PORTAL
Program On Regulation, Therapeutics, And Law

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Via Electronic Submission

Centers for Medicare & Medicaid Services
75000 Security Boulevard
Baltimore, Maryland 21244

RE: Comments on CMS' Medicare Drug Price Negotiation Program Initial Guidance

We are members of the Program On Regulation, Therapeutics, And Law (PORTAL) at Brigham and Women's Hospital and Harvard Medical School. PORTAL is one of the largest, non-pharmaceutical industry-funded academic research centers in the US devoted to investigating drug prescribing, outcomes, and policy. We applaud CMS' initial guidance on the implementation of Medicare price negotiation under the Inflation Reduction Act of 2022. Effective implementation of this policy is vital to ensure that Medicare beneficiaries and taxpayers benefit from fair drug prices. We recently published a study simulating the impact of price negotiation from 2018-2020 and found that, in just the first 3 years of drug price negotiation, Medicare could lower prescription drug spending by 5% by accepting the statutory ceiling price in the law, and even more if negotiations lead to lower prices.[1]

In this submission, we provide some specific comments aimed at sharpening and clarifying key pieces of the framework for drug price negotiation. Overall, we are supportive of the approach outlined by CMS. The issues raised here are meant to provide constructive feedback to help strengthen the guidance, minimize the likelihood that brand-name manufacturers avoid fair negotiations, and anticipate effects on the pharmaceutical supply chain.

Sincerely,
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[1] Rome BN, Nagar S, Egilman AC, et al. Simulated Medicare Drug Price Negotiation Under the Inflation Reduction Act of 2022. *JAMA Health Forum.* 2023;4(1):e225218. doi:10.1001/jamahealthforum.2022.5218.

30.1 Identification of Qualifying Single Source Part D Drugs for Initial Price Applicability Year 2026

CMS plans to treat fixed-dose combinations separately from drugs that contain the same active ingredients / active moieties. While this may be sensible in some cases, it creates an opportunity for drugmakers to avoid negotiation by splitting the market between drugs with a fixed-dose combination alternative. For example, antiretrovirals to treat human immunodeficiency virus (HIV) are frequently marketed as fixed-dose combinations; if drugmakers could co-formulate new molecular entities with a variety of older ones, they could maintain lower Medicare spending on each product to delay being selected for negotiation or, in some cases, prohibit selection by keeping products below the $200 million Medicare spending threshold necessary to be selected. CMS should instead consider aggregating sales for fixed-dose combinations with other dosage forms containing the newest active ingredient if the products are made by the same company.

By contrast, under the current guidelines, CMS plans to aggregate the sales of active ingredients with different indications and/or routes of delivery, which may be problematic. For example, fluticasone propionate is approved as a nasal spray to treat nonallergic rhinitis (Flonase, NDA 020121) and as an orally inhaled powder to treat asthma (Flovent, NDA 020833). Both products are made by GlaxoSmithKline. Flonase has marketed generic versions that would preclude it from being selected for negotiation, but Flovent does not yet have generic competition. As a result, aggregating sales for these two different products would preclude CMS from negotiating prices for Flovent, which had gross Medicare spending of nearly half a billion dollars in 2021. One potential solution is for CMS to manually review products with different routes of administration before they are aggregated, and to only aggregate such products if the labeled indication(s) are similar.

The guidance also states that bona fide generic or biosimilar competition for *"any strength or dosage form of a potential qualifying single source drug"* would disqualify a drug from being considered for negotiation. This poses a problem, because drug companies frequently engage in product hopping from one formulation to another, actively moving patients to the newer version that often has longer patent protection. If generic or biosimilar competition for the drug's earliest version precludes negotiation, the newer version of the product should still be eligible for negotiation. We recommend that CMS determine if a given drug would be eligible for negotiation if the strength or dosage forms with generic competition were excluded. For example, if a brand-name drug comes in 2 different formulations and has generic competition for only 1 of these formulations, then the other formulation should still be eligible for price negotiation if its annual gross Medicare spending is above the $200 million threshold and if the drug has no other reasons for exclusion.

