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Department of Health and Human Services
Centers for Medicare & Medicaid Services
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Re: Medicare Program; Inflation Reduction Act (IRA) Medicare Drug Price Negotiation Program Draft Guidance; Comment Request (IPAY 2028)

Halozyme, Inc. (Halozyme) appreciates the opportunity to submit comments on the Draft Guidance for Implementation of Sections 1191 – 1198 of the Social Security Act (SSA) for Initial Price Applicability Year (IPAY) 2028 and Manufacturer Effectuation of the Maximum Fair Price in 2026, 2027, and 2028 (IPAY 2028 Draft Guidance). At Halozyme, we are focused on innovative and disruptive solutions that provide new therapeutic options that could significantly improve the patient treatment experience. We have two subcutaneous (under the skin) drug delivery technologies that significantly streamline treatment and can offer patients potential benefits including reduced side-effects, improved effectiveness, a more comfortable experience, improved convenience, and reduced treatment time.

In finalizing the Draft Guidance, we urge CMS to adhere to the definition of qualifying single source drug (QSSD) adopted in the IPAY 2026 and 2027 guidance documents for fixed combination products for clinical, scientific, legal, and policy reasons. This approach would align with the important clinical benefits that fixed combinations offer for patients and healthcare providers (HCPs) alike.

I. Executive Summary

CMS should maintain the definition of QSSD adopted in the IPAY 2026 and 2027 guidance documents for fixed combination products. The addition of Part B drugs to the Inflation Reduction Act (IRA) Medicare Drug Price Negotiation Program (the Program) does not justify the creation of a new QSSD policy for a subset of fixed combination products. Specifically, CMS should not adopt its proposal to disregard active ingredients that it views as "not therapeutically active against the disease state," or alternatively, not "biologically active" or causing "clinically meaningful differences," in identifying QSSDs (the Proposal). This Proposal lacks an adequate basis, because the statute has not changed, and the QSSD definition applies equally to Part B and D drugs. The Proposal also raises legal and policy issues, as noted below.

If CMS decides to deviate from its IPAY 2026 and 2027 approach to identifying QSSDs, CMS should find that Halozyme's human hyaluronidase is an active ingredient with biological and therapeutic activity that provides clinically meaningful effects in fixed combination products, and therefore that fixed combinations of human hyaluronidase and antibodies should be considered distinct QSSDs from the individual active ingredients.

In particular, subcutaneous fixed combination products containing Halozyme's human hyaluronidase and specific antibodies provide meaningful

therapeutic advantages for patients and the public health. For example, these products can reduce side effects, improve efficacy, reduce patient burden associated with receiving treatment, and reduce HCP burden. These products also have been demonstrated to reduce overall cost to the healthcare system and patients. When compared to an antibody given intravenously as a single component product, subcutaneous delivery of a fixed combination containing Halozyme's human hyaluronidase and the specific antibody can enable, for example:

- Meaningfully lower incidence of infusion-related reactions, a potentially life-threatening side effect;
- Meaningfully lower incidence of serious adverse events (SAEs) that result in hospitalization and death;
- Meaningfully improved overall survival;
- Improved patient comfort and decreased emotional distress associated with treatment;
- A reduction in patient treatment time and patient costs related to the site of treatment care;
- A reduction in infection risk by eliminating the need for an intravenous access device (e.g. a port) in some patients;
- A reduction in cancer patients' exposure to infections by reducing the length of time spent in hospital infusion centers;
- A reduction in HCP resources and time required for treatment preparation and administration; and
- A reduction in the chance of a dosing error by the use of a fixed dose combination that does not require the pharmacist to calculate the dose based on individual patient weight.

This evidence demonstrates that subcutaneous delivery of a fixed combination with Halozyme's human hyaluronidase results in clinically meaningful benefits. Accordingly, if CMS finalizes the Proposal despite the concerns explained in this comment, CMS should find that Halozyme's human hyaluronidase is biologically active and therapeutically active when combined with an antibody in a fixed combination product, given its clinically meaningful, beneficial effects on patient feeling, safety and/or effectiveness, and its pharmacological activity.

More fundamentally, the Proposal is flawed as a matter of law. The Proposal creates multiple definitions of "biological product," which conflicts with the statute, *Loper Bright Enterprises v. Raimondo*, and the President's memorandum issued on April 9, 2025, which directs the repeal of unlawful regulations that contravene *Loper Bright*. The Proposal also conflicts with FDA's approval of Halozyme's human hyaluronidase combinations as fixed combination products under 21 C.F.R. § 300.50 and the SSA's orphan-drug exclusion from QSSD status. Further, the Proposal diverges from precedent without reasoned explanation and is arbitrary and capricious for creating inconsistent definitions of biological product across agencies.

Finally, the Proposal is flawed as a matter of policy. The Proposal discourages the development of fixed combination products that benefit patients and can reduce the cost of care. It also undermines government efficiency by requiring CMS to conduct a fact-intensive assessment of fixed combination aggregation issues and disrupts research and development planning by creating uncertainty about which fixed combination products will be aggregated.

For the foregoing reasons, Halozyme urges CMS to retain its IPAY 2026 and 2027 approach to QSSD aggregation of fixed combination products.

II. Background

A. Statutory Definition of QSSD for Biological Products

Under the statute, a QSSD is eligible for selection into the Program.[1] For biological products, the IRA defines QSSD as follows:

> "(B) BIOLOGICAL PRODUCTS.—A ***biological product***—
>
> > "(i) that is licensed under section 351(a) of the Public Health Service Act and is marketed under section 351 of such Act;
> >
> > "(ii) for which, as of the selected drug publication date with respect to such initial price applicability year, at least 11 years will have elapsed since the date of such licensure; and
> >
> > "(iii) that is not the reference product for any biological product that is licensed and marketed under section 351(k) of such Act."[2]

Since issuing the draft version of the IPAY 2026 Guidance, CMS has interpreted "biological product" in this provision to mean "active ingredient" or combination of "active ingredients."

Specifically, to identify QSSDs, CMS aggregates all dosage forms and strengths of a biological product with the "same active ingredient" and the same BLA holder, inclusive of products that are marketed pursuant to different BLAs.[3] Then, to determine the date of licensure for a potential QSSD that is a biological product licensed under more than one application, CMS uses the earliest date of licensure of the application assigned to the BLA holder for the active ingredient.[4]

B. CMS's IPAY 2026 & 2027 Guidance: Recognition That Fixed Combinations Are Separate QSSDs

In the IPAY 2026 and 2027 Guidances, CMS indicated that, "[i]f a drug is a fixed combination drug with two or more active moieties / active ingredients, the distinct combination of active moieties / active ingredients will be considered as one active moiety / active ingredient for the purpose of identifying potential qualifying single source drugs."[5] There are several important aspects of this interpretation:

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[1] SSA § 1192(c)-(e).

[2] SSA § 1192(e)(1)(B) (emphasis added).

[3] *See* IPAY 2026 Final Guidance at 99; IPAY 2027 Final Guidance at 168; IPAY 2028 Draft Guidance at 11.

[4] *See* IPAY 2026 Final Guidance at 101. *See* IPAY 2027 Final Guidance at 170. *See* draft IPAY 2028 Guidance at 14.

[5] *See* IPAY 2026 Final Guidance at 100. *See* IPAY 2027 Final Guidance at 169.

- CMS included a footnote stating that "[f]or purposes of the Negotiation Program, the term 'fixed combination drug' has the meaning specified in 21 C.F.R. § 300.50,"[6] which is FDA's regulation governing fixed-combination drugs for humans.

- In IPAY 2026 and 2027, CMS rejected comments disagreeing with this approach to fixed combination products.[7] For example, some commenters had opposed this policy on the theory that "by allowing strategic development by manufacturers of combination products that would not differ significantly from the original single product, not contribute directly to the drug's therapeutic effect, and provide minimal additional patient benefit."[8] In other words, these comments suggested a conceptually similar approach to the Proposal.

