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Submitted via email to: IRAREbateandNegotiation@cms.hhs.gov

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RE: Medicare Drug Price Negotiation Program: Initial Memorandum, Implementation of Sections 1191 – 1198 of the Social Security Act for Initial Price Applicability Year 2026, and Solicitation of Comments

Dear. Dr. Seshamani:

The Massachusetts Biotechnology Council (MassBio) appreciates this opportunity to submit comments on the initial guidance regarding implementation of the Medicare Drug Price Negotiation Program (the “Negotiation Program”) established by section 11001 and 11002 of the Inflation Reduction Act (IRA) (the “Guidance”).

MassBio represents the premier global life sciences and healthcare hub of Massachusetts, which has a vibrant biomedical research and development community that is a global leader for medical discovery and innovation. MassBio’s 1,600+ member organizations are dedicated to preventing, treating, and curing diseases through transformative science and technology that brings value and hope to patients. MassBio’s mission is to advance Massachusetts’ leadership in the life sciences to grow the industry, add value to the healthcare system, and improve patient lives.

MassBio is deeply concerned about the impact the Negotiation Program will have on the future development of innovative and life-saving therapies, as well as on the world-leading small and emerging biotech companies based in Massachusetts. Through both a member survey and the collection of anecdotal evidence, MassBio has already identified concerning signals with respect to the IRA’s impact on innovation in Massachusetts. Based on these early signals, we believe the program’s framework will likely lead to less investment in biotech companies that work on the most difficult and risky science, and thus ensure significantly fewer resources are dedicated to the development of rare disease drugs and the hardest to treat diseases such as Alzheimer’s disease, cancer, and diabetes.

Given the potential impact on innovation and thus on vulnerable patient access to life-saving therapies, we urge CMS to adopt a “do no harm” approach in implementing this program that errs on the side of mitigating against the potential disincentives created by the program’s framework, and that allows the agency to make corrections as needed to preserve innovation.

We also urge CMS to carefully examine the impact of the law in Massachusetts. In light of Massachusetts’ unique role as the hub of companies directly engaged in research, development, and manufacturing of innovative products that improve the lives of people in the United States, Massachusetts

will be a “canary in the coal mine” in terms of changes to the system, and will thus be a good test case to see how IRA implementation affects the biotech industry. MassBio also plans to continue to survey our membership and perform other data-driven approaches to monitor the impact of the law, and we look forward to serving as a resource for CMS as the agency begins to track the impact of the IRA, particularly in Massachusetts.

Below we provide an overview of the innovation ecosystem in Massachusetts, as well as our comments on specific aspects of the Guidance, which are informed by the initial survey of our diverse and extensive membership. We would also appreciate the opportunity to meet with CMS to further develop and explain these ideas.

I. Background: The Innovation Ecosystem in Massachusetts

The innovation ecosystem is crucial to bringing a biopharmaceutical product to market and is composed of three, interrelated parties that interact in collaborative processes to move products from bench to bedside. These parties include: (1) small biotech companies and academia; (2) venture capital firms; and (3) larger pharmaceutical companies. Each of these parties serves a unique and vital role:

- Small biotech companies and the academic research community often partner to gather the necessary talent, engage in research, and pursue the latest scientific discoveries with the potential to develop viable treatments for a wide range of diseases and medical conditions.
- Venture capital firms provide equity investments in new and emerging biotech companies, to allow these companies to have the necessary capital and resources to advance through the different stages of the drug research and development process, particularly from proof of concept to actual clinical development.
- Large pharmaceutical companies help with the costly and burdensome process of bringing a new drug to market by contributing expertise and additional resources to the drug development pipeline, particularly through the use of diverse arrangements with emerging biotech companies, including acquisitions, licensing, and co-promotion.

All of these parties are essential components of the drug development and commercialization process. However, as the recent collapse of the Silicon Valley Bank has shown, this ecosystem is fragile and can be significantly disrupted if just one of the parties suffers a setback. For instance, while not a direct target of the law, venture capital investment choices do not operate in a vacuum, and are significantly impacted by long-term market dynamics, the ability to obtain a return on investment, and the inherent opportunity cost of specific investment decisions.

