PORTAL
Program On Regulation, Therapeutics, And Law

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Centers for Medicare and Medicaid Services (CMS)
7500 Security Boulevard
Baltimore, Maryland 21244-1859

RE: Information Collection Request – Medicare Drug Price Negotiation Program IPAY 2027 Research-Focused Experience Questions

On behalf of the Program On Regulation, Therapeutics, And Law (PORTAL) in the Division of Pharmacoepidemiology and Pharmacoeconomics at Brigham and Women's Hospital and Harvard Medical School, we appreciate the opportunity to submit information to inform CMS' assessment of drugs selected for Initial Price Applicability Year 2027 (IPAY 2027) of the Medicare Drug Price Negotiation Program.

Our research group is one of the largest academic research centers in the US dedicated to investigating the regulation, use, evidence, and cost of prescription drugs; no faculty or staff members in our Division have any financial support from the pharmaceutical industry.

We have included below a summary of some peer-reviewed publications from our group that we think may be valuable as CMS conducts an evidence-based assessment of selected drugs, their therapeutic alternatives, and the indication(s) they treat. For each selected drug, a brief summary of each relevant publication is provided.

IPAY 2027 Selected Drugs with Relevant PORTAL Publications

Trelegy Ellipta (fluticasone-umeclidinium-vilanterol)

1. **Comparative Effectiveness and Safety of Single Inhaler Triple Therapies for Chronic Obstructive Pulmonary Disease: New User Cohort Study**[1]

   In an observational cohort study published in *BMJ*, Feldman and coauthors assessed the comparative effectiveness and safety of Trelegy Ellipta and Breztri Aerosphere (budesonide-glycopyrrolate-formoterol) in chronic obstructive pulmonary disease (COPD). The authors found that Breztri Aerosphere was associated with a 9% higher risk of moderate or severe COPD exacerbations and a similar risk of pneumonia hospitalizations compared to Trelegy Ellipta among patients with COPD treated in routine clinical practice.

2. **Patenting Strategies on Inhaler Delivery Devices**[2]

   In a 2023 analysis published in *Chest*, Demkowicz et al. reviewed the device patents listed in the FDA Orange Book for brand-name inhalers for asthma and COPD approved between 1986 and 2020, including Trelegy Ellipta. These device patents represented approximately half of all patents on inhalers listed in the Orange Book, with more than three-quarters of device patents making no mention of the active ingredients or the products on which they are listed. Device patents were found to extend market exclusivity by a median of 5.5 years, delaying market entry for generic competitors. However, the seven device patents listed for Trelegy Ellipta were not found to provide additional market exclusivity beyond that provided by other non-device patents.

3. **Manufacturer Revenue on Inhalers After Expiration of Primary Patents, 2000-2021**[3]

   In a 2023 *JAMA* research letter, Feldman and colleagues analyzed drug manufacturer revenue on 39 brand-name inhalers before and after expiration of patents on their active ingredient(s). They found that manufacturers earned substantially more revenue on inhalers after the expiration of active ingredient patents ($67.2 billion before; $110.3 billion after) due to sustained market exclusivity from secondary patents on features including the delivery device, formulations, and methods of use. However, primary patents specific to Trelegy Ellipta had not yet expired at the time of publication.

4. **Added Therapeutic Benefit of Top-Selling Brand-name Drugs in Medicare**[4]

   In a 2023 study published in *JAMA*, Egilman and colleagues examined the added therapeutic benefit of the 50 highest-selling drugs in Medicare in 2020 as assessed by the national health technology assessment agencies in France, Germany, or Canada. They found that 27 drugs (55%) had a low added therapeutic benefit rating by at least one country's HTA, representing $19.5 billion (35%) of estimated net Medicare spending in 2020 on the top 50 single-source drugs. Trelegy Ellipta received a "low" added therapeutic benefit rating in Canada, France, and Germany, with a "Moderate" absolute therapeutic benefit rating in France.

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[1] Feldman WB, Suissa S, Kesselheim AS, et al. Comparative effectiveness and safety of single inhaler triple therapies for chronic obstructive pulmonary disease: new user cohort study. *BMJ*. 2024;387:e080409. doi:10.1136/bmj-2024-080409

[2] Demkowicz BJ, Tu SS, Kesselheim AS, Carrier MA, Feldman WB. Patenting Strategies on Inhaler Delivery Devices. *Chest*. 2023;164(2):450-460. doi:10.1016/j.chest.2023.02.031

[3] Feldman WB, Tu SS, Alhiary R, Kesselheim AS, Wouters OJ. Manufacturer Revenue on Inhalers After Expiration of Primary Patents, 2000-2021. *JAMA*. 2023;329(1):87. doi:10.1001/jama.2022.19691