- As recently as October 2024, CMS rejected this idea. In responding to these comments, CMS stated that it "believes that a fixed combination drug is distinct in its composition from the individual active moieties / active ingredients" and reaffirmed "its approach on fixed combination drugs, which treats the distinct combination of . . . active ingredients as one . . . active ingredient for the purpose of identifying qualifying single source drugs."[9]

- CMS also explained that it identifies "active ingredients" using the RxNorm database. This database does not distinguish between active ingredients based on their perceived biological or therapeutic activity or their specific pharmacological function in the product.[10]

C. CMS Seeks Comment on Proposed Reversal in the IPAY 2028 Draft Guidance

Despite its prior approach in the IPAY 2026 and 2027 final guidance documents, CMS included the following Proposal in the IPAY 2028 Draft Guidance:

> CMS believes that treating distinct combinations of active moieties / active ingredients as one active moiety / active ingredient for the purpose of identifying potential qualifying single source drugs is generally appropriate. However, CMS acknowledges that there may exist fixed combination drugs for which one of the active ingredients or active moieties contained is ***not biologically active against the disease state(s) the drug is indicated for and thus does not result in a clinically meaningful difference***. An example might include the addition of active moiety / active ingredient X to a different active moiety / active ingredient Y, where active moiety / active ingredient X ***affects the bioavailability*** of active moiety / active ingredient Y but is ***not therapeutically active against***

[6] *See* IPAY 2026 Final Guidance at 100, fn. 34. *See* IPAY 2027 Final Guidance at 169, fn. 63.

[7] *See* IPAY 2026 Final Guidance at 13; IPAY 2027 Final Guidance at 14.

[8] IPAY 2027 Final Guidance at 14.

[9] *See* IPAY 2026 Final Guidance at 13-14. *See* IPAY 2027 Final Guidance at 14-15.

[10] *See* CMS, *Frequently Asked Questions: Medicare Prescription Drug Price Negotiation Program for Initial Price Applicability Year 2026* (link). *See also* IPAY 2026 Final Guidance at 13-14; IPAY 2027 Final Guidance at 16.

> ***the disease state*** that active moiety / active ingredient Y is indicated for. In this example, the addition of active moiety / active ingredient X does not result in a clinically meaningful difference. CMS is soliciting comments on whether the addition of drugs payable under Part B may impact the fixed combination drug policy described in this draft guidance. In particular, CMS is soliciting comments on how CMS might consider grouping such fixed combination drug products with products containing at least one but not all of the active moiety(ies) / active ingredient(s) into the same potential qualifying single source drug for both drugs payable under Part B and/or covered under Part D, including input on terminology that could facilitate the effectuation of such a policy.[11]

The IPAY 2028 Draft Guidance provides no further details on this Proposal, nor does it explain how CMS intends to implement this Proposal, if adopted.

III. Halozyme's human hyaluronidase is biologically and therapeutically active and results in clinically meaningful differences.

If CMS adopts the Proposal, antibody-human hyaluronidase fixed combination products qualify for fixed combination treatment. The human hyaluronidase in these fixed combinations is biologically and therapeutically active and results in clinically meaningful differences compared to single-entity antibody products.

A. Human hyaluronidase is biologically and therapeutically active.

Halozyme's human hyaluronidase is biologically active because it increases permeability of tissues in the subcutaneous space through the degradation of hyaluronic acid, thus enabling a large volume of drug to be administered by subcutaneous drug delivery. Human hyaluronidase has a different molecular target than the antibody or antibodies with which it is sometimes co-formulated. Hyaluronidase targets and degrades hyaluronan, and a co-formulated antibody targets a specific antigen (e.g., expressed on the surface of certain cancer cells). The hyaluronidase increases the dispersion and absorption of the co-administered antibody when administered subcutaneously.

Human hyaluronidase's specific enzymatic activity is to split the glucosaminidic bond between C1 of an N-acetylglucosamine moiety and C4 of a glucuronic acid moiety and degrade hyaluronan.[12] When combined with an antibody, human hyaluronidase effectively "opens up" space in the subcutaneous region (usually in the abdomen) to allow the other drug to be injected under the skin rapidly and without tissue damage. Without human hyaluronidase, rapid subcutaneous delivery subcutaneous delivery of an antibody or antibodies is limited to just ~2 milliliters, significantly restricting the use of subcutaneous delivery as many drugs to be effective require higher doses. Subcutaneous delivery of multiple antibodies used to treat cancer, neurological disease, and immune disease today is only possible because of coformulation with human hyaluronidase. With Halozyme's human hyaluronidase, today's approved fixed combination products range in volume from 5 mL to 23 mL, delivered in as little as 20 seconds for 5 mL, 3 minutes for up to 15 mL, and 10 minutes for 23 mL. The combined

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[11] IPAY 2028 Draft Guidance at 13.

[12] *See, e.g.*, Hylenex, Prescribing Information, § 12.1 (link).

antibody is dispersed in the subcutaneous space and is then absorbed by the patient's body. The patient's hyaluronic acid levels then return to normal, typically within 24 hours.

FDA has recognized that human hyaluronidase is an active ingredient, which FDA defines as "any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals."[13] FDA has therefore determined that human hyaluronidase has pharmacological activity. There is no requirement in FDA's regulations that an active ingredient's pharmacological effect must be directly active against the disease state itself. If human hyaluronidase were not biologically and therapeutically active, FDA would characterize it as product component other than an active ingredient, such as an excipient or degradant,[14] which it has not.

Further bolstering this conclusion, FDA has approved Halozyme's Hylenex,[15] a human hyaluronidase, as a single-entity biological product with a standalone BLA for use:

- in subcutaneous fluid administration for achieving hydration;
- to increase the dispersion and absorption of other injected drugs; and
- in subcutaneous urography for improving resorption of radiopaque agents.[16]

FDA also has recognized that hyaluronidase is an active ingredient in fixed combinations. Ingredients to enhance the safety or effectiveness of the principal active component are active ingredients per 21 C.F.R. § 300.50—the regulation that CMS relies upon in the IPAY 2026 and 2027 guidance documents and the IPAY 2028 Draft Guidance.[17]

B. Human hyaluronidase results in clinically meaningful differences.

Human hyaluronidase provides clinically meaningful differences as part of a fixed combination. Patients receiving antibody treatment routinely fight to survive and to maintain basic functions and independence. Receiving treatment subcutaneously of a fixed combination of an antibody and human hyaluronidase, compared to intravenous administration of an antibody only, has been comprehensively demonstrated to have a clinically meaningful positive impact on how a patient feels, functions, and/or whether the patient survives.[18]

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[13] 21 C.F.R. § 210.3(b)(7).

[14] *See, e.g.*, FDA Final Guidance, Using the Inactive Ingredient Database at 1 n. 2 (July 2019) (link) (defining "excipients" to mean any *inactive ingredients* that are added intentionally to therapeutic and diagnostic products, *but that are not intended to exert therapeutic effects at the intended dosage*.").

[15] FDA originally approved Hylenex in 2005 in an application under section 505(b)(2) of the FDCA. On March 23, 2020, the former NDA was deemed a BLA under section 7002(e)(4) of the Biologics Price Competition and Innovation Act.

[16] *See* Hylenex Prescribing Information §§ 1.1-1.3 (link).

[17] *See infra* note 62 and accompanying text.

[18] These metrics of clinical benefit are consistent with FDA's articulation of clinical benefit in its patient reported outcomes guidance. *See, e.g.*, Final Guidance, Principles for Selecting, Developing, Modifying and Adapting Patient-Reported Outcome Instruments for Use in Medical Device Evaluation at 1 (Jan. 26,

- **Subcutaneous delivery of a fixed combination with human hyaluronidase has resulted in a meaningfully lower incidence of infusion-related reactions compared to the antibody given intravenously as a single component product.** Patients receiving antibodies intravenously can experience "infusion-related reactions," which are characterized by nausea, headache, tachycardia, low blood pressure, rash, and shortness of breath. Not only do these reactions have a profound impact on how the patient feels, but also they can have life-threatening consequences: an infusion reaction can be a true medical emergency, that can result in deployment of nursing and medical staff and a "crash-cart," containing cardiac and respiratory emergency medications and equipment in case the patient requires resuscitation.[19]

    - Subcutaneous delivery of a fixed combination of an antibody with human hyaluronidase has been demonstrated with two important cancer treatments to reduce the rate of infusion-related reactions by a factor of 3- fold and 5- fold respectively, compared to the antibody delivered intravenously.[20] Specifically, patients receiving one of these two antibodies were found to have an approximately 3.5-in-10 and 6.5-in-10 chance of experiencing an infusion reaction, respectively, but this risk decreases significantly with subcutaneous delivery of a fixed combination to an approximately 1-in-10 chance of a reaction. The reduced rate of infusion-related reactions provides a clinically important improvement in the benefit-to-risk profile for both the physician and patient.