As noted above, in early 2023, MassBio surveyed its membership regarding the IRA’s immediate impacts, as well as member perspectives regarding certain regulatory and legislative policies that could mitigate those impacts.¹ A diverse cross-section of members responded to this survey, with a third of respondents having 10 employees or less. The majority of respondents indicated that they have already reconsidered their business strategy as a result of the IRA, and the vast majority also indicated that they have seen a shift in how investors are generally approaching biotech investments. This is consistent with other reports showing evidence that the IRA may be causing companies to reconsider their current approach to the drug development process, such as by cancelling early-stage pipeline projects, focusing

¹ Survey results on file at MassBio. We would be happy to provide the survey results to CMS, upon request.

on larger indications, developing fewer uses for existing medicines, and shifting away from small-molecule products.²

The MassBio member survey also asked about policy priorities to help maintain the biotech ecosystem as CMS implements the IRA, supplemented by qualitative input by a diverse group of executives from members. We describe these policy priorities in greater detail as part of our comments, below.

II. Section 30: Identification of Selected Drugs for Initial Price Applicability Year 2026

While MassBio understands that CMS has limited time to implement the Negotiation Program for initial price applicability year 2026, we are deeply concerned that CMS is issuing section 30 of the Guidance as “final.” The identification of selected drugs is among the most significant policies for the Negotiation Program, and many of the policies CMS outlines in the Guidance are inconsistent with the statute and likely to result in operational issues. By issuing these policies as final, CMS has denied interested stakeholders the opportunity to provide input, and further denied itself the opportunity to learn from those comments. MassBio is submitting comments in the hopes that CMS will reconsider elements of its approach going forward.

A. Section 30.1: CMS’s Qualifying Single Source Drug Definition is Overbroad and Not Supported by the Statute.

CMS is defining the term “qualifying single source drug” (QSSD) to include all dosage forms and strengths of the drug with the same active moiety (or, for biologics, active ingredient) and the same holder of a New Drug Application (NDA) (or, for biologics, a Biologics License Application (BLA))—inclusive of products that are marketed pursuant to different NDAs/BLAs. In addition, for purposes of counting the 7(drugs)/11(biologics) years that must elapse, CMS will use the earliest date of approval of the initial FDA application number assigned to the NDA/BLA holder for the active moiety/active ingredient.

CMS’s interpretation of the term QSSD is overly broad and is not supported by the statute. For both small-molecule drugs and large-molecule biological products, the underlying statute clearly sets the QSSD definition to the *singular* approval by the Food and Drug Administration (FDA) under which the product is marketed.³ The statute does not give CMS the authority to expand the statute’s focus on a singular FDA approval to a definition that encompasses multiple different FDA approvals through the addition and utilization of an “active moiety/ingredient” test.

Furthermore, this overly broad interpretation is at odds with the practical reality of the drug development process. Given the high cost to run clinical trial for a new product and the limited success rate for wholly new therapies, drugs are generally developed by initially seeking approval for and launching smaller or more limited indications—such as orphan diseases—to show proof-of-concept. Then, as the data and science advance, developers seek additional approvals for larger indications, as well as new dosage forms, strengths and formulations. This approach is consistent with the iterative approach to clinical advancement generally applied in medicine, and also mitigates some of the risk of clinical development.

² See R. Wolrath, *How the Inflation Reduction Act is already changing how biotechs do business*. Boston Business Journal (March 13, 2023); see also J. Waldrop, *Inflation Reduction Act undermines rare disease research*. Boston Herald (Feb. 28, 2023); see also D. Beasley, *Drug companies favor biotech meds over pills, citing new U.S. Law*, Reuters (Jan. 13, 2023).

³ See section 1192(e)(1) of the Social Security Act.

