf>

<sup>14</sup> id

<sup>15</sup> FDA. (2020, February 21). *Drug Shortages: Root Causes and Potential Solutions*. Retrieved July 6, 2023, from <https://www.fda.gov/media/131130/download>

active pharmaceutical ingredients (APIs) produced for use in the United States market between 2020 and 2021 were manufactured by a single facility; an additional third was manufactured by two or three facilities.<sup>16</sup>

Coupled with this is the complexity of manufacturing generic drugs, which requires significant and necessary investment by generic manufacturers. Unfavorable pricing dynamics that lead to little to no margins for manufacturers also preclude their investment into robust risk management plans and redundant supply chains that would mitigate the effect of manufacturing interruptions or increased demand. Besides the lack of financial incentives available to reward manufacturers should they take proactive steps to prevent manufacturing disruptions, there exist no current market penalties for manufacturers who fail to take appropriate steps to modernize their equipment and facilities to ensure a robust and reliable supply.

### ***3. What are the regulatory challenges to manufacturing drugs in the United States, as compared to other countries? Please specify which agency issued and enforced such Regulations.***

The United States does not have distinctively unique or burdensome requirements for manufacturing relative to other countries with stringent regulatory authorities. FDA and other stringent regulatory authorities such as the European Medicines Agency (EMA) have worked in recent years to further align regulatory standards. In 2021, the Generic Drug Cluster was established to facilitate information exchange among regulatory agencies, "offering a confidential forum for exchange of discussion on policies in development, including draft guidances for industry, and the scientific basis for decisions on those policies" and "addressing long-term safety issues to ensure a global safety net for generic drugs through confidential sharing of reports."<sup>17</sup> Adequately resourcing this initiative is an important opportunity to ensure an even regulatory playing field for generic manufacturing, identify efficiencies and lower costs through information sharing, and promote coordination towards a global regulatory environment for supply chain stability and resilience.

Regulatory burden in relation to oversight of manufacturing facilities in the United States does not result in higher costs of manufacturing compared to other countries. KPMG, a major accounting and auditing firm, ranked the United States fifth (after Canada, Taiwan, South Korea, and Malaysia) in an index comparing costs of doing business (CoDB) among 16 leading pharmaceutical manufacturing exporters to the United States. The same analysis found that the United States had the second highest score (exceeded only by Switzerland) for Ease of Doing Business<sup>18</sup>, suggesting that regulatory burden in the United States for manufacturing is lower than nearly all other comparator countries.<sup>19</sup>

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<sup>16</sup> Socal, M. P., Ahn, K., Greene, J. A., & Anderson, G. F. (2023). Competition and vulnerabilities in the global supply chain for US generic active pharmaceutical ingredients. *Health Affairs*, 42(3), 407–415. <https://doi.org/10.1377/hlthaff.2022.01120>

<sup>17</sup> USFDA. Global Generic Drug Affairs. Available from: <https://www.fda.gov/drugs/generic-drugs/global-generic-drug-affairs>

<sup>18</sup> The "Ease of Doing Business" score was calculated based on quantitative indicators within the World Bank Group annual report titled "Doing Business" ranking 190 countries. Indicators that comprised the "Ease of Doing Business Score" include "number of days to start a business and registering property" and "burden of government regulation."

<sup>19</sup> KPMG. Cost of manufacturing operations around the globe. Available from: <https://tax.kpmg.us/content/dam/tax/en/pdfs/2020/cost-manufacturing-operations-globe.pdf>

Review times in the United States are favorable compared to those observed in Europe: a review of FDA and European Medicines Agency (EMA) review times for novel drugs from 2015-2017, which includes the manufacturing review and inspections to approve a new drug for market use, found considerably shorter review times for FDA than EMA (median difference 121.5 days, IQR 29 to 189).<sup>20</sup> Another earlier study of novel therapies approved between 2001 and 2010 found that FDA reviewed new drug and new biologic applications more quickly than the EMA or Health Canada and that a large majority were first approved for use in the United States.<sup>21</sup>

Some elements of the US regulatory environment are uniquely supportive of generic entry and diffusion. The Creating and Restoring Equal Access to Equivalent Samples (CREATES) Act of 2019 allows generic drug manufacturers to sue originator companies refusing access to product samples required for assembling dossiers for generic drug applications.<sup>22</sup> Lack of access to product samples for product equivalence demonstration had been an important bottleneck in generic drug development, as well as medical research.