- **Subcutaneous delivery of a fixed combination with Halozyme's human hyaluronidase has resulted in a meaningfully lower incidence of serious adverse events (SAEs) compared to the antibody given intravenously as a single component product.** FDA defines SAEs as those that result in a birth defect, congenital anomaly, disability or permanent damage, hospitalization, death, or are life-threatening.[21] Most SAEs are based on the need for hospitalization. SAEs affect how a patient functions, feels, and survives. For example, with an antibody used in the treatment of lung cancer, the rate was 30% lower with subcutaneous delivery of a fixed combination compared to intravenous antibody delivery (i.e., a rate of 19% versus 27%).[22] In addition, subcutaneous delivery of fixed combination of an antibody and human hyaluronidase used in the treatment of lung cancer resulted in a lower rate of a serious and potentially fatal adverse

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2022) (link) ("Patient-reported outcome (PRO) instruments facilitate the systematic collection of how patients feel, function, and survive as valid scientific evidence to support the regulatory and healthcare decision-making process.").

[19] *See* A. Barroso et al, Management of Infusion-Related Reactions in Cancer Therapy: Strategies and Challenges, ESMO (2024) (link).

[20] *See* Mateos M-V et al, Subcutaneous versus Intravenous Daratumumab in Patients with Relapsed or Refractory Multiple Myeloma (COLUMBA): A Multicentre, Open-Label, Non-Inferiority, Randomised, Phase 3 Trial, Lancet Haematology, 7(5):e370-e380 (May 2020) (link); *see also* Leighl N et al, Subcutaneous Versus Intravenous Amivantamab, Both in Combination With Lazertinib, in Refractory Epidermal Growth Factor Receptor–Mutated Non–Small Cell Lung Cancer: Primary Results From the Phase III PALOMA-3 Study, J of Clin Oncol, 42(30):3593-3605 (June 10, 2024) (link) (NSCLC Study).

[21] *See* FDA, What is a Serious Adverse Event? (May 18, 2023) (link). *See also* FDCA § 505-1(b)(4).

[22] Burotto M, et al, Brief Report: Updated data from IMscin001 Part 2: A Randomised Phase III, Open-Label, Multicentre Study Examining the Pharmacokinetics, Efficacy, Immunogenicity, and Safety of Atezolizumab Subcutaneous versus Intravenous Administration in Previously Treated Locally Advanced or Metastatic Non-Small-Cell Lung Cancer , J Thor Onc,19: 1460-1466 (2024) (link).

event of thromboembolism (9% versus 14%) compared to the treatment with the same antibody delivered intravenously.[23]

- **Subcutaneous delivery of a fixed combination with Halozyme's human hyaluronidase results in meaningfully improved overall survival compared to the antibody given intravenously as a single component product**. Patients with a specific type of lung cancer—EGFR mutated non-small cell lung cancer—had a dismal chance of survival until the advent of new targeted therapeutic agents given intravenously. One new treatment, an antibody, was approved for intravenous administration in 2021; it was later approved for administration with a second drug in 2024.[24] A large study evaluated, as an exploratory endpoint, the impact on patient survival of subcutaneous delivery of a fixed combination of human hyaluronidase at a dose of the antibody designed to match the intravenously delivered drug exposure. This study was completed and the results published in 2024.[25] The risk of death for patients receiving the subcutaneously delivered drug was 38% lower compared with intravenous administration. At 12 months, 65% of the patients receiving the subcutaneous product were alive compared with 51% who received treatment intravenously.

- **Subcutaneous delivery of a fixed combination with Halozyme's human hyaluronidase results in improved patient comfort and decreased emotional distress compared to the antibody given intravenously as a single component product**. Multiple studies have assessed patient-reported outcomes that evaluate patient preferences for receiving an antibody treatment subcutaneously with human hyaluronidase compared to intravenous delivery of the antibody alone.[26] Patients overwhelmingly reported a strong preference for subcutaneous delivery of a fixed combination. The most commonly cited reasons for this preference included: less time spend at a clinic, more comfort during administration, feeling the treatment was less emotionally distressing, and lower levels of injection site pain.[27] Further, as compared with the intravenous delivery of an antibody, a higher proportion of patients with multiple myeloma that were treated with subcutaneous delivery of the same antibody with human hyaluronidase reported at *every* timepoint in which they were asked that:

    - They "*never*" thought about discontinuing treatment;
    - Treatment was "*much easier*" than they expected; and

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[23] *See* NSCLC Study (link).

[24] *See* Approval Letter, BLA 761210 (May 21, 2021) (link); Approval Letter, BLA 761210/S-003 (Mar. 1, 2024) (link).

[25] *See* NSCLC Study (link).

[26] *See* Aguiar-Ibáñez r, et al, Differences Between Intravenous and Subcutaneous Modes of Administration in Oncology from the Patient, Healthcare Provider, and Healthcare System Perspectives: A Systematic Review, Adv Ther, 41:4396–4417 (2024) (link) (Perspectives Study); *see also* Usmani SZ, et al, Greater Treatment Satisfaction in Patients Receiving Daratumumab Subcutaneous vs. Intravenous for Relapsed or Refractory Multiple Myeloma: COLUMBA Clinical Trial Results, J Canc Res Clin Onc, 147:619-631 (2021) (link) (Treatment Satisfaction Study).

[27] *See* Treatment Satisfaction Study (link).

- Side-effects were *much better* than they expected.[28]

- As an additional example, patients treated with subcutaneous delivery of an antibody in fixed combination with human hyaluronidase for the treatment of multiple cancers, including lung cancer, reported preferring the fixed dose combination (71% vs. 21%) compared to intravenous delivery of the antibody, with the reason cited being "requires less time in the clinic," "feels more comfortable during administration," "feels less emotionally distressing," and "lower level of injection-site pain."[29]

A=Patient Preference
B=for those preferring SC, reasons for preference, with patients selecting up to 2 reasons

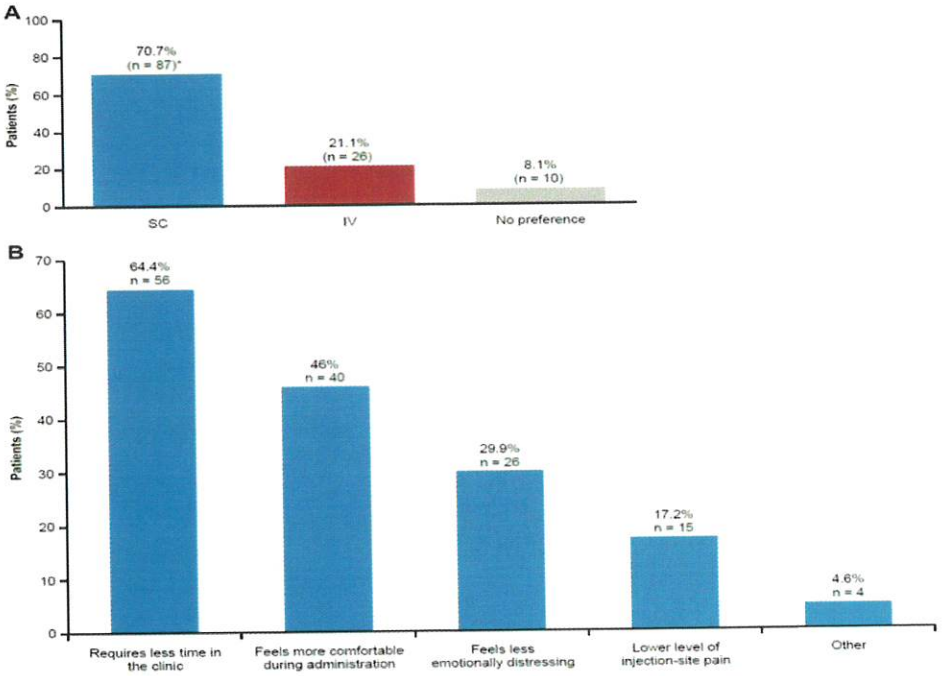

Figure 2. Patients' *(A)* preferred administration method and *(B)* reasons for preferring atezolizumab SC over IV. *95% confidence interval: 61.8 to 78.6. The patient preference questionnaire completion rate was 98% (n = 123 of 126); 126 patients completed cycle 5 of treatment and were alive on cycle 6 on day 1. *(A)* Question 1 of the patient preference questionnaire: "All things considered, which route of administration did you prefer?" *(B)* Question 2 of the patient preference questionnaire had responses from 87 patients: "If you have a preference for one of the administration routes, what are the two main reasons for your preference?" IV, intravenous; SC, subcutaneous.