Because drugs are developed in this stepwise fashion, some of the most critical drugs have—over time—received FDA approval for multiple indications that continue to treat patients across multiple disease states. However, CMS’s interpretation significantly interferes with this approach by defining QSSD overly broadly, such that CMS will use the earliest approval date across an array of products grouped together by active moiety/active ingredient, in some cases grouping products approved under separate NDAs/BLAs. This will lead to a pre-negotiation period for a given product that starts *before that product was even approved*, creating a significant disincentive to pursue additional approvals, to the detriment of certain patient populations. In addition, going forward, drug developers may seek ways to obtain approval for larger indications from the outset, dampening the rate of therapeutic innovation for smaller patient populations with unmet need. This is not ideal for patients.

For these reasons, MassBio strongly urges CMS to revise the agency’s QSSD definition to instead focus on the approval standard required by statute.

B. Section 30.1.1: CMS Should Implement the Orphan Drug Exclusion in a Manner that Continues to Incentivize the Development of Rare Disease Therapies.

In the Guidance, CMS states that to be considered for the IRA’s orphan drug exclusion, a drug or biological product must (1) be designated as a drug for only one rare disease or condition under section 526 of the FD&C Act; and (2) be approved by the FDA only for one or more indications within such designated rare disease or condition. Notably, to qualify for the orphan drug exclusion, *all dosage forms and strengths and different formulations of the QSSD must meet the criteria for exclusion.*

MassBio is concerned that the narrow scope of the orphan drug exclusion, combined with CMS’s overly broad QSSD definition, creates a strong disincentive for developers to continue to develop new indications and formulations for existing orphan therapies. However, we support CMS’s commitment to “consider[] whether there are additional actions the agency can take in its implementation of the Negotiation Program to best support orphan drug development,” and urge the agency to adopt policies along these lines.

Rare diseases, as defined by the FDA are conditions that impact fewer than 200,000 patients nationwide, and are inherently under-researched, under-diagnosed, and under-treated. Although much progress has been made since the enactment of the Orphan Drug Act (ODA) 40 years ago, over 90 percent of known rare diseases do not have therapies or treatments. This scarcity in therapies is due to a variety of reasons, including the resource and time investment needed to generally design, develop and bring a drug to market,⁴ as well as the low success rate of this process.⁵ There are also plethora of challenges specific to developing drugs for rare diseases, as the low number of actual patient numbers for certain diseases makes it difficult to establish an adequately sized and diverse patient population for a clinical trial, as well as obtain the high-quality patient data necessary to evaluate clinical trial outcomes.

That said, there has fortunately been a recent surge in the development of drugs for rare disease populations,⁶ with much of this development occurring in Massachusetts.⁷ Today, 40 percent of therapies

⁴ It can take 10 to 15 years and \$1-2B for a drug to be designed, developed and approved for use in patients. I.V. Hinkson, B. Madej, E.A. Stahlberg. *Accelerating therapeutics for opportunities in medicine: a paradigm shift in drug discovery Front Pharmacol*, 11 (2020), p. 770

⁵ 90 percent of developed drugs are unsuccessful. H. Dowden, J. Munro. *Trends in clinical success rates and therapeutic focus Nat Rev Drug Discov*, 18 (2019), pp. 495-496.

⁶ The annual number of orphan drug designation requests has steadily increased from 2012 through 2016 and has remained greater than 500 annually since 2016. In 2020, the Office of Orphan Products Development received 753 new requests for designation, a 41% increase from 2019. See <https://www.fda.gov/news-events/fda-voices/rare-disease-day-2021-fda-shows->

in the pipeline are in rare disease. Furthermore, given the nature of rare diseases, therapies developed for a particular rare disease can often be the starting point in the translation of new scientific discoveries to clinical medicine. Thus, as new data emerge, developers are able to identify promising new uses, including additional orphan indications, for existing therapies. For example, many new therapies are gene-based, and each genetically defined disease is a new indication for a particular therapy.