#### ***4. How can federal agencies, such as Centers of Medicare and Medicaid (CMS), better address the economic forces driving shortages? Are these agencies using their current authorities effectively?***

Under the Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012, the FDA was granted additional authority to respond to national medical product shortages. Increased regulatory powers such as the requirement of early reporting of shortages from manufacturers, as well as expedited review of generics and distribution, were successful in decreasing drug shortages since enactment.<sup>23</sup> However, the number of shortages remained high as the legislation did not address the systemic economic forces discussed above driving shortages. Federal agencies such as CMS and FDA have certain ability to effect changes, although legislative reform and increased appropriations are key to enable both agencies to address drug shortages effectively and sustainably and ensure that supply chains are transparent, resilient, and produce high-quality medications.

First, federal agencies such as CMS and the FDA should have more transparent oversight of the supply chain. Currently, the FDA does not receive adequate data on supply chain issues, relying on voluntary compliance efforts from manufacturers, as they do not have mandatory reporting requirements.<sup>24</sup> The FDA gathers some information from manufacturers on anticipated

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<sup>20</sup> Joppi R, Bertele V, Vannini T, Garattini S, Banzi R. Food and Drug Administration vs European Medicines Agency: Review times and clinical evidence on novel drugs at the time of approval. *Br J Clin Pharmacol*. 2020 Jan;86(1):170-174. doi: 10.1111/bcp.14130. Epub 2019 Dec 16. PMID: 31657044; PMCID: PMC6983504.

<sup>21</sup> Downing, N. S., Aminawung, J. A., Shah, N. D., Braunstein, J. B., Krumholz, H. M., & Ross, J. S (2012). Regulatory Review of Novel Therapeutics — Comparison of three regulatory agencies. *New England Journal of Medicine*, 366(24), 2284–2293. <https://doi.org/10.1056/nejmsa1200223>

<sup>22</sup> Access to Product Samples: The CREATES Act. Available from: <https://www.fda.gov/drugs/guidance-compliance-regulatory-information/access-product-samples-creates-act>

<sup>23</sup> Chen, S. I., Fox, E. R., Hall, M. K., Ross, J. S., Bucholz, E. M., Krumholz, H. M., & Venkatesh, A. K. (2016, May 1). Despite Federal Legislation, Shortages of Drugs Used in Acute Care Settings Remain Persistent and Prolonged. *Health Aff (Millwood)*, 35(5), 798-804. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6712565/>

<sup>24</sup> Gupta, R., Dhruva, S. S., Fox, E. R., & Ross, J. S. (2017, October 23). The FDA Unapproved Drugs Initiative: An Observational Study of the Consequences for Drug Prices and Shortages in the United States. *J Manag Care Spec Pharm*, (2017 Oct;23(10)), 1066-1076. <https://doi.org/10.18553/jmcp.2017.23.10.1066>

disruptions, but these data are limited and do not adequately assess supply chain vulnerabilities.<sup>25</sup> With the appropriate data, FDA and CMS could rate generic manufacturers by the resilience of their supply chain, this rating could then be incorporated by payers to adjust reimbursement for generic drugs appropriately, in a similar way as value-based modifiers adjust payments to providers based on the quality of medical services provided. This adjustment of reimbursement rates for generic drugs would create an economic incentive for manufacturers to improve and modernize their manufacturing systems, as manufacturers with demonstrated resilient supply chains would be able to sell their products at a higher price (since pharmacies and providers would be in turn reimbursed at a higher rate when dispensing generic products from highly rated manufacturers). Such a star rating system could be based on FDA's Center for Drug Evaluation and Research (CDER) Quality Management Maturity (QMM) programs that assess the resiliency and robustness of drug supply chains.<sup>26</sup> This system would address the drug shortages problem by incentivizing pharmacies and providers to purchase products from companies with resilient supply chains.