See footnote for image source.[30]

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[28] *See* Treatment Satisfaction Study (link).

[29] Capuzzo F, et al, Primary Results from IMscin002: A study to Evaluate Patient Preferences and Perceptions of Health Care Professionals for Atezolizumab Subcutaneous versus Intravenous for the Treatment of NSCLC, JTO Clin Res Rep 6:1-11 (2025) (link) (Patient Preferences Study).

[30] *See* Patient Preferences Study (link).

- These findings indicate that patients receiving subcutaneous delivery of cancer treatment with human hyaluronidase are less likely to discontinue or interrupt treatment, potentially increasing the likelihood of survival.

- **Subcutaneous delivery of a fixed combination with Halozyme's human hyaluronidase reduces patient treatment time and can reduce patient costs related to site of care.** When combined with an antibody, Halozyme's human hyaluronidase allows the other active ingredient to be injected subcutaneously in just minutes. Without this option, many treatments for serious illnesses (such as cancer, neurological diseases, and autoimmune diseases) can only be administered by lengthy intravenous infusions due to their large volume. Very frequently, the patient will need to receive this intravenous treatment in an infusion suite at a hospital or infusion center in a process that can take half a day or more: a pharmacist must prepare the drug for administration; the patient must wait for it to be prepared by the pharmacist in addition to the actual treatment administration time, which can be several hours; and the patient must wait during the required observation time after treatment for monitoring for emergence of infusion-related reactions.[31] FDA has acknowledged that switching from intravenous administration to a less burdensome route of administration provides a major contribution to patient care.[32]

    - Multiple studies with subcutaneous delivery of one or more biological products in combination with human hyaluronidase have demonstrated a significantly shorter treatment time—minutes instead of hours—and a shorter required observation time due to the lower occurrence of infusion related reactions.[33]

    - As another benefit, subcutaneous delivery also can occur in a doctor's office or at home, reducing the travel burden for patients and reducing their out-of-pocket costs as a result of avoiding more costly hospitals and infusion suite settings.[34] Indeed, a patient testimonial highlights the benefits of subcutaneous administration:

        > *With the IV antibody, a typical day was we would wake up and get in the car before sunrise so we get to the cancer center typically around 7:30 am and go in for labs, and they get the labs back an hour later and be upstairs to see my doctor maybe around 8:30 or 9 am. That visit would typically be about 20 minutes to 30 minutes. I would then go to the infusion center by about 10:30 am and do the intake stuff that takes a little bit of time . . . they need to order the premeds and the IV antibody to be sent to the infusion center. And really it's about this time that the trauma starts to kick in because I have these veins . . . stab*

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[31] *See* Patient Preferences Study (link).

[32] *See* FDA, Clinical Superiority Findings for Radicava ORS (edaraone) Oral Suspension (last visited June 5, 2025) (link) ("Radicava's oral suspension route of administration advances the ease and comfort of administration without the complications and risks associated with IV administration," which is particularly important "in the context of a chronic . . . disease that requires long-term treatment.").

[33] *See* Perspectives Study (link).

[34] McCloskey C, et al, A Systematic Review of Time and Resource Use Costs of Subcutaneous versus Intravenous Administration of Oncology Biologic in a Hospital Setting, PharmacoEconomics, 7:3-36 (2023) (link).

one . . . go for another vein . . . I then do the premeds, that would generally take one hour to get through IV Benadryl, IV steroids, and then the IV antibody would arrive typically around at 12:30 pm or 1 pm. That first dose is a superlong infusion. For the majority of my time it was a 3-hour infusion. We would get done then with that at 4:00-4:30 pm and then we would drive home, in the traffic . . . so this experience was sunrise to sunset.

With subcutaneous antibody now I typically show up and see my doctor at 9:00 am, see her for about 20 minutes . . . I get upstairs . . . the nurse checks everything out and calls pharmacy and they send the Subcutaneous antibody over in a few minutes and [it takes about] five minutes for the injection of subcutaneous antibody. From time I walk in those doors at around 8:00 am, I will be out the door by 9:30.

I've had 61 doses of subcutaneous antibody since January of 2021. If you took those 61 doses and those were still IV, at a 90-minute infusion that would have been 91 hours versus a 5-minute subcutaneous, which is a total 5 hours. ***That really is treatment scheduled around life. That is a reinvented patient experience. Why is that so important? Because when you have cancer time is everything.***

- **Subcutaneous delivery of a fixed combination with Halozyme's human hyaluronidase can reduce infection risk for patients by eliminating the need for an intravenous device (e.g., a port).** To avoid the need for multiple needle pricks and to ease administration burdens for healthcare providers, patients receiving intravenous treatments commonly undergo a surgical procedure to implant a port-a-cath into a vein. This port-a-cath serves as a catheter that that can be reused for each intravenous infusion without the need for additional vein punctures.

  - Although port-a-caths are convenient and can reduce patient discomfort, they are a source of infection, which can result in septic shock and even death. This risk is of particular importance in patients receiving chemotherapy, whose ability to fight infection can be seriously compromised. A recent JAMA article reports the rate of infection of 4.8 per 1000 catheter days.[35]

  - Subcutaneous delivery of a fixed combination with human hyaluronidase does not require a port-a-cath, as it is delivered as a simple injection under the skin, often in the abdominal area. The availability of several cancer treatments with human hyaluronidase that are administered subcutaneously has resulted in some cancer patients being able to move away from having any of their treatments intravenously, if their particular regimen of cancer treatments is administered entirely as pills or subcutaneous injections, mitigating the discomfort of having a port-a-cath and the attendant infection risks. As an example of this, for patients with the blood cancer multiple myeloma, the availability of an antibody treatment given subcutaneously with human hyaluronidase enabled patients receiving a commonly used four-drug treatment regimen to avoid the need for

[35] *See* Munsch et al, Complication Rates of Central Venous Catheters, A Systematic Review and Meta-Analysis, JAMA Internal Medicine, Volume 184, No. 5, 474-482 (March 2024) (link) (CVC Study).

intravenous treatment, where the three other treatments were already given orally or subcutaneously.

- In a similar context with "a central venous access device (CVAD), which is associated with an increased risk of thromboembolic events and access-associated infections," FDA determined, that the same drug administered subcutaneously provided greater safety for patients.[36]

- **Subcutaneous delivery of a fixed combination with Halozyme's human hyaluronidase can reduce cancer patients' exposure to infection by reducing the length of time spent in infusion facilities**. Despite advances in oncology care, infections remain a major cause of morbidity and mortality among cancer patients. Increased risks for infection are attributed, in part, to immunosuppression caused by the underlying malignancy and by the cancer treatment itself. Patients with cancer frequently are in healthcare settings and can be exposed in these settings to other patients that might have transmissible infections.

  - The CDC has highlighted that outpatient oncology facilities where infusion facilities are often located vary greatly in their attention to and oversight of infection control and prevention.[37] For example, there were a number of outbreaks of viral hepatitis and bacterial bloodstream infections in outpatient facilities that resulted from breaches in basic infection prevention practices (e.g., syringe reuse, mishandling of intravenous administration sets). A specific CDC guide is in effect to provide direction on basic infection control to better protect vulnerable patients.[38] The availability of subcutaneous delivery with human hyaluronidase allows for some patients to be treated at home or in a doctor's office. For patients who are still treated in infusion facilities, subcutaneous delivery with human hyaluronidase allows them to spend significantly less time in the infusion facility and thus have fewer hours of potential exposure to infectious pathogens.