30.1.1 Orphan Drug Exclusion from Qualifying Single Source Drugs

We have concerns about this exclusion. First, we do not see a good reason why drugs treating rare diseases that earn more than $200 million in Medicare sales should be excluded from negotiation. The fact that drugs qualify based on Medicare sales is a marker that they are commercially successful. It costs less for drug companies to develop orphan-designated drugs than drugs that treat common conditions.[2]

Second, this exclusion, as implemented, could have unintended consequences for the repurposing of rare disease drugs to treat other rare diseases. For example, pomalidomide (Pomalyst) was initially approved by the FDA in 2013 to treat multiple myeloma, a condition for which the drug was granted an orphan designation in 2003. In 2018, the drug was granted a second orphan designation for the treatment of Kaposi sarcoma, and the

[2] Wouters OJ, McKee M, Luyten J. Estimated Research and Development Investment Needed to Bring a New Medicine to Market, 2009-2018. *JAMA*. 2020; 323(9):844-853. doi:10.1001/jama.2020.1166.

drug's label was expanded to include the treatment of AIDS-related Kaposi sarcoma in 2020. Had this second indication not been added to the drug's label, the drug might have qualified for the orphan drug exclusion. This creates a perverse incentive, in which a maker of a commercially successful rare disease drug may choose not to study the drug's effectiveness and safety for other indications.

While CMS cannot remove the sole-orphan exemption from the IRA, there is an important issue that CMS should address in guidance. To be eligible for this exclusion, the guidance specifies that drugs must *"be designated as a drug for only one rare disease or condition under section 526 of the FD&C Act."* Drug companies frequently seek orphan designations several years before these conditions may be added to the drug's labeling. In cases where a drug is currently approved for a single orphan-designated disease but has one or more additional orphan designations that are not yet FDA-approved, drugmakers may seek to withdraw the designated indication if doing so would allow them to qualify for the orphan drug exclusion. We would suggest that CMS clarify how such withdrawn designations will be handled regarding this exclusion. We recommend that such withdrawals should not exempt manufacturers from drug price negotiation.

30.1.3 Plasma-Derived Product Exclusion from Qualifying Single Source Drugs

We also have concerns about the exclusion of plasma-derived products. First, we do not see a good reason why otherwise eligible plasma-derived products should be excluded from negotiation: there were at least 5 such products with Medicare spending over $200 million in 2021, all of which are immunoglobulins. Rather, the fact that prices remain high despite the availability of multiple therapeutically similar immunoglobulin products suggests that this is a product class that could benefit from Medicare price negotiation. Further, highly expensive plasma-derived products such as factor replacement therapy pose major affordability and access problems for many patients.

We recognize that CMS cannot amend the IRA to include plasma-derived products. However, we believe that CMS could better clarify which products will be considered plasma-derived. The statute defines a plasma-derived product as "a biological product that is derived from human whole blood or plasma." CMS should clarify whether, for example, cellular and gene therapies that may be derived using apheresis from a patient's blood would therefore be entirely excluded from negotiation. We do not believe that such products should be excluded and would recommend that CMS explicitly identify such products in its final guidance as eligible for drug price negotiation.

The initial CMS guidance states that CMS will identify plasma-derived products from the following FDA website: https://www.fda.gov/vaccines-blood-biologics/blood-blood-products/approved-blood-products. This page includes a list of fractionated plasma products but also includes a list of all biologic products regulated by the FDA Center for Biologics Evaluation and Research, which includes a wide range of products, not all of which are likely to meet the definition of plasma-derived products. We recommend that CMS clarify the definition so that only fractionated plasma products (and not those listed on the "Licensed Biological Products with Supporting Documents" page) will be excluded from negotiation. These products are listed here: https://www.fda.gov/vaccines-blood-biologics/approved-blood-products/fractionated-plasma-products.

40.2.1 Confidentiality of Proprietary Information

"CMS is seeking comment about the proper balance between the public's interests in transparency and the protection of business information in this context."

We urge CMS to be very selective about which data elements it treats as confidential proprietary information. The status quo is that prescription drug prices are shrouded in secrecy; there have been several efforts in recent years to make prices more transparent for consumers, including via state transparency laws.[3,4] Drug manufacturers, insurers, and pharmacy benefit managers have all fought to maintain the secrecy of discounts and prices through the supply chain. However, the resulting information asymmetry harms patients who are partially or fully exposed to the full pre-discount price based on their health insurance status or benefit design. It also impedes manufacturer competition and limits accountability on whether rebates are being translated into savings for insurers and patients. Transparency is a core element of competitive markets.

While CMS may have reasons to treat some data elements as proprietary during this first round of negotiation, we recommend that the guidance clarify that CMS reserves the right to re-classify elements as non-proprietary in subsequent years. For example, while individual net prices negotiated between the manufacturer and each Part D plan may be confidential, the weighted average net price across all Part D plans may not be subject to the same restraints. Average net prices for selected drugs have been published in staff reports released as part of an investigation by the US House Committee on Oversight and Accountability.[5] Similar arguments could be used to improve transparency of Medicaid best prices, 340B discounts, and federal supply schedule and Big 4 prices.