There is a wide range of options available in generating necessary data to adequately monitor and regulate against shortages. At the lowest end of added administrative burden, the FDA could simply request that manufacturers give longer notice for discontinuation of products for commercial reasons (i.e., 18 months as enforced in other jurisdictions) and report annual manufacturing volumes as they have requested as part of their budget request for Fiscal Year 2024.<sup>27</sup> Such requirements would demand data already collected by firms and pose little to no threat in terms of commercial secrecy or advantage. A more intensive and likely more effective approach would be for firms to report data on production capacity, and for the FDA and actors like the Government Accountability Office (GAO) and CMS to evaluate this data to identify and predict mismatches between supply and demand and proactively notify relevant departments to encourage firm entry, supply expansion, and shortage aversion.

Pharmaceutical supply chains are global. Solving shortages in the United States requires collaboration with other regulatory authorities to map global supply, particularly for at risk products such as those with single-source API producers or those in frequent shortage. The backbone of any mapping and collaboration is a shared language; the FDA should work with other regulators and international actors like the World Health Organization (WHO) to standardize reporting standards and data indicators for shortages, which currently are not standardized even within FDA data.

Through the Coronavirus Aid, Relief, and Economic Security (CARES) Act, the FDA currently has authority to have additional oversight of drug supply chains, via identification, prevention, and visibility into supply chains, but data needs to be accessible in order to translate this authority into benefit.<sup>28</sup> CMS has the statutory ability to request mandatory participation in

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<sup>25</sup> Office of the Assistant Secretary for Planning and Evaluation (ASPE). (2023, May). Impact of Drug Shortages on Consumer Costs.

<sup>26</sup> Maguire, J., Fisher, A., Harouaka, D., Rakala, N., Lundi, C., Yambot, M., Viehmann, A., Stiber, N., Gonzalez, K., Canida, L., Buhse, L., & Kopcha, M. (2023, January 10). Lessons from CDER's Quality Management Maturity Pilot Programs. *AAPS Journal*.

<sup>27</sup> Summary of FY 2024 Legislative Proposals - U.S. Food and Drug Administration. (n.d.-b). <https://www.fda.gov/media/166049/download>

<sup>28</sup> FDA. (2023, April 5). *Coronavirus Aid, Relief, and Economic Security Act (CARES Act) Drug Shortage Mitigation Efforts*. Retrieved July 1, 2023, from <https://www.fda.gov/drugs/drug-shortages/coronavirus-aid-relief-and-economic-security-act-cares-act-drug-shortage-mitigation-efforts>



surveys to identify drug, spending, distribution, and utilization information.<sup>29</sup> To remedy the accessibility issue, this authority could be expanded to request mandatory survey data on manufacturing and supply, as well as on current shortages. Additionally, FDA has also put forward legislative proposals in their Fiscal Year 2024 funding request to expand the notification requirements from manufacturers to include alerting the FDA of increases in demand, submission of the firm's quality management policies, and manufacturing quantities along with other reporting requirements.<sup>30</sup> This notification process could also be tied to a survey with certain incentives such as lower Generic Drug User Fees in new legislation.

Second, CMS and FDA could also lower the burden of generic drug user fees under the Generic Drug User Fee Act (GDUFA) to incentivize new generic manufacturers to enter the market as such fees may be far too burdensome.<sup>31</sup> There is a litany of different miscellaneous fees such as an annual facility fee that add up to enormous costs for makers. As generic firms rely on narrow margins under the current reimbursement structure, fees become an additional financial barrier to generic drug applications, known as Abbreviated New Drug Applications (ANDAs).<sup>32</sup> However, new ANDAs are an essential harbinger of generic supply allowing the entry of additional generic manufacturers onto the market. This legislation could lower fees specifically for drugs approved for indications that are currently in shortage.

Third, FDA and CMS could develop new risk-monitoring and drug supply rating systems similar to those outlined above. The new CMMI high value drug list model includes provisions for monitoring and evaluating this list.<sup>33</sup> CMS could expand this provision for supply chain risk-monitoring systems in collaboration with manufacturers. Similarly, FDA could develop its QMM program on generic drug facilities or other facilities that are experiencing shortages. Additionally, CMS could create a centralized, managed technology platform that establishes government visibility into supply chain reporting via new public private partnerships (PPP).<sup>34</sup> However, as mentioned above, manufacturers are unlikely to have incentives to collaborate, especially since PPP's can be costly and restrictive.