  - FDA leadership has lauded these benefits. In June 2020, when FDA approved Phesgo two antibodies, pertuzumab and trastuzumab, in a fixed combination with human hyaluronidase for subcutaneous injection to treat adult patients with HER2-positive breast cancer, the Director of the FDA's Oncology Center of Excellence stated in the public press release, "[c]urrently, most patients with HER2-positive breast cancer receive trastuzumab and pertuzumab at infusion centers. With a new administration route, Phesgo offers an out-patient option for patients to receive trastuzumab and pertuzumab," which was particularly important during the coronavirus pandemic during which it was critical "to keep a strong focus on patients with cancer who constitute a vulnerable population at risk of contracting the disease."[39]

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[36] *See* FDA, Clinical Superiority Findings for Hizentra (link) ("Data demonstrated that patients treated with Hizentra subcutaneously had fewer of these [thromboembolic events and access-associated infections] than patients treated with IGIV via CVADs. Therefore, Hizentra provides greater safety than the previously approved IGIV formulation of immune globulin for CIDP as maintenance therapy . . . .").

[37] CDC, Basic Infection Control and Prevention Plan for Outpatient Oncology Settings (April 15, 2024) (link).

[38] CDC, Basic Infection Control and Prevention Plan for Outpatient Oncology Settings (Dec. 2011) (link).

[39] FDA Press Release, FDA Approves Breast Cancer Treatment That Can Be Administered At Home By Health Care Professional (June 29, 2020) (link).

- **Subcutaneous delivery of a fixed combination of an antibody with Halozyme's human hyaluronidase reduces HCP resources and time required for treatment preparation and administration compared to the antibody given intravenously as a single component product**. Multiple studies have consistently found both in and outside the United States that pharmacy, nurse, and doctor time and related costs associated with administering antibodies subcutaneously with human hyaluronidase for cancer are meaningfully lower when compared to the antibody administered intravenously. When infusion suite capacity is full and staff shortages can occur, use of the more efficient subcutaneous delivery also can enable more patients to receive treatment each day.[40]

    - Some have argued that, while combining biological products with hyaluronidase offers greater convenience and fewer infusion reactions, it may also increase overall healthcare spending.[41] These critics appear to take this position based largely on conjecture and despite recognizing "that newer hyaluronidase versions had similar or lower costs than the intravenous version[.]"[42] They also acknowledge that their analysis "did not account for potential savings associated with reduced time and cost" from the fixed combinations and that the transition to "could lead to direct healthcare savings due to lower administration fees and indirect savings from less patient and caregiver time spent receiving infusions."[43] Indeed, we have found a reduction, not an increase, in total healthcare spending as a result of hyaluronidase reformulations. A recent systematic literature review assessed the economic costs of antibodies delivered subcutaneously in fixed combination with hyaluronidase compared to intravenous administration of the antibody alone:

        > Economic costs associated with treatment, reported by 14 studies, were consistently higher for IV compared with SC therapy administration despite considerabl[e] heterogeneity in how costs were measured and reported across studies. Differences in direct costs were driven primarily by HCP time, day unit/hospitalization time, consumables, and drug wastage, whereas drug costs were similar between groups. Indirect cost savings were also observed for SC over IV administration in a subset of studies that reported these data and were driven primarily by the differential impact on patient and/or caregiver work productivity.[44]

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[40] State of Cancer Report 2023, LeanTaaS Institute (link).

[41] Kim J, Medicare Spending and Use of Subcutaneous Biologic Formulations with Hyaluronidase, the Oncologist (2025) (link) (Spending Study).

[42] *See* Spending Study at 2 (link). This article also speculates about the potential impact of fixed combinations of human hyaluronidase and antibodies on competition from biosimilars of the intravenous antibodies. But the vast majority of the intravenous antibody drugs mentioned in the article's Table 1 were approved fewer than twelve years ago. Accordingly, reference product exclusivity for the antibody drug, not competitive dynamics, is the likely reason for the lack of biosimilar competition. *See* PHSA § 351(k)(7).

[43] Spending Study at 3 (link).

[44] *See* Perspectives Study (link).

- Subcutaneous delivery of a fixed combination with human hyaluronidase also offers the following patient benefits:[45]
    - Reduces patient travel, and caregiver support costs, and other indirect patient out-of-pocket expenditures compared to that for intravenous delivery;
    - Allows for administration to occur at alternative sites of care that can be closer to a patient's home, reducing both patient and caregiver travel time burden;
    - Typically decreases the time spent at any site of care when compared to intravenous administration, as explained in the patient testimonial; and
    - Allows for certain therapies to be self-administered at home, eliminating the need for patients to travel to a medical facility, which decreases a patient's and caregiver's time absent from work.[46]

In sum, human hyaluronidase is biologically and therapeutically active and results in clinically meaningful differences. Subcutaneous fixed combination products containing human hyaluronidase and specific antibodies provide meaningful therapeutic advantages for patients and the public health. As explained above, these products can reduce side effects, improve efficacy, reduce patient burden, and reduce healthcare practitioner burden. These products also reduce overall cost to the healthcare system and patients. For these reasons, even if CMS adopts the Proposal, it should find that antibody plus human hyaluronidase fixed combinations are distinct QSSDs from the antibodies formulated alone.

IV. The Proposal is flawed as a matter of law.

A. The Proposal would create two meanings of "biological product" and does not reflect the single, best reading of the SSA—contrary to *Loper Bright*.

The Proposal conflicts with recent U.S. Supreme Court case law and executive action.

In *Loper Bright Enterprises v. Raimondo*, the Court held that agencies and reviewing courts must adopt the "single, best meaning" of statutory provisions.[47] The President also issued a memorandum directing the repeal of unlawful regulations that contravene *Loper Bright*.[48] CMS's Proposal under is flawed under *Loper Bright* for several reasons.

First, CMS now proposes to give the statutory phrase "biological product" two different meanings. To date, as explained above, CMS has interpreted "biological product" in the QSSD

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[45] *See* Perspectives Study (link); *see also* CVC Study (link).

[46] This benefit to patients is meaningful, especially to the considerable number of patients living in rural, tribal, or other remote regions across the U.S. who may not otherwise be able access life-changing therapies. Levitt LA, et al, Closing the Rural Cancer Care Gap: Three Institutional Approaches, JCO Onc Prac, 16:422-431 (2020) (link). *See also* Vyvgart Hytrulo, Prescribing Information, § 2 Dosage and Administration (link) ("VYVGART HYTRULO prefilled syringe may be administered by patients and/or caregivers after proper instruction in subcutaneous injection technique").

[47] *Loper Bright Enters. v. Raimondo*, 603 U.S. 369, 400 (2024) ("Courts instead understand that such statutes, no matter how impenetrable, do—in fact, must—have a single, best meaning.").

[48] The White House, Directing the Repeal of Unlawful Regulations (April 9, 2025) (link).

definition to mean "active ingredient" or combination of "active ingredients" and has used the RxNorm database to identify active ingredients. Now, changing course, CMS proposes to adopt—for certain fixed combination products only—a second, unique interpretation of "biological product" that requires consideration of biological activity, therapeutic activity, and/or clinically meaningful differences and disregards a component's active ingredient status, as recognized by FDA. This dualistic approach cannot be squared with the U.S. Supreme Court's decision in *Loper Bright*. An agency may not interpret the exact same statutory term, "biological product," one way for certain products and another way for other products. This phrase must have one single, best meaning. CMS's Proposal does not adhere to this requirement.

Second, CMS's Proposal also does not represent the best reading of the SSA in violation of the Supreme Court's holding. CMS's original approach—that "biological product" means active ingredient or combination of active ingredients for all biological products, including all fixed combinations—comported with *Loper*. It best fit the statutory text, which makes no mention of "therapeutically active," "biologically active," or "clinically meaningful" criteria for identifying QSSDs. Instead, the statutory QSSD definition applies to "[a] biological product . . . that is licensed under section 351(a) of the Public Health Service Act [PHSA]."[49] Under section 351(a), FDA has licensed antibody-human hyaluronidase combinations—separately from individual antibodies—as fixed combinations with two active ingredients.[50] It has also, as noted, licensed a biological product with human hyaluronidase as the sole active ingredient.[51] Thus, an antibody-human hyaluronidase combination qualifies as a separate "biological product" licensed under 351(a) of the PHSA. CMS's original interpretation therefore aligned with the statute.[52]

In contrast, the Proposal conflicts with the statute. There is no statutory qualifier in either the SSA or PHSA that permits CMS to treat certain fixed combination products differently than others. In particular, given the SSA's express reliance on licensing decisions under section 351(a) of the PHSA and the separate licensure of fixed combination products from individual antibodies, there is no statutory basis for applying the QSSD definition differently for only some fixed combination products. CMS's Proposal thus conflicts with the statutory focus on the product that is licensed under section 351(a) by FDA and the text of the QSSD definition more generally.