In addition, given substantial public interest, we would recommend that CMS include as many details as possible about the negotiation process that helps patients understand how CMS arrived at the maximum fair price, including data used to derive the initial offer, the amount of the initial offer, amount of the manufacturer's counteroffer, and any new information that informed a change between the initial offer and the final MFP.

50.2 Evidence about Therapeutic Alternatives for the Selected Drug

"CMS is soliciting comment on other metrics, in addition to QALYs, that may treat extending the life of an individual who is elderly, disabled, or terminally ill as of lower value than extending the life of an individual who is younger, nondisabled, or not terminally ill and that CMS should also exclude from consideration when developing offers and reviewing counteroffers."

We believe that CMS should consider both life extension and improved quality of life when measuring the comparative effectiveness of a selected drug and therapeutic alternatives. In many cases, drugs do not extend life, such as symptomatic treatments for arthritis. In these cases, the use of QALYs or other measures that assess quality of life is non-discriminatory. In cases where drugs do extend life, CMS should consider alternative measures that incorporate quality of life but treat extended life equally for all individuals. One example of such a measure is the equal value life year gained (evLYG). The use of such measures would be helpful for CMS in determining a maximum fair price, and we believe they align with the statutory requirements.

[3] Feldman WB, Rome BN, Avorn J, Kesselheim AS. The Future of Drug-Pricing Transparency. *New Eng J Med* 2021; 384:489-491. doi: 10.1056/NEJMp2033734.
[4] 2023 State Legislative Action to Lower Pharmaceutical Costs. National Academy for State Health Policy. Updated March 31, 2023. https://nashp.org/2023-state-legislative-action-to-lower-pharmaceutical-costs/
[5] Chairwoman Maloney Releases Comprehensive Staff Report Culminating the Committee's Sweeping Drug Pricing Investigation. US House Committee on Oversight and Accountability. Published December 10, 2021. https://oversightdemocrats.house.gov/news/press-releases/chairwoman-maloney-releases-comprehensive-staff-report-culminating-the-committee

60.1 Establishment of a Single Proposed MFP for Negotiation Purposes

The choice by CMS to negotiate prices for a 30-day equivalent supply rather than per unit is sensible for many drugs used to treat chronic conditions. However, in some cases, 30 days may not be the optimal time frame by which to evaluate drugs. For example, some drugs are administered once (e.g., a 1-time gene therapy) or used for a short, fixed period to treat an acute condition (e.g., an antibiotic or antiviral). For this reason, CMS may wish to allow for flexibility in selecting an alternative supply of the drug if it is not used chronically.

This same concern applies when comparing the price of the selected drug to the prices of therapeutic alternatives. If the therapeutic alternatives have a different dosing schedule than the selected drug, comparing prices per 30-day supply may not be sensible. For example, denosumab is an injection given every 6 months for treating osteoporosis; therapeutic alternatives may include oral bisphosphonates (often dosed once a week) and injected bisphosphonates (dosed once a year). Comparing prices per 30-day supply, in this case, may not adequately capture variations in the price of treatment, and CMS should consider using the annual cost of treatment instead.

60.3.2 Developing a Starting Point for the Initial Offer

"If there are multiple therapeutic alternatives, CMS intends to consider the range of net prices and/or ASPs as well as the utilization of each therapeutic alternative to determine the starting point within that range."

For selected drugs with multiple therapeutic alternatives, we would recommend that the lowest net price for a therapeutic alternative serve as the starting point for the initial offer. Such an approach would ensure that any amount that CMS pays in excess of the lowest-cost alternative is justified by the drug's comparative safety and effectiveness.

"If the selected drug has no therapeutic alternative, if the price of the therapeutic alternatives identified is above the statutory ceiling for the MFP (described in section 60.2 of this memorandum), or if there is a single therapeutic alternative with a price above the statutory ceiling, then CMS intends to determine the starting point for the initial offer based on the Federal Supply Schedule (FSS) or "Big Four Agency" price ("Big Four price")."

In case when a selected drug has no pharmacologic therapeutic alternatives, we would recommend CMS consider using prices negotiated by other countries as a starting point for the initial offer, especially if foreign prices are lower than the FSS or Big Four price. Nearly every other large, industrialized country has a process for evaluating evidence and negotiating prices when drugs are first approved. CMS should leverage these existing assessments to determine a maximum fair price.

60.6.1 Explanation for the MFP

"Section 1195(a)(2) of the Act requires CMS to publish an explanation for the MFP no later than March 1 of the year prior to the initial price applicability year, which will be March 1, 2025 for initial price applicability year 2026."