New legislation could include a GDUFA waiver process that lowers fees for manufacturers with an approved ANDA, particularly for those drugs that FDA has designated as "essential" in return for firms routinely submitting comprehensive data and notifications on their drug(s). FDA in their legislative proposals as part of their Fiscal Year 2024 budget request has outlined several of these data elements that could be required from manufacturers including on manufacturing volume, original manufacturers of active pharmaceutical ingredients, and other

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<sup>29</sup> Park, E. (2023, May 30). *New CMS Proposed Rule Could Help State Medicaid Programs Negotiate Greater Supplemental Rebates for Certain High-Cost Drugs*. Georgetown Center for Children and Families. Retrieved July 1, 2023, from <https://ccf.georgetown.edu/2023/05/30/new-cms-proposed-rule-could-help-state-medicaid-programs-negotiate-greater-supplemental-rebates-for-certain-high-cost-drugs/>

<sup>30</sup> Office of the Assistant Secretary for Planning and Evaluation (ASPE). (2023, May). *Impact of Drug Shortages on Consumer Cost*

<sup>31</sup> Dong, K., Boehm, G., & Zheng, Q. (2017, June). Economic Impacts of the Generic Drug User Fee Act Fee Structure. *Value in Health*, 20(6), 792-798. <https://doi.org/10.1016/j.jval.2016.05.003>

<sup>32</sup> Wosińska, M. E. (2023, February 9). *Drug shortages and IRA inflation rebates: Considerations for CMS | Brookings*. Brookings Institution. Retrieved July 1, 2023, from <https://www.brookings.edu/articles/drug-shortages-and-rebates/>

<sup>33</sup> U.S. Department of Health and Human Services. (n.d.). *A Report in Response to the Executive Order on Lowering Prescription Drug Costs for Americans*. CMS Innovation Center. Retrieved July 1, 2023, from <https://innovation.cms.gov/data-and-reports/2023/eo-rx-drug-cost-response-report>

<sup>34</sup> *National Strategy for a Resilient Public Health Supply Chain - July 2021*. (2021, July 13). ASPR. Retrieved July 1, 2023, from <https://www.phe.gov/Preparedness/legal/Documents/National-Strategy-for-Resilient-Public-Health-Supply-Chain.pdf>

supply chain information.<sup>35</sup> User fees, many of which are annual, would be lowered only if manufacturers remain consistent and standardized in their survey reporting. The benefits of this model would be direct and flow to manufacturers.<sup>36</sup> Conditioning the reduction in fees on providing reliable information would also prevent potential gaming by manufacturers as the additional requirements on fees would prevent companies from engaging in short-term gain from quick market entry and exit. To address the potential shortfall from having a reduction in total user fees as a result of such conditioned waivers, this legislation could also appropriate supplemental Congressional funding specific to the activities that the FDA leverages fees for.

Outside of new legislation, FDA could also further leverage other existing programs to address drug shortage problems. For example, the FDA has recently promoted advanced manufacturing to manufacturers, which can improve product quality and process performance. However, the FDA has not clearly streamlined these programs, which has caused manufacturer uncertainty in terms of regulatory challenges with approval. The FDA could document and finalize clear performance goals with industry to encourage advanced manufacturing adoption.<sup>37</sup> Additionally, the FDA could promote and expand its current remote inspections process. This expansion could expedite medical product production by speeding up inspection processes, allowing the agency to be more targeted in its on-site inspections.<sup>38</sup> Remote inspections could aid in ensuring a continuous supply of medical products and avoid shortages, as manufacturers are better able to quickly respond to demand needs and increase supply without regulatory burden.<sup>39</sup>

Grant-making and organizations with significant research capacity like the National Institutes of Health (NIH) and Biomedical Advanced Research and Development Authority (BARDA) could invest in process manufacturing research. Investments could also be made in research around stability and other interventions that improve the shelf life of products. As one example of the application of such research, two recent studies demonstrated longer thermostability of insulin (a medicine with strict cold chain requirements) outside of refrigeration than previously known.<sup>40,41</sup> The FDA already extends allowed medication expiration dates in cases of emergency, where data are available that supports that any extension does not pose a risk to patients.<sup>42</sup> Generating evidence on product safety and stability is useful in averting wastage of products, extending supply, and in better understanding when it is safe to use products, particularly in emergencies and supply shortages. However, there is little incentive for manufacturers to conduct this research. Instead, federal agencies with grantmaking authorities