Finally, the addition of Part B drugs to the Program does not justify the Proposal. The statute has not changed, and the relevant parts of the QSSD definition—i.e., the text providing

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[49] SSA § 1192(e).

[50] *See, e.g.*, Darzalex Faspro (daratumumab and hyaluronidase-fihj), Herceptin Hylecta (trastuzumab and hyaluronidase-oysk), Hyqvia (Immune Globulin Infusion (Human), 10% with Recombinant Human Hyaluronidase), Ocrevus Zunovo (ocrelizumab and hyaluronidase-ocsq), Opdivo Qvantig (nivolumab and hyaluronidase-nvhy), Phesgo (pertuzumab, trastuzumab, and hyaluronidase-zzxf), Rituxan Hycela (rituximab and hyaluronidase human), Tecentriq Hybreza (atezolizumab and hyaluronidase-tqjs), Vyvgart Hytrulo (efgartigimod alfa and hyaluronidase-qvfc).

[51] *See* Hylenex recombinant (hyaluronidase human). *See also* Amphadase (hyaluronidase), Hydase (hyaluronidase), Vitrase (hyaluronidase).

[52] Given that FDA has licensed *biological products* containing human hyaluronidase as an active ingredient, including as the sole active ingredient, it is necessarily the case that human hyaluronidase is "applicable to the prevention, treatment, or cure of a disease or condition of human beings." *See* PHSA § 351(i)(1).

when a "[a] biological product" is a QSSD—apply equally to Part B and D drugs. Specifically, the QSSD definition states:

> "(1) IN GENERAL.—For purposes of this part, the term 'qualifying single source drug' means, with respect to an initial price applicability year, subject to paragraphs (2) and (3), ***a covered part D drug (as defined in section 1860D–2(e)) that is described in any of the following or a drug or biological product for which payment may be made under part B of title XVIII*** that is described in any of the following:
>
> . . .
>
> "(B) BIOLOGICAL PRODUCTS.—A biological product—
>
> "(i) that is licensed under section 351(a) of the Public Health Service Act and is marketed under section 351 of such Act;
>
> "(ii) for which, as of the selected drug publication date with respect to such initial price applicability year, at least 11 years will have elapsed since the date of such licensure; and
>
> "(iii) that is not the reference product for any biological product that is licensed and marketed under section 351(k) of such Act.[53]

As discussed above, CMS interprets subparagraph (B) and the term "biological product" in particular (as well as the similar provisions for drugs) for purposes of its aggregation methodology. This text is exactly the same for Part B and Part D drugs. Thus, the inclusion of Part B drugs provides no basis for novel aggregation methodology in IPAY 2028.

In sum, the statutory interpretation reflected in the Proposal does not represent the single, best meaning and thus cannot stand. CMS should abandon the Proposal to avoid violating the Administrative Procedure Act (APA) with an inconsistent and invalid statutory interpretation.

B. CMS's Proposal second-guesses FDA's expert determinations.

The Proposal conflicts with FDA's regulation that CMS invokes and FDA's conclusions about components' status as active ingredients.

As noted, the IPAY 2026 and 2027 Guidances and the IPAY 2028 Draft Guidance cross-reference FDA's definition of fixed combination drug at 21 C.F.R. § 300.50 for purposes of the aggregation principle. This regulation applies to:

> Two or more drugs . . . combined in a single dosage form when each component makes a contribution to the claimed effects and the dosage of each component (amount, frequency, duration) is such that the combination is safe and effective for a significant

[53] SSA § 1192(e)(1) (emphasis added).

> patient population requiring such concurrent therapy as defined in the labeling for the drug.[54]

The regulation recognizes "[s]pecial cases of this general rule are where a component is added:" "(1) To enhance the safety or effectiveness of the principal active component; and (2) To minimize the potential for abuse of the principal active component."[55] FDA interprets "component" as active ingredient.[56]

FDA has provided examples of fixed combinations that fall into these categories. For combinations in which one active ingredient is intended to "[p]rovide a direct effect that either potentiates or makes another active ingredient more tolerable," the agency gives the example of "using carbidopa to provide a lower dose of levodopa to minimize side effects."[57] For combinations in which one active ingredient is intended to "minimize an adverse reaction associated with another active ingredient," the agency has given as an example "using pyridoxine to minimize the toxicity of isoniazid;" and for combinations in which one active ingredient is intended to "reduce the abuse potential associated with another active ingredient" the agency has given the example of "using an opioid antagonist to reduce the abuse potential of an oral opioid product following manipulation for purposes of abuse."[58]

The regulation and FDA's examples highlight that an active ingredient in a fixed combination must have a clinically meaningful effect to be present in a fixed combination at all. Thus, CMS's continued reliance on this regulation underscores that active ingredients that serve either of these latter functions described as "special cases" of the general rule should be considered active ingredients for aggregation purposes. The Proposal to revisit clinical meaningfulness a second time thus is in tension with the very regulation that CMS cites.

The regulatory history of 21 C.F.R. § 300.50 supports this conclusion. The regulation was originally proposed over 50 years ago in 1971 in a proposed rule, which explained:[59]

> It is the consensus of these informed experts that a fixed dose combination drug must have an advantage to the patient over and above that obtained when one of the individual ingredients is used in the usual safe and effective dose. No drug should be present in a fixed combination unless its inclusion clearly enhances safety or efficacy and the fixed ratio of doses is safe and effective for all indications and for patient.[60]

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[54] 21 C.F.R. § 300.50.

[55] *Id.*

[56] 80 Fed. Reg. 79,776, 79,786 (Dec. 23, 2015) (link) (2015 Proposed Fixed Combination and Co-Packaged Drugs Rule) ("we have interpreted 'component' in § 300.50 to mean active ingredient.").

[57] *Id.* at 79,786.

[58] *Id.*

[59] Proposed Rule, "Proposed Statement Amplifying Policy on Drugs in Fixed Combinations," 36 Fed. Reg. 3126 (Feb. 18, 1971). *See also* Final Rule, "Fixed-Combination Prescription Drugs for Humans," 36 Fed. Reg. 20,037 (Oct. 15, 1971).

[60] *Id.*

This longstanding regulation makes clear that for FDA to approve a fixed combination product, "each ingredient designated as active" must contribute to the total effect of the drug. As noted, FDA defines "active ingredient" as "any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals."[61]

FDA has regarded antibody-human hyaluronidase combinations as fixed combination products under 21 C.F.R. § 300.50. For example, FDA cited the fixed combination regulation, 21 C.F.R. § 300.50, in its review materials for one such product.[62] As explained above, FDA has also recognized that human hyaluronidase is an active ingredient. If FDA considers antibody-human hyaluronidase combinations to be fixed combination products under 21 C.F.R. § 300.50, then, like any other active ingredient in a fixed combination product, human hyaluronidase necessarily contributes to the total effect of the drug, enhances safety and/or efficacy, and furnishes pharmacological activity.

Indeed, in these fixed combinations, human hyaluronidase is similar to the example FDA has provided (e.g., carbidopa) for a component of a fixed combination product that "[p]rovide[s] a direct effect that either potentiates or makes another active ingredient more tolerable."[63] Carbidopa is used to allow use of a lower dose of levodopa to minimize side effects—in other words, CMS might conclude that it "affects the bioavailability of [levodopa] but is not therapeutically active against [Parkinson's disease]." Nevertheless, FDA recognizes as carbidopa as an active ingredient that affects how levodopa is dosed in a manner that affects safety or effectiveness. Similarly, as explained in section III, without human hyaluronidase, rapid subcutaneous delivery of an antibody is limited to just ~2 milliliters, significantly restricting the use of subcutaneous delivery as many drugs require higher doses to be effective. Human hyaluronidase thus affects the amount of drug that can be delivered subcutaneously at a given time, in a way that can affect safety or effectiveness (e.g., by lowering the rate of infusion-related reactions and other potential adverse events as compared to the single component antibody administered intravenously).