However, these new indications still require costly clinical trials, regulatory approvals and adherence to regulatory requirements and the narrow scope of the orphan drug exclusion creates a strong disincentive to undertake these investments, even though the science is there and could benefit vulnerable populations. Furthermore, because of the limited scope of the exclusion, companies may be disincentivized from developing therapies for rare diseases to begin with, and to instead prioritize indications with larger patient populations from the outset.

MassBio urges CMS to implement the orphan drug exclusion in a way that promotes and is consistent with the underlying purposes and goals of the ODA: to create the necessary financial incentives to accelerate the development of rare disease drug development. Specifically, in addition to narrowing the agency's QSSD definition, as described above, CMS should exercise its regulatory discretion to start the pre-negotiation period for orphan drugs upon loss of the orphan drug exclusion (i.e., when the product obtains approval for a new indication for a different disease or condition), rather than when the QSSD was initially approved. This approach is within CMS's discretion to implement the statute and would shield the product from the IRA's negotiation provisions for the entire time the orphan drug exclusion applies.

III. Section 50: Negotiation Factors.

A. Section 50.1: CMS Define R&D Costs More Broadly.

The IRA directs CMS, for purposes of negotiating the MFP of a selected drug, to consider certain "manufacturer-specific data," which includes: research and development (R&D) costs; current unit costs of production and distribution; prior Federal financial support for novel therapeutic discovery and development; data on pending and approved patent applications; exclusivities recognized by the FDA and FDA applications and approvals; and market data and revenue and sales volume data in the United States. In implementing this requirement, we urge CMS to define R&D costs more broadly. In the Guidance, CMS states that it "is considering R&D costs to mean a combination of costs incurred by the Primary Manufacturer for all FDA-approved indications of a drug falling into" certain categories, which include basic pre-clinical research costs, post-investigational New Drug (IND) application costs, completed FDA-required phase IV trials, post-marketing trials, abandoned and failed drug costs, and all other R&D costs. However, CMS's proposed approach overlooks certain investments critical to drug development.

First, by focusing solely on R&D expenditures made by the Primary Manufacturer, CMS's proposed definition overlooks contributions made by the Secondary Manufacturer and others. As noted above, drug development is often a collaborative process, involving investments by both small biotech companies and larger pharmaceutical companies. This can take the form of licensing arrangements, co-promotion agreements, and other arrangements. By looking only at the expenditures made by the manufacturer that holds the NDA/BLA, CMS is ignoring a large portion of R&D costs. We also note that

[sustained-support-rare-disease-product-development-during-public#:~:text=The%20annual%20number%20of%20orphan,a%2041%25%20increase%20from%202019.](#)

⁷ D, Seiffert, *Massachusetts owns the orphan drug market. Here's the proof*, Boston Business Journal (Nov. 9, 2015), <https://www.bizjournals.com/boston/blog/bioflash/2015/11/massachusetts-owns-the-orphan-drug-market-here-s.html>.

this approach is not supported by the statute, which looks at research costs of the “manufacturer,” a term that’s defined quite broadly to refer to:

any entity which is engaged in—

(A) the production, preparation, propagation, compounding, conversion, or processing of prescription drug products, either directly or indirectly by extraction from substances of natural origin, or independently by means of chemical synthesis, or by a combination of extraction and chemical synthesis, or

(B) in the packaging, repackaging, labeling, relabeling, or distribution of prescription drug products.⁸

CMS should therefore consider R&D spend from across the innovation ecosystem. However—contrary to CMS’s proposals in the Guidance—it should not be the responsibility of the Primary Manufacturer to collect this information from Secondary Manufacturers or others. Not only is there no statutory basis for this approach, Primary Manufacturers generally lack access to information regarding the business operations of other manufacturers, and requiring companies to share this sensitive information amongst themselves would add burden and create legal risk. Therefore, CMS should instead enter into a Negotiation Agreement with each manufacturer—including Secondary Manufacturers—to govern the submission, use, and disclosure of the data CMS needs for the Negotiation Program.