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<sup>35</sup> Summary of FY 2024 Legislative Proposals - U.S. Food and Drug Administration. (n.d.-b). <https://www.fda.gov/media/166049/download>

<sup>36</sup> Mattingly II, T. J., & Conti, R. M. (2022, May). Ensuring a high-quality and resilient supply chain of essential medications means paying more. *J Manag Care Spec Pharm.*, 28(5), 573-576. <https://doi.org/10.18553/jmcp.2022.28.5.573>

<sup>37</sup> *Drug Manufacturing: FDA Should Fully Assess Its Efforts to Encourage Innovation*. (2023, March 10). GAO. Retrieved July 1, 2023, from <https://www.gao.gov/products/gao-23-105650>

<sup>38</sup> Church, R., Gertner, H., & Zeta, L. (2021, April 15). *FDA issues guidance on conducting remote interactive evaluations during the COVID-19 pandemic*. Hogan Lovells. Retrieved July 2, 2023, from <https://www.engage.hoganlovells.com/knowledgeservices/news/fda-issues-guidance-on-conducting-remote-interactive-evaluations-during-the-covid-19-pandemic>

<sup>39</sup> Bolislis, W. R., de Lucia, M. L., Dolz, F., Mo, R., Nagaoka, M., Rodriguez, H., Woon, M. L., Yu, W., & Kuhler, T. C. (2021, November 1). Regulatory Agilities in the Time of COVID-19: Overview, Trends, and Opportunities. *Clinical Therapeutics*, 43(1).

<sup>40</sup> Kaufmann B, Boule P, Berthou F, Fournier M, Beran D, Ciglencecki I, Townsend M, Schmidt G, Shah M, Cristofani S, Cavailler P. Heat-stability study of various insulin types in tropical temperature conditions: new insights towards improving diabetes care. *PLoS One*. 2021 Feb 3;16(2):e0245372.

<sup>41</sup> Pendsey S, James S, Garrett TJ, Nord AB, Pendsey S, Malmodin D, Karlsson G, Maniam J, Atkinson MA, Forsander G, Ogle GD. Insulin thermostability in a real-world setting. *The Lancet Diabetes & Endocrinology*. 2023 May 1;11(5):310-2.

<sup>42</sup> USFDA. Expiration Dating Extension. Available from: <https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/expiration-dating-extension>

might consider supporting this research as it would provide other potential alternative approaches for ensuring adequate supply, especially during shortages and public health emergencies.

Finally, HHS should establish a single point of responsibility for drug shortages to work across federal agencies more effectively. Previously, then FDA Commissioner Scott Gottlieb established the Agency Drug Shortages Task Force, which included representatives from FDA, CMS, the Office of the Assistant Secretary for Preparedness and Response, Department of Veterans Affairs and Department of Defense. It is unclear whether this Task Force has continued their work. Considering the recent rise in drug shortages and the need for a coordinated response across multiple agencies, HHS should re-establish such a group.

**5. *How does the current generic drug reimbursement structure in federal programs, including those programs' mandatory discounts and rebates, contribute to drug shortages, and what solutions exist?***

As discussed above, the current generic drug reimbursement structure is consistent across payers and not exclusive to federal programs and has been an economic driver contributing to drug shortages. Under the current reimbursement structure, providers and pharmacies get reimbursed for generic drugs based on a fixed rate, and they select the specific product to administer or dispense. By selecting the generic with the lowest acquisition cost, providers and pharmacies maximize margin. This reimbursement system prioritizes lower prices with limited consideration for ensuring high-quality and resilient supply chains. As a result, generic manufacturers have little financial incentive to improve and modernize their manufacturing practices.

Since 1990, manufacturers are required to provide statutory rebates to Medicaid state programs for outpatient drugs reimbursed by Medicaid. For branded drugs, Medicaid rebates are calculated as the sum of a base rebate, which is the greater of 23.1% average manufacturer price or the best discount provided to any entity, and an inflationary component, which penalizes post-launch increases in prices above inflation. For generic drugs, Medicaid rebates are calculated as the sum of a base rebate of 13% of average manufacturer price and a similarly calculated inflation rebate. After the passage of the Inflation Reduction Act (IRA), manufacturers are also required to pay inflation penalties for drugs reimbursed by Medicare. These inflation rebates, however, will only penalize increases in prices above inflation after 2021. Mandatory inflation rebates are also triggered for single source generics or generic drugs with only one manufacturer when the average Medicare price per patient is more than \$100. To prevent drug shortages, the IRA allows CMS to reduce or waive inflation rebates for Medicare Part B biosimilars and single source Part D generics that experience supply chain disruptions, for both current and future shortages.<sup>43</sup>