[4] Egilman AC, Rome BN, Kesselheim AS. Added Therapeutic Benefit of Top-Selling Brand-name Drugs in Medicare. *JAMA*. 2023;329(15):1283. doi:10.1001/jama.2023.4034

Breo Ellipta (fluticasone-vilanterol)

1. **Chronic Obstructive Pulmonary Disease Exacerbations and Pneumonia Hospitalizations Among New Users of Combination Maintenance Inhalers**[5]

   In a cohort study of more than 60,000 patients with COPD in US commercial claims data, Feldman and colleagues assessed if combination inhalers with long-acting muscarinic antagonists (LAMAs) and long-acting beta-agonists (LABAs) were associated with reduced incidence of COPD exacerbations and pneumonia hospitalization versus inhalers with LABAs and inhaled corticosteroids (ICSs), including Breo Ellipta. They found that patients receiving LAMA-LABA inhalers had an 8% lower rate of moderate or severe COPD exacerbations and a 20% lower rate of pneumonia hospitalization compared to those receiving ICS-LABA therapy.

2. **Patenting Strategies on Inhaler Delivery Devices**[6]

   In a 2023 analysis published in *Chest*, Demkowicz et al. reviewed the device patents listed in the FDA Orange Book for brand-name inhalers for asthma and COPD approved between 1986 and 2020, including Trelegy Ellipta. These device patents represented approximately half of all patents on inhalers listed in the Orange Book, with more than three-quarters of device patents making no mention of the active ingredients or the products on which they are listed. Device patents were found to extend market exclusivity by a median of 5.5 years, delaying market entry for generic competitors. The 8 device patents listed for Breo Ellipta were found to extend the drug's market exclusivity by an additional 5.4 years, despite some of these patents having no reference to Breo Ellipta's active ingredients.

3. **Manufacturer Revenue on Inhalers After Expiration of Primary Patents, 2000-2021**[7]

   In a 2023 *JAMA* research letter, Feldman and colleagues analyzed drug manufacturer revenue on 39 brand-name inhalers before and after expiration of patents on their active ingredient(s). They found that manufacturers earned substantially more revenue on inhalers after the expiration of active ingredient patents ($67.2 billion before; $110.3 billion after) due to sustained market exclusivity from secondary patents on features including the delivery device, formulations, and methods of use. However, primary patents specific to Breo Ellipta had not yet expired at the time of publication.

4. **Added Therapeutic Benefit of Top-Selling Brand-name Drugs in Medicare**[8]

   In a 2023 study published in *JAMA*, Egilman and colleagues examined the added therapeutic benefit of the 50 highest-selling drugs in Medicare in 2020 as assessed by the national health technology assessment agencies in France, Germany, or Canada. They found that 27 drugs (55%) had a low added therapeutic benefit rating by at least one country's HTA, representing $19.5 billion (35%) of estimated net Medicare spending in 2020 on the top 50 single-source drugs. Breo Ellipta received a "low" added therapeutic benefit rating in Canada, France, and Germany, with an "Important" absolute therapeutic benefit rating in France.

[5] Feldman WB, Avorn J, Kesselheim AS, Gagne JJ. Chronic Obstructive Pulmonary Disease Exacerbations and Pneumonia Hospitalizations Among New Users of Combination Maintenance Inhalers. *JAMA Intern Med*. 2023;183(7):685. doi:10.1001/jamainternmed.2023.1245
[6] Demkowicz et al. *Chest*. 2023.
[7] Feldman et al. *JAMA*. 2023.
[8] Egilman et al. *JAMA*. 2023.

Ozempic; Rybelsus; Wegovy (semaglutide)

1. **Patents and Regulatory Exclusivities on GLP-1 Receptor Agonists**[9]

   In a 2023 *JAMA* special communication, Alhiary et al. characterized the patents and regulatory exclusivities obtained on GLP-1s for the treatment of diabetes and weight loss, including Ozempic, Rybelsus, and Wegovy. They found that brand manufacturers listed a median of 10.5 patents per product in the FDA Orange Book and obtained a median of 2 regulatory exclusivities at the time of FDA approval and 1 exclusivity after approval, resulting in a median duration of market exclusivity of 18.3 years post-FDA approval.

2. **Delivery Device Patents on GLP-1 Receptor Agonists**[10]

   A 2024 analysis by Alhiary and colleagues in *JAMA* identified delivery device patents listed in the FDA Orange Book for 10 GLP-1 drug-device combinations. Of the 188 patents listed for these products, 107 (57%) were delivery device patents, none of which mentioning the active ingredient or chemical structure of the drug on which they were listed. For Ozempic, 21 of 25 (84%) Orange Book patents were on the delivery device, and 75% of the patents on Ozempic litigated by generic manufacturers were device patents with no mention of semaglutide. These patents contribute to patent thickets that have the potential to delay generic entry.