We would encourage CMS to publish the explanations for the published MFPs before the statutory deadline, ideally alongside the published MFPs, which must be published by September 1, 2024, for the first 10 negotiated drugs. Transparency around these explanations will provide essential information for a variety of

stakeholders, including state governments and private payers that may wish to use this information as part of their own drug price negotiation processes.

90.4 Monitoring for Bona Fide Marketing of Generic or Biosimilar Products

"CMS is seeking comment on the most effective ways to monitor whether robust and meaningful competition exists in the market after a selected drug ceases to be a selected drug."

The CMS guidance states that drugs will be excluded from negotiation once they have bona fide generic or biosimilar competition. CMS has identified several tools that it may use to monitor for bona fide competition, including assessing whether the generic drug or biosimilar is consistently available for purchase by wholesalers and whether patients can access generic and biosimilar versions in pharmacies and clinics. CMS also plans to analyze the share of generic or biosimilar uptake based on Medicare claims data. We think that each of these approaches is important, though determining the minimum thresholds required for bona fide generic competition will be challenging.

One type of generic or biosimilar competition that, in our opinion, should not count as bona fide competition, regardless of market share, is entry based on "limited-supply agreements." These agreements occur when a brand-name manufacturer agrees to allow for generic or biosimilar competition (usually in exchange for dropping litigation) and the generic or biosimilar firms agree to release their products in a limited fashion according to agreed-upon terms. Brand-name manufacturers may have a strong financial incentive to avoid Medicare negotiation, and a possible strategy to do so may be via limited-supply agreements with generic or biosimilar firms. For example, a brand-name company may allow a generic firm to obtain 20% market share in the US (leaving 80% for the brand-name firm) for a period so that its drug is excluded from Medicare negotiation during that time.

While the nature of legal settlements between brand-name and generic firms is often shrouded in secrecy, we know that limited-supply agreements already occur in the pharmaceutical industry. In our review of Hatch-Waxman patent challenges from 2003 to 2022 (also known as "paragraph IV certifications"), for example, we uncovered limited-supply agreements for at least 4 high-cost brand-name products: Lamictal[6] (lamotrigine), Solodyn[7] (minocycline), ProAir HFA[8,9] (albuterol), and Revlimid[10,11] (lenalidomide). In the case of ProAir HFA, the brand-name firm Teva agreed to settle litigation with Perrigo in June 2014 and allow the limited release of generic albuterol inhalers from December 2016 to June 2018, at which point limits would no longer apply. In this case, Perrigo's generic product did not end up receiving FDA approval until 2020. Bristol Myers Squibb entered into agreements with at least two generic firms (Dr. Reddy and Sun Pharma) to allow limited-

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[6] Fields K. Direct Purchasers of Lamictal Certified as a Class in Pay-for-Delay Case. Faruqi & Faruqi, LLP. Published December 17, 2018. https://www.faruqilaw.com/blog/292/direct-purchasers-of-lamictal-certified-as-a-class-in-pay-for-delay-case

[7] Complaint filed by Rite Aid Corporation and Rite Aid Hdqtrs. Corp. against Medicis Pharmaceutical Corp., in Case 1:15-cv-00673-YK, filed on April 6, 2015, available at http://business.cch.com/ald/RiteAidMedicisComplaint.pdf

[8] Palmer E. Teva Reaches Settlement in ProAir® HFA Patent Case. *Fierce Pharma*. https://www.fiercepharma.com/pharma/teva-reaches-settlement-proair%C2%AE-hfa-patent-case. Published June 20, 2014.

[9] Teva Reaches Settlement in ProAir® HFA Patent Case. Teva Pharmaceutical Industries Ltd. Published June 20, 2014. https://www.tevapharm.com/news-and-media/latest-news/teva-reaches-settlement-in-proair-hfa-patent-case/

[10] Sagonowsky E. After win at patent office, Bristol Myers inks Revlimid deal with Dr. Reddy's. *Fierce Pharma*. https://www.fiercepharma.com/pharma/after-patent-win-at-pto-bms-inks-revlimid-settlement-dr-reddy-s. Published September 17, 2020.

[11] Kansteiner F. Bristol Myers inks another Revlimid patent settlement—this time with Sun Pharma—as copycats near. *Fierce Pharma*. https://www.fiercepharma.com/manufacturing/bristol-myers-settles-sun-pharma-for-limited-revlimid-generic-launch-2022. Published June 22, 2021.

supply sales for generic lenalidomide beginning in 2026. Such agreements may be more pervasive than is publicly known. Generic entry according to limited-supply agreements should not, in our view, count as bona fide generic competition. Rather, IRA negotiation should include brand-name drugs and biologics with limited-supply agreements so long as these drugs and biologics would otherwise qualify.