In addition, CMS’s proposed definition for abandoned or failed drug costs suggests the agency will only consider failed or abandoned product costs for products with some relation to the selected drug at issue (i.e., same active moiety, active ingredient, mechanism of action and therapeutic class). Although these categories capture many of the costs incurred in the development of a given drug, MassBio urges CMS to clarify that it will also allow manufacturers to allocate R&D costs for abandoned and/or failed research *that is not attributable to any particular product* across a manufacturer’s selected drugs. Developers often incur significant costs in the early stages of the pre-clinical discovery and development process that may not be tied to any particular product, but that were instrumental in moving the needle of scientific discovery forward and laying the groundwork for subsequent innovations that do lead to life-saving therapies. This aspect of R&D is a vital component to the larger process, and should be a material factor considered by the agency.

B. Section 50.2: CMS Should Consider Robust Data on Therapeutic.

The IRA further directs CMS to consider “evidence about therapeutic alternatives.” This includes the extent to which the selected drug represents a therapeutic advance and the extent to which the selected drug and the therapeutic alternatives address unmet medical needs for a condition for which treatment or diagnosis is not addressed adequately by available therapy. CMS must also consider the FDA-approved prescribing information for the selected drug and therapeutic alternatives, and evidence on the comparative effectiveness of the selected drug and its therapeutic alternatives.

There are several factors and sources that CMS should consider in assessing a drug’s comparative effectiveness, whether it represents a therapeutic advance, or addresses an unmet need. We provide the following recommendations, and would welcome the opportunity to meet with the agency to further discuss these and other factors and sources the agency should consider as part of this assessment:

- Patient-centered definitions of value;

⁸ Social Security Act (SSA) § 1191(c)(1) (referencing SSA § 1847A(c)(6)(A), which in turn references SSA § 1927(k)(5)).

- Real-world evidence;
- Multiple-criteria decision analysis that considers multiple conflicting criteria in decision-making;
- Clinical effectiveness ratings, such as those issued by the United States Preventive Services Task Force (USPSTF); and
- Clinical compendia

We also recommend—consistent with the statutory requirement to consider FDA-approved prescribing information—that CMS focus solely on the approved indications for a given therapy.

C. Section 50.2: CMS Should Consider Data on Therapeutic Alternatives in a Non-Discriminatory Manner.

MassBio strongly supports CMS’s proposal not to use information found by CMS that treats extending the life of individuals in these populations as of lower value, for example certain uses of quality-adjusted life-years (QALYs), in the negotiation process. This policy aligns with prohibitions set forth in statute, and will help ensure that CMS is not evaluating the value of a given therapy in a manner that discredits its benefit to the neediest and most vulnerable populations. However, we are concerned that certain data sources may violate this prohibition in a discrete way, for example, by describing the research methodology without use of the term “QALY,” or by including a QALY analysis as a component of the research methodology without disclosing as much. MassBio therefore recommends that CMS disclose to manufacturers, as part of the negotiation process, all evidence that was considered by CMS in developing the initial MFP offer. A manufacturer can then use that information to ensure that any such data that involves QALYs and other similarly problematic metrics—either directly or indirectly—are not included in the manufacturer’s counteroffer.

IV. Section 60: Negotiation Process

A. CMS Should Adopt Certain Guiding Principles for Implementation of Negotiation Provisions to Promote Innovation.

As CMS proceeds with implementation of the Negotiation Program, MassBio urges the agency to pursue an approach that creates the greatest degree of certainty for developers by adopting a predictable, transparent methodology for applying the relevant negotiation factors, which should then be updated over time to recognize the value of continued innovation. As explained above, investment in the drug development process and the innovation ecosystem is significantly impacted by the long-term market dynamics at play. Thus, to enable developers and their investors to make informed investments today, CMS’s methodology should reflect the value that a product provides over its lifecycle and create incentives to invest in new therapeutic areas with unmet need.