In sum, CMS's Proposal to differentiate among certain fixed combinations as described in 21 C.F.R. § 300.50 does not align with the longstanding regulation or FDA's approach to implementing that rule. Moreover, the fact that FDA regards antibody-human hyaluronidase combinations as fixed combination products under 21 C.F.R. § 300.50 provides further evidence that human hyaluronidase necessarily results in a clinically meaningful difference in the fixed combination product and is therapeutically active. As recognized in the text of the SSA, FDA is the agency charged with licensing biological products, including fixed combinations, and CMS should not second-guess FDA's determinations that human hyaluronidase is an active ingredient that plays a clinically meaningful role in antibody-human hyaluronidase combinations.

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[61] 21 C.F.R. § 210.3(b)(7).

[62] Cross-Discipline Team Lead Review, BLA 761064 at 21 fn. 4 (June 7, 2017) (link) ("The applicable regulations would be 21 CFR 300.50 Fixed-combination prescription drugs for humans. For labeling purposes, the term 'combination' is recommended.").

[63] 80 Fed. Reg. at 79,786.

C. The Proposal is inconsistent with the orphan-drug exclusion.

CMS's Proposal conflicts with the orphan-drug exclusion in the IRA. Under section 1192(e)(3) of the SSA, QSSD "does not include" "[a] drug that is designated as a drug for only one rare disease or condition under section 526 of the Federal Food, Drug, and Cosmetic Act [FDCA] and for which the only approved indication (or indications) is for such disease or condition."[64]

FDA has long interpreted "drug" in section 526 of the FDCA to mean "principal molecular structural features" of biological products.[65] For purposes of section 526 of the FDCA, FDA considers fixed combination and single-entity active ingredient products to be different "drugs" that require separate orphan-drug designations.[66] Given the SSA's express reference to the "drug" designated "under section 526" of the FDCA, Congress intended to adopt FDA's interpretation of "drug" for purposes of the orphan-drug exclusion.

For purposes of section 526 of the FDCA, FDA considers a fixed combination of an antibody with human hyaluronidase to be a different drug from the antibody. For example, based on FDA's website, FDA does not consider Vyvgart (efgartigimod alfa) and Vyvgart Hytrulo (efgartigimod alfa in combination with human hyaluronidase) to be the "same drug."[67] Nor does FDA consider Rituxan (rituximab) or Rituxan Hycela (rituximab in combination with human hyaluronidase) to be the "same drug."[68]

Therefore, the Proposal would conflict with this FDA interpretation and the statute's reference to FDA's designation decisions. Under CMS's Proposal, some fixed combinations would be considered to be the same "biological product" as an individual active ingredient within the fixed combination—even though FDA would say these are two different "drugs" under section 526. In this respect, the Proposal would result in absurd consequences. For example, a fixed combination of active ingredients X and Y could be aggregated with a biological product containing only active ingredient Y. But FDA would have granted separate orphan-drug designations to X and X+Y because they are different "drugs" under section 526 of the FDCA. It is unclear whether CMS would say that this type of QSSD can *never* qualify for the orphan-drug

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[64] SSA § 1192(e)(3)(A).

[65] 80 Fed. Reg. 79,776, 79,786 (Dec. 23, 2015).

[66] FDA, Office Director's Decisional Memorandum, NDA 21-844, at 1 (Dec. 12, 2005) (link) (stating that "fixed-combination drug products are not considered 'the same drug' as single ingredient products under the Orphan Drug Act and implementing regulations" and finding that IPLEX, a fixed-combination of rhIGF-1 and rhIGFBP-3, was not blocked from approval by exclusivity granted to INCRELEX, which contains rhIGF-1).

[67] Vyvgart Hytrulo is listed in the orphan-drug database (link) as having orphan-drug exclusivity for treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) antibody positive, but there is no evidence that FDA has made a finding that Vyvgart Hytrulo is clinically superior to Vyvgart. *See* FDCA § 527(c); *See also* 21 C.F.R. § 316.34(c); FDA Clinical Superiority Website (link).

[68] Rituxan SC is listed in the orphan-drug database (link) as having orphan-drug exclusivity for treatment of adult patients with previously untreated and previously treated chronic lymphocytic leukemia in combination with fludarabine and cyclophosphamide, but there is no evidence that FDA has made a finding that Rituxan SC is clinically superior to Rituxan. *See* FDCA § 527(c); *See also* 21 C.F.R. § 316.34(c); FDA Clinical Superiority Website (link).

exclusion. This "potential QSSD" would need to have two orphan-drug designations under section 526, but a product with two designations is not eligible for the orphan-drug exclusion.

This absurdity shows that the Proposal is out of step with the longstanding meaning of "drug" in section 526 of the FDCA and FDA's designation of fixed combination products containing human hyaluronidase. These considerations underscore that the Proposal does not represent the single, best reading of the statute.

D. The Proposal departs from precedent without adequate explanation or fair notice.

CMS's Proposal is a clear departure from its IPAY 2026 and IPAY 2027 guidance. CMS has not provided adequate explanation for the proposed change. CMS also has failed to consider industry's reliance interests on the existing policy or provide industry with adequate notice of how CMS would determine that a component—that FDA has determined to be an active ingredient in a fixed-combination product—is not therapeutically or biologically active and does not produce a "clinically meaningful difference."

In *FCC v. Fox Television Stations*, the Supreme Court held that when an agency's "prior policy has engendered serious reliance interests that must be taken into account," "[i]t would be arbitrary and capricious to ignore such matters. . . . [A] reasoned explanation is needed for disregarding facts and circumstances that underlay or were engendered by the prior policy."[69] As recently as October 2024, CMS reaffirmed the approach to aggregation of all fixed combination products per the IPAY 2026 and 2027 guidance documents and rejected comments suggesting a test similar to the Proposal. The agency has provided no reasoned explanation for the abrupt change in approach from IPAY 2026 and IPAY 2027. As noted, nothing about the inclusion of Part B products in IPAY 2028 justifies the change, as the relevant parts of the QSSD definition are the same for Part B and D drugs. CMS also has not considered the reliance interests at stake if the Proposal is adopted.

Moreover, as the D.C. Circuit has explained, "[r]ule of law principles require that parties have fair notice and an opportunity to conform their behavior to legal rules."[70] CMS has proposed a vague, thinly described, and potentially inconsistent test in its Proposal. The fixed combination products that CMS intends to fall under this Proposal are "not biologically active against the disease state(s) the drug is indicated for and thus do[] not result in a clinically meaningful difference," and CMS also provides an example of a component in a fixed combination product that "affects the bioavailability of active moiety / active ingredient Y but is not therapeutically active against the disease state."[71] We have identified no statutory or regulatory definition of "biologically active," "therapeutically active," or "clinically meaningful differences" in the context of fixed combination products.[72]

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[69] *FCC v. Fox Television Stations, Inc.*, 556 U.S. 502, 515–16 (2009). *See also Dep't of Homeland Security v. Regents of the Univ. of California*, 591 U.S. 1, 30 (2020) ("When an agency changes course, . . . it must be cognizant that longstanding policies may have engendered serious reliance interests that must be taken into account.").

[70] *See Circus Circus Casinos, Inc. v. NLRB*, 961 F.3d 469, 476 (D.C. Cir. 2020). *See also id.* at fn 2.

[71] IPAY 2028 Draft Guidance at 13.

[72] The term "clinically meaningful difference" appears within the definition of a "biosimilar" in the PHSA, but it has a very circumscribed meaning that is not related to QSSD aggregation issues. PHSA § 351(i)(2) (noting that, among other things, biosimilarity requires "no clinically meaningful differences between the

It is difficult to divine what is the actual test here that CMS is proposing and what its key teams mean. The description raises many questions, including:

- Is the test whether the component is biologically active against the disease state and will CMS's conclusion on biological activity determine if there are no clinically meaningful differences? Or is the test two parts, where the component must not be active against the disease state and must not provide a clinically meaningful difference to be subject to the new policy?

- Is there a reason CMS uses "biologically active" in one passage but "therapeutically active" in another?

- Does this test apply not only to fixed combination products but also co-packaged products?