It is unlikely that inflation rebates play a major role in generic drug shortages, as inflation rebates are only triggered by increases in drug prices above inflation. As described above, the race to the bottom of acquisition costs triggered by the current reimbursement structure is

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<sup>43</sup> Wosińska, M. E. (2023, February 9). *Drug shortages and IRA inflation rebates: Considerations for CMS* | Brookings. Brookings Institution. Retrieved July 1, 2023, from <https://www.brookings.edu/articles/drug-shortages-and-rebates/>

considered the main reason behind the insufficient financial incentives for manufacturers to ensure a resilient supply chain. Therefore, it is unlikely that generic products that go on shortage due to decreased profit margin are subject to inflation rebates, as they would not have taken increases in prices above inflation (most likely, they would have seen decreases in prices since launch).

In our response to question 4, we propose an innovative payment model that would tie reimbursement rates for generic products to a rating system measuring the resilience of the drug supply chain. This adjustment of reimbursement rates for generic drugs would create an economic incentive for manufacturers to improve and modernize their manufacturing systems, as manufacturers with demonstrated resilient supply chains would be able to sell their products at a higher price (since pharmacies and providers would be in turned reimbursed at a higher rate when dispensing generic products from highly rated manufacturers). Several other solutions to the reimbursement structure have been previously proposed to reduce drug shortages. First, inflation rebates should not be reduced for high-margin products (including single-source generics) as rebates based on price increases would not adversely affect these manufacturers' ability to stay in the market. Manufacturers with high-margin generic and brand name drugs are responsible for ensuring a consistent supply and distribution model. There is more incentive for these manufacturers to stay in the market, just as it is for these manufacturers to research and develop high-cost drugs. When considering which manufacturers receive rebates for their drugs, CMS could consider factors that contribute to a high-margin profit structure, such as market size, spending per claim, and manufacturing complexity, which is publicly available information.<sup>44</sup>

Second, CMS could recommend that pharmacy benefit managers (PBMs) eliminate price ceilings, known as maximum allowable costs, on FDA's list of essential medicines as well as FDA's current list of drugs in shortage.<sup>45</sup> These costs cap reimbursement with an intent to lower costs, but they also pressure manufacturers to exit the market if there is no sufficient return on investment for a drug that is costly to manufacture. This would require additional negotiation with CMS and other payers to ensure that prices are not artificially inflated to an egregious amount and are consistent with data on manufacturing costs and the rest of the market.

Third, CMS could write contracts with a "failure to supply" penalty clause. These contracts would impose financial penalties on manufacturers that fail to provide essential medicines. However, this could have certain drawbacks and would have to be paired with other legislation that ensures the availability of alternative supply chains, as generic manufacturers could be pressured to exit the market if facing overwhelming cost pressures or insurmountable quality issues. Additionally, penalties could lead to hoarding from buyers and suppliers and subsequently, price stimulation due to artificially constrained supply.

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<sup>44</sup> Wosińska, M. E. (2023, February 9). *Drug shortages and IRA inflation rebates: Considerations for CMS* | Brookings. Brookings Institution. Retrieved July 1, 2023, from <https://www.brookings.edu/articles/drug-shortages-and-rebates/>

<sup>45</sup> Mattingly II, T. J., & Conti, R. M. (2022, May). Ensuring a high-quality and resilient supply chain of essential medications means paying more. *J Manag Care Spec Pharm.*, 28(5), 573-576. <https://doi.org/10.18553/jmcp.2022.28.5.573>

**6. *Given that supply chain issues can trigger manufacturing delays and disruptions that result in shortages, are further incentives necessary to address manufacturing issues?***

Regulatory incentives such as the designation of “priority generics” allowing for FDA expedited review of certain generics could be coupled with requirements to the drug sponsor to provide information on their supply chains and for their manufacturing facilities to achieve a minimum level of quality and resilience. Only when these standards have been met would a generic drug be eligible for “priority review.” Federal agencies including CMS could also employ other conditional incentives, coupling coverage and reimbursement as described above with required efforts for manufacturers to have a robust and resilient supply chain and provide timely information to federal agencies on the status of their supply to allow for timely intervention should there be a risk of manufacturing delays or disruptions that result in shortages.