3. **Added Therapeutic Benefit of Top-Selling Brand-name Drugs in Medicare**[11]

   In a 2023 study published in *JAMA*, Egilman and colleagues examined the added therapeutic benefit of the 50 highest-selling drugs in Medicare in 2020 as assessed by the national health technology assessment agencies in France, Germany, or Canada. They found that 27 drugs (55%) had a low added therapeutic benefit rating by at least one country's HTA, representing $19.5 billion (35%) of estimated net Medicare spending in 2020 on the top 50 single-source drugs. Ozempic received a "low" added therapeutic benefit rating in Canada, France, and Germany, with a "Moderate" absolute therapeutic benefit rating in France.

4. **Heterogeneity of antidiabetic treatment effect on the risk of major adverse cardiovascular events in type 2 diabetes: a systematic review and meta-analysis**[12]

   In a 2020 exploratory analysis published in *Cardiovascular Diabetology*, D'Andrea and colleagues assessed the potential impact of patient baseline characteristics on the effect of GLP-1s and SGLT-2s to reduce risk of major adverse cardiovascular events (MACE). Among the patients enrolled in 10 clinical trials included in the analysis, the authors found a 14% reduction in risk of MACE in patients with history of cardiovascular disease while there was no effect among at-risk patients without history of cardiovascular events. Greater treatment benefits were observed among patients with chronic kidney disease receiving SGLT-2s and for patients with uncontrolled diabetes receiving GLP-1s or SGLT-2s.

[9] Alhiary R, Kesselheim AS, Gabriele S, Beall RF, Tu SS, Feldman WB. Patents and Regulatory Exclusivities on GLP-1 Receptor Agonists. *JAMA*. 2023;330(7):650. doi:10.1001/jama.2023.13872
[10] Alhiary R, Gabriele S, Kesselheim AS, Tu SS, Feldman WB. Delivery Device Patents on GLP-1 Receptor Agonists. *JAMA*. 2024;331(9):794. doi:10.1001/jama.2024.0919
[11] Egilman et al. *JAMA*. 2023.
[12] D'Andrea E, Kesselheim AS, Franklin JM, Jung EH, Hey SP, Patorno E. Heterogeneity of antidiabetic treatment effect on the risk of major adverse cardiovascular events in type 2 diabetes: a systematic review and meta-analysis. *Cardiovasc Diabetol*. 2020;19(1):154. doi:10.1186/s12933-020-01133-1

Pomalyst (pomalidomide)

1. **Trends in Use and Evidence of Adherence to Risk Evaluation and Mitigation Strategy Pregnancy Testing Requirements for Thalidomide, Lenalidomide, and Pomalidomide in the USA, 2000–2020**[13]

   In a 2024 analysis published in *Drug Safety*, Mahesri and coauthors used commercial and public claims data to evaluate patients' use of and adherence to three teratogenic drugs subject to FDA-imposed risk evaluation and mitigation strategies (REMS): thalidomide, lenalidomide, and pomalidomide (Pomalyst). Lenalidomide was the most widely used drug during the study period, with patients on lenalidomide and pomalidomide demonstrating more persistent use than patients using thalidomide. Women of childbearing potential represented 3% of all patients initiating these drugs, yet low evidence of adherence to REMS-required pregnancy testing was found among these patients.

2. **Patents on Risk Evaluation and Mitigation Strategies for Prescription Drugs and Generic Competition**[14]

   In *JAMA*, Sarpatwari and colleagues identified active patents covering risk evaluation and mitigation strategies (REMS) listed in the FDA Orange Book for Pomalyst and other small molecule drugs with non-drug class-wide REMS through 2022. Ten patents listed in the Orange Book for Pomalyst covered the drug's REMS, representing 50% of Pomalyst's Orange Book patent portfolio. All 10 REMS patents for Pomalyst were challenged by generic manufacturers, with only 2 being invalidated, which may have contributed to delays in generic entry.

3. **Analysis of Risk Evaluation and Mitigation Strategies for Teratogenic Drugs: Variation in Primary and Secondary Prevention Measures**[15]

   A 2023 publication in *PLOS Medicine* by Brown, Kesselheim, and Sarpatwari compared REMS-required contraception use and pregnancy testing requirements for drugs with teratogenic risks. The authors find that across the 10 drugs reviewed, considerable variation existed in the stringency of the REMS requirements, including differences in the timing and frequency of pregnancy testing and which contraceptives were required. This variation was not fully explained by the drugs' respective teratogenicity.