Furthermore, it is not clear what approach CMS will take to aggregate fixed combination products that fall within the scope of the Proposal, if adopted. Under one approach, to identify certain fixed combination products as QSSDs that fall under the Proposal, CMS might aggregate for any single BLA holder all dosage forms and strengths of products (a) containing the same combination of active ingredients as a given fixed combination product and (b) containing a single ingredient within that fixed combination product. Then CMS might apply the 11-year requirement in the definition of QSSD by looking to the earliest date of licensure of either of the individual components for certain fixed combination products but not others.

Alternatively, CMS might identify certain fixed combination products as QSSDs that fall under the Proposal by aggregating for any single BLA holder all dosage forms and strengths of products (a) containing the same combination of active ingredients as a given fixed combination product and (b) containing what it considers to be the single "biologically" or "therapeutically" active component within the fixed combination product. Unlike the prior approach, this approach would exclude products CMS has deemed to contain the "biologically" or "therapeutically" "inactive" component from the scope of aggregated products. Then, CMS might apply the 11-year requirement in the definition of QSSD to that narrower group of products but in a similar manner as the prior approach. CMS has failed to give any indication of what approach it might be taking here.

In sum, CMS has not appropriately explained the basis for its proposed change in statutory interpretation, and regulated industry does not have fair notice of the most basic aspects of how the Proposal would be implemented.

E. The Proposal is arbitrary and capricious in contravention of the APA.

The APA requires a court to set aside agency actions, findings, and conclusions found to be "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law."[73] As noted above, not only does the Proposal create two definitions of biological product, but also it conflicts with FDA's regulation of fixed combination products. This discrepant treatment of these functionally indistinguishable fixed combination products by CMS itself and also between CMS and FDA is the essence of the meaning of arbitrary and capricious government action.

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biological product and the reference product in terms of the safety, purity, and potency of the product."). If anything, this provision indicates that Congress knows how to specify when differences must be clinically meaningful—or not—and chose to exclude any such requirement from the QSSD definition.

[73] 5 U.S.C. § 706(2)(A).

Courts have repeatedly held that "an agency must treat similar cases in a similar manner unless it can provide a legitimate reason for failing to do so."[74] CMS has provided no legitimate reason.

Moreover, as discussed above, CMS's Proposal, if adopted, may result in the disparate treatment of fixed combination products that are orphan drugs when assessing whether they qualify for the orphan-drug exclusion from the definition of a QSSD and when assessing whether they otherwise meet the definition of a QSSD. Again, this discrepant treatment constitutes arbitrary and capricious agency action that must be set aside.

Finally, CMS's Proposal comes as an abrupt about-face less than a year after having a different, uniform policy for fixed combination products. As discussed above, there is not an adequate explanation for this change or the Proposal itself. The timing of the change and the thinness of the explanation put into high relief how arbitrary the policy is.

V. The Proposal is flawed as a matter of policy.

A. The Proposal discourages fixed combination products that help patients and reduce burden on healthcare resources.

As explained in section IV.D, it is not clear what approach CMS would take with respect to aggregation and application of the 11-year selection timeline for the fixed combination products identified in the Proposal, if adopted. However, any approach under the Proposal will have the effect of discouraging the development of fixed combination products and conflicts with FDA's policies encouraging their development. FDA has explained the importance of fixed combination products:

> Fixed-combinations are becoming increasingly important from patient and public health perspectives. Combination therapy is emerging as the standard of care in certain disease settings, such as cancer, cardiovascular disease, and infectious disease (for example, in human immunodeficiency virus (HIV) infections/acquired immunodeficiency syndrome (AIDS)). In recognition of the importance of such combination therapies, FDA has encouraged the development of these therapies through various policies and initiatives. For example, FDA recently finalized its guidance for industry titled *Codevelopment of Two or More New Investigational Drugs for Use in Combination* (Codevelopment Guidance). In the Codevelopment Guidance, FDA explained the potential therapeutic benefits of combination therapies, including improvement in treatment response, lower risk of developing resistance, and lower rates of adverse events.[75]

Although FDA clearly recognizes the importance of fixed combination products and has various policies to encourage their development, CMS's Proposal does exactly the opposite and discourages their development. Given concerns over CMS determining that one of the

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[74] *See Bracco v. Shalala*, 963 F. Supp. 20, 27-28 (D.D.C. 1997).

[75] Final Guidance, New Chemical Entity Exclusivity Determinations for Certain Fixed-Combination Drugs (Oct. 2014) (link). *See also* Final Guidance, Guidance for Industry Codevelopment of Two or More New Investigational Drugs for Use in Combination at 2 (June 2013) (link) ("FDA believes guidance is needed to assist sponsors in the codevelopment of two or more new investigational drugs.").

components in a fixed combination product does not result in a clinically meaningful difference, companies might avoid developing such products when, as explained in section III and confirmed by FDA, they provide significant therapeutic advantages.

B. The Proposal runs counter to government efficiency and creates administrative burden for CMS.

The April 9, 2025 Presidential Memorandum explicitly calls on agencies to review and repeal onerous regulations.[76] The Proposal would increase agency burden and therefore should be abandoned.

The Proposal would appear to require CMS to make case-by-case decisions about whether to aggregate a fixed combination with an individual active ingredient. CMS would need to make those decisions based on an ambiguous and fact-specific test, rather than deferring to the decision FDA already made on the issue. Implementation of the Proposal thus would be administratively taxing.

For example, it would require CMS staff to have or obtain the medical knowledge necessary to make assessments of clinical differences of every fixed combination that might be selected for the Program. Alternatively, implementation might involve an intensive interagency consult process with FDA. Resolution of the complex orphan-drug exclusion issues raised above also would require substantial administrative resources. Building an appropriate administrative record for such decisions would be time consuming as well.

This process therefore would undermine the Administration's goals to reduce red tape and enhance government efficiency.[77] It would be much less onerous to defer to FDA's expert decision that fixed combinations of biologics have at least one different active ingredient from a single-entity biological product, as reflected in FDA's licensure decisions under section 351(a) of the PHSA.

For the sake of conserving the government's scarce resources and maximizing governmental efficiency and productivity, the Proposal should be abandoned.

C. The Proposal creates uncertainty because it would be difficult to predict which fixed combination products will be aggregated and which will not.

Given how many unanswered questions there are about the Proposal, it would be challenging for industry and the public to predict which fixed combination products will and will not be aggregated. As explained in section IV.D, the Proposal lacks details regarding CMS's proposed test to identify the subset of fixed combination products affected by the Proposal, and the terms CMS employs in describing the Proposal are unclear and vague. Moreover, even if the Proposal were clear, it would require case-by-case CMS determinations regarding aggregation that will be difficult to predict.

This inability to forecast how CMS will implement this Proposal will inevitably disrupt research and development planning and strategic business partnerships that have brought to market fixed combination products that offer significant therapeutic advantages. In other words, this lack of clarity will stifle investment in fixed combinations—despite their therapeutic

[76] The White House, Directing the Repeal of Unlawful Regulations (April 9, 2025) (link).

[77] *See, e.g.*, Executive Order 14219, § 1 (February 19, 2025).

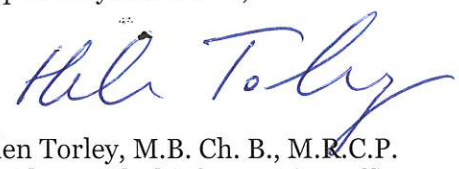
importance, as recognized by FDA and discussed above. Industry and investors will have no clarity as to whether they will have an 11-year period to recoup investment in a novel fixed combination or potentially no period at all. Furthermore, other stakeholders will also lose the predictability afforded by CMS's interpretation from IPAYs 2026 and 2027. Payors and investors will find it more difficult to predict which fixed combinations will be subject to the Program. These issues will be punted to an opaque CMS process that is divorced from FDA's science-based determinations.

To avoid these negative policy outcomes, CMS should revert to its approach to fixed combination aggregation as described in the IPAY 2026 and 2027 Guidances.

VI. Conclusion

For the reasons described above, Halozyme urges CMS to adhere to the definition of QSSD adopted in the IPAY 2026 and 2027 guidance documents for fixed combination products. If CMS decides to deviate from its IPAY 2026 and 2027 approach in identifying QSSDs, CMS should find that Halozyme's human hyaluronidase is an active ingredient with biological and therapeutic activity that provides clinically meaningful effects in fixed combination products, and therefore that fixed combinations of human hyaluronidase and antibodies should be considered distinct QSSDs from the individual active ingredients.

Respectfully submitted,



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