**8. *Would innovative CMS reimbursement models for drugs at risk of shortage status better allow manufacturers of these drugs to meet production and patient demand? What factors should be incorporated into any model seeking to address shortages?***

First, Congress could also take legislative action through a pay-for-performance model that encourages a healthy supply chain via hospital purchasing rather than manufacturer incentives.<sup>46</sup> This could be implemented by CMS as a value-based mechanism that rewards hospitals for building a stockpile of essential medicines and selecting vendors that are less likely to experience supply chain disruptions. For outpatient drugs dispensed by PBMs, pharmacies, and generic source programs, supply agreements between generic manufacturers and distributors could be attached to a similar pay-for-performance model, rewarding distributors who maintain a healthy flow of quality generics. CMS has statutory experience with value-based models, and in this case would rely on development of FDA’s QMM program as mentioned earlier.

Second, CMS could handle reimbursement on a case-by-case basis, as CMS currently has statutory authority to increase or decrease rebates.<sup>47</sup> Assessing rebate reductions on a case-by-case basis would be necessary and would also compel sponsors to provide manufacturer supply chain data as there is an economic incentive to provide proprietary data. Greater reductions could occur when there is a clear supply chain shock that is external to company control, such as hurricanes and other catastrophic weather events. This would still require data to determine which makers are experiencing supply chain issues.

**10. *How might uncertainty in the drug coverage process, particularly as it relates to National Coverage Determinations (NCD) and coverage paradigms like Coverage with Evidence Development (CED), affect competition and, ultimately, the supply of drugs? What can be done to promote greater certainty in that process for FDA-approved drugs?***

CMS’s National Coverage Determinations (NCD) and other coverage paradigms including Coverage with Evidence Development (CED) would not impact shortages of generic

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<sup>46</sup> Wosińska, M. E., & Frank, R. G. (2023, June 3). *Federal Policies to Address Persistent Generic Drug Shortages*. Brookings Institution. Retrieved July 1, 2023, from [https://www.brookings.edu/wp-content/uploads/2023/06/20230621\\_ES\\_THP\\_GSI\\_Report\\_Final.pdf](https://www.brookings.edu/wp-content/uploads/2023/06/20230621_ES_THP_GSI_Report_Final.pdf)

<sup>47</sup> Wosińska, M. E. (2023, February 9). *Drug shortages and IRA inflation rebates: Considerations for CMS* | Brookings. Brookings Institution. Retrieved July 1, 2023, from <https://www.brookings.edu/articles/drug-shortages-and-rebates/>

drugs, which comprise nearly all the reported drug shortages by the FDA. Firstly, NCD and CED are infrequently used for any drugs, as nearly all NCDs/CEDs apply to therapeutic medical devices and diagnostic tests. Secondly, NCD and CED are applied to drug products immediately following FDA approval, when these products are under intellectual property protection through patents and other FDA-awarded exclusivities. Thus, when CMS would be potentially issuing an NCD or considering CED, the drug product in question would not be facing competition in the form of generic or biosimilar. Medicare Part D coverage is also required for prescription drugs in six protected classes – immunosuppressants, antidepressants, antipsychotics, anticonvulsants, antiretrovirals, and antineoplastics, thus allowing manufacturers of such products to be able to anticipate coverage decisions. There is no evidence that such coverage paradigms from CMS for largely branded drug products would impact drug shortages.

***11. Are there any guardrails that Congress should to consider related demonstration projects, including via the CMS’ Innovation Center, that would help protect against drug shortages? Are there any proactive demonstrations that would prevent drug shortages?***

Given the various economic and regulatory drivers contributing to drug shortages, it is clear there is no single silver bullet for effectively addressing this longstanding problem. Currently, CMS’ Innovation Center (CMMI) has no demonstration projects focused on drug shortages.<sup>48</sup> However, any of the aforementioned recommendations targeted towards CMS such as requiring manufacturers to provide data around supply chain quality and resiliency, rating manufacturers on supply chain quality and resiliency parameters, and adjusting reimbursement or rebate for essential products or at risk of shortage could be piloted by CMMI. In fact, CMMI should be given flexibility to pilot varied approaches without restriction from Congress and provide public evaluations of such approaches toward informing more long-term implementation to effectively address drug shortages.