For example, in the context of determining whether a selected drug represents a therapeutic advance as part of the negotiation process, MassBio urges the agency to consider the recent renaissance in the development of small-molecule drugs, which are increasingly complex, and to reject the common misconception that small-molecule drugs are not inherently innovative, or as innovative as biologics.⁹ CMS should similarly reject the notion that small-molecule drugs are less innovative or represent less of a therapeutic advance in the treatment of disease. Furthermore, it should be noted that small molecule

⁹ H. Boehm, *The Renaissance of Small Molecule Drug Discovery*, Pharmacy Times (Aug. 9, 2022), <https://www.pharmacytimes.com/view/the-renaissance-of-small-molecule-drug-discovery>.

drugs are often reproduced as generics, once the original drug patent expires, which can in turn further increase the availability of treatment options for vulnerable patient populations. However, as mentioned above, recent reports suggest that the IRA may be causing developers to shift away from small-molecule products to begin with. If this disincentive leads to less development of small-molecule drugs, it follows that it will also negatively impact the availability of generics, to the detriment of patients.

Thus, to in order to preserve access to small-molecule products and biologics alike, CMS should adopt an approach that ensures that maximum fair price (“MFP”) is set at or near the ceiling price for products that represent a therapeutic advance or address an unmet need. This approach would both create predictability and enable long-term investment in innovative small-molecule products as well as biologics. This will be especially important during the early years of the Negotiation Program, while there is significant uncertainty and a very short window for implementation. During this time, CMS can and should err on the side of mitigating against the potential harm resulting from the disincentives created by the program’s framework.

In that vein, CMS should also ensure that application of the negotiation factors is designed to promote health equity and reduce health disparities. Indeed, under the IRA, CMS must consider “the extent to which the selected drug and the therapeutic alternatives to the drug address unmet medical needs for a condition for which treatment or diagnosis is not addressed adequately by available therapy.” CMS can do this by placing greater weight on the promotion of health equity and reduction of health disparities, which are accomplished in part by creating and maintaining incentives for investment in therapies that address unmet need for underserved patient populations, including patients suffering from rare disease.

B. CMS Should Continually Monitor the IRA’s Impact on the Innovation Ecosystem.

As mentioned above, in early 2023, MassBio surveyed its membership regarding the IRA’s immediate impacts, and member perspectives regarding certain regulatory and legislative policies that could mitigate those impacts. MassBio plans to continue to survey our membership and perform other data-driven approaches to monitor the impact of the law, and we hope to have the opportunity be a resource for CMS as it begins to track the impact of the IRA.

Likewise, as CMS proceeds with implementation of the law, MassBio urges the agency to similarly prioritize building the necessary infrastructure to track the impact of the IRA on the innovation ecosystem. This will be vital given the long-standing relationship between innovation and increased access to life-saving therapies, and the need for the agency to “do no harm” in the implementation of this new program. For instance, CMS could track the following metrics, using CMS’s own data and certain data available from the FDA, to assess the IRA’s impact over time.

- Number of new technology add-on payment (NTAP) applications for drugs and biologics;
- Requests for pass-through status under the Hospital Outpatient Prospective Payment System (OPPS);
- Number of new NDCs in average sales price (ASP) reporting data;
- Number of NDA/BLA submissions (tracking proportion of small-molecule vs. large-molecule over time);
- Number of supplemental BLA/NDA submissions;
- Number of applications for orphan drug designation (ODD);
- Percent of products with an ODD that are approved by FDA;
- Number of applications for breakthrough therapy designation;

- Number of applications for fast-track designation; and
- Number of applications for regenerative medicine advanced therapy designation.

We further urge CMS to publicly report these data to inform both the public and policymakers in Congress, and to establish a dynamic framework pursuant to which significant decreases in the metrics captured above trigger reconsideration of the negotiation process implemented by the agency.

V. Conclusion

MassBio thanks CMS for your consideration of our comments. As the IRA will have a significant impact across our diverse membership, we would appreciate the opportunity to meet with CMS to discuss these comments and other IRA-related issues of interest to our members.

Best regards,

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