4. **Added Therapeutic Benefit of Top-Selling Brand-name Drugs in Medicare**[16]

   In a 2023 study published in *JAMA*, Egilman and colleagues examined the added therapeutic benefit of the 50 highest-selling drugs in Medicare in 2020 as assessed by the national health technology assessment agencies in France, Germany, or Canada. They found that 27 drugs (55%) had a low added therapeutic benefit rating by at least one country's HTA, representing $19.5 billion (35%) of estimated net Medicare spending in 2020 on the top 50 single-source drugs. Pomalyst received a "high" added therapeutic benefit rating in Canada and Germany and a "low" rating in France, with a "Important" absolute therapeutic benefit rating in France.

[13] Mahesri M, Sarpatwari A, Huybrechts KF, et al. Trends in Use and Evidence of Adherence to Risk Evaluation and Mitigation Strategy Pregnancy Testing Requirements for Thalidomide, Lenalidomide, and Pomalidomide in the USA, 2000–2020. *Drug Saf*. 2024;47(9):909-919. doi:10.1007/s40264-024-01443-3
[14] Sarpatwari A, Kohli S, Tu SS, Kesselheim AS. Patents on Risk Evaluation and Mitigation Strategies for Prescription Drugs and Generic Competition. *JAMA*. 2024;331(11):976. doi:10.1001/jama.2024.0924
[15] Brown BL, Kesselheim AS, Sarpatwari A. Analysis of risk evaluation and mitigation strategies for teratogenic drugs: Variation in primary and secondary prevention measures. *PLoS Med*. 2023;20(3):e1004190. doi:10.1371/journal.pmed.1004190
[16] Egilman et al. *JAMA*. 2023.

Xtandi (enzalutamide)

1. **Government Funding for the Development of Enzalutamide**[17]

   In a 2024 *JAMA Oncology* analysis, Gyawali and colleagues detail US federal government contributions to the development of Xtandi (enzalutamide) through funding awarded by the National Institutes of Health and the Department of Defense. They find prior to Xtandi's FDA approval in 2012, the government contributed at least $74.5 million to the drug's development, including $16.5 million of public funding to support basic science related to the discovery of Xtandi prior to 2003, when Michael Jung and Charles Sawyer reportedly began collaborating on research related to Xtandi at the University of California, Los Angeles. The supplemental appendix of this analysis includes a narrative review of Xtandi's development.

2. **Added Therapeutic Benefit of Top-Selling Brand-name Drugs in Medicare**[18]

   In a 2023 study published in *JAMA*, Egilman and colleagues examined the added therapeutic benefit of the 50 highest-selling drugs in Medicare in 2020 as assessed by the national health technology assessment agencies in France, Germany, or Canada. They found that 27 drugs (55%) had a low added therapeutic benefit rating by at least one country's HTA, representing $19.5 billion (35%) of estimated net Medicare spending in 2020 on the top 50 single-source drugs. Xtandi received a "low" added therapeutic benefit rating in Canada and a "high" rating in France and Germany, with an "Important" absolute therapeutic benefit rating in France.

Calquence (acalabrutinib)

1. **Trends in Medicare Spending on Oral Drugs for Chronic Lymphocytic Leukemia From 2014 to 2020**[19]

   In a 2023 research letter in *JAMA Network Open*, Cliff and colleagues examine trends in Medicare Part D annual spending on oral drugs for chronic lymphocytic leukemia (CLL), including Calquence (acalabrutinib). Between 2014 to 2020, annual net Medicare spending on six oral CLL drugs increased from $254 million to $3.7 billion across all indications. Imbruvica (ibrutinib) represented 77% of this spending in 2020 despite facing brand-name competition from less expensive oral CLL drugs like Calquence. While net spending per 30-day supply increased for Imbruvica during the study period, net spending for other oral CLL drugs remained relatively stable or slightly decreased.

[17] Gyawali B, Jung EH, Mooney H, Avorn J, Kesselheim AS. Government funding for the development of enzalutamide. *JAMA Oncol*. Published online December 19, 2024. doi:10.1001/jamaoncol.2024.5661
[18] Egilman et al. *JAMA*. 2023.
[19] Cliff ERS, Kesselheim AS, Rome BN, Feldman WB. Trends in Medicare Spending on Oral Drugs for Chronic Lymphocytic Leukemia From 2014 to 2020. *JAMA Netw Open*. 2023;6(4):e237467. doi:10.1001/jamanetworkopen.2023.7467