***13. What factors would lead to a generic drug receiving approval but not coming to market?***

There are a variety of different strategies implemented by brand name drug manufacturers to deter or delay the availability of generics in the market, including those generic drugs receiving approval but not coming to market. Although Congress has historically encouraged competition and lower prices via the Hatch-Waxman Act, which provided 180 days of exclusive rights for the first generic company to file an ANDA, generic drugs have faced additional challenges from brand name drug manufacturers, such as alternative exclusivity mechanisms and market injunctions for generics that face litigation.<sup>49</sup>

Additionally, the drug patent process provides brand name manufacturers the ability to maintain monopoly pricing and supply. Egregious patent gaming, such as when brand name manufacturers acquire “secondary patents,” prevents generic alternatives from being made available on the market.<sup>50</sup> An additional strategy known as product hopping involves brand name

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<sup>48</sup> CMS. (n.d.). Innovation models: CMS Innovation Center. <https://innovation.cms.gov/innovation-models#views=models&key=drug>

<sup>49</sup> Carrier, M. A. (2009, October). Unsettling drug patent settlements: a framework for presumptive illegality. *Mich Law Rev*, 108(1), 37-80. <https://pubmed.ncbi.nlm.nih.gov/20535881/>

<sup>50</sup> Gupta, R., Shah, N. D., & Ross, J. S. (2019, February). GENERIC DRUGS IN THE UNITED STATES: POLICIES TO ADDRESS PRICING AND COMPETITION. *Clin Pharmacol Ther.*, 105(2), 329-337. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6355356/>

manufacturers switching the dosage or form of their drug available on the market, with little to no therapeutic benefit compared to the original product and precluding automatic substitution with the generic, effectively extending their patent before expiration.<sup>51</sup> Brand name manufacturers also use “reverse-payment” or “pay-for-delay” settlements, where the brand name manufacturer and first generic manufacturer agree to withdraw patent challenges in exchange for monetary compensation, effectively preventing multiple generic competitors from entering the market.<sup>52</sup> Skinny labeling, an approval pathway used by generic manufacturers to seek approval for unpatented uses of brand-name drugs, is currently an essential method granted by Congress under the Hatch-Waxman Act of 1984 to provide cost-reducing competition in the market.<sup>53</sup> This method has been recently under threat and could face additional litigation pressure from brand-name manufacturers.<sup>54</sup> It is essential to maintain the integrity of this pathway as a method for fair competition.

The FDA could remove barriers that prevent against the market entry of multiple generic manufacturers approved to treat the same condition or disease. Moreover, several of FDA’s legislative proposals as part of their Fiscal Year 2024 budget could also be passed by Congress. FDA. For instance, under current law, brand-name manufacturers can file patents and maintain exclusivity of their drug for years without commercially marketing their drug. FDA has proposed amending this legislation to allow FDA to approve subsequent generic applications unless the brand-name manufacturer markets the drug within 180 days of patent approval.

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<sup>51</sup> Jones, G. H., Carrier, M. A., Silver, R. T., & Kantarjian, H. (2016, March 17). Strategies that delay or prevent the timely availability of affordable generic drugs in the United States. *Blood*, 127(11), 1398-1402. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4915805/#B7>

<sup>52</sup> Gupta, R., Shah, N. D., & Ross, J. S. (2019, February). GENERIC DRUGS IN THE UNITED STATES: POLICIES TO ADDRESS PRICING AND COMPETITION. *Clin Pharmacol Ther.*, 105(2), 329-337. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6355356/>

<sup>53</sup> Walsh, B. (2021, October 19). *Skinny labeling: A pathway for Timely Generic Drug Competition*. Commonwealth Fund. <https://www.commonwealthfund.org/blog/2021/skinny-labeling-pathway-timely-generic-drug-competition>

<sup>54</sup> Silverman, E. (2023, May 15). *U.S. Supreme Court declines bid by Teva to hear “skinny labeling” case with implications for Generic Drug Access*. STAT. <https://www.statnews.com/pharmalot/2023/05/15/supreme-court-generic-drugs-scotus-teva-gsk/>