**PORTAL**
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**To:** Chris Klomp, CMS Deputy Administrator and Director of the Center for Medicare, Centers for Medicare & Medicaid Services

**Re:** Comments related to the May 12, 2025 Draft Guidance on the Medicare Drug Price Negotiation Program

# Halting Hyaluronidase Hopping: Why CMS Should Prevent Strategic Reformulations from Undermining the Medicare Drug Price Negotiation

On May 12, 2025, the Centers for Medicare and Medicaid Services (CMS) released a draft guidance for implementing the Medicare Drug Price Negotiation Program under the Inflation Reduction Act (IRA) for the initial price applicability year 2028. Among several technical updates is a proposed clarification in Sec 30.1, which could have outsized implications for the program's success.

Under the IRA, CMS is required to aggregate data across dosage forms and strengths of a drug when identifying qualifying single source drugs. To operationalize this process, CMS has adopted the terminology "active moieties" and "active ingredients." As defined by the U.S. Food and Drug Administration (FDA), an "active moiety" is the core physiologically active molecule of a drug, while an "active ingredient" is a broader concept that refers to any substance intended to have pharmacological activity. For fixed combination drugs that contain multiple active ingredients or moieties, CMS previously indicated in guidance that they would be treated separately from a products containing each individual active ingredient or moiety.

In its new 2025 draft guidance, however, CMS solicited feedback for implementing a clarification to this policy. The guidance states in Section 30.1 (page 13): *"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."*

Thus, CMS proposes that they would group these fixed-dose combination products with other products containing the therapeutically active ingredient. This clarification is essential to safeguarding the IRA's negotiation framework from manufacturer tactics that seek to reset or delay negotiation timelines by exploiting minor reformulations without meaningful clinical impact.

CMS's proposal is timely because a growing number of intravenously infused biologic drugs that could otherwise be eligible for price negotiation in the next few years have been re-marketed with hyaluronidase to allow subcutaneous administration. Although subcutaneous versions of medications can be more convenient and better tolerated than intravenous formulations, the addition of hyaluronidase does not modify the therapeutic activity of the products against the target disease. The FDA defines hyaluronidase as a separate active ingredient in these products, which means that under prior CMS guidance these would have be treated as fixed-dose combination products separate from the original non-hyaluronidase versions for the purposes of determining eligibility for Medicare price negotiation. This would have allowed manufacturers to engage in "hyaluronidase hopping": introducing new versions of drugs co-formulated with hyaluronidase with the effect of delaying price negotiation since the newer hyaluronidase versions would not be subject to negotiation until several years after the original intravenous version.

In a recent study,[1] we found that as of December 2024, at least nine biologics had hyaluronidase versions either approved or in late-stage clinical development. In 2022, Medicare spending on these products totaled $10.3 billion. For example, daratumumab (Darzalex) was first approved in 2015 for multiple myeloma; a subcutaneous coformulation (Darzalex Faspro) was later approved in 2020, and by 2022 Darzalex Faspro accounted for 82.9% of the Medicare Part B spending on daratumumab products.

The financial stakes of CMS's draft guidance are perhaps most acute for pembrolizumab (Keytruda), the world's top-selling drug in 2024, with $29.5 billion in sales. Keytruda was approved in 2014 and will likely be eligible to be selected for Medicare price negotiation in 2026, the first year Part B drugs are eligible for selection. However, a hyaluronidase version of Keytruda is expected to launch in

[1] John Kim, Aaron S Kesselheim, Edward R Scheffer Cliff, Benjamin N Rome, Medicare spending and use of subcutaneous biologic formulations with hyaluronidase, *The Oncologist*, Volume 30, Issue 6, June 2025, oyaf149, https://doi.org/10.1093/oncolo/oyaf149

the US by October 2025.[2] Considered as a separate product, this new version would not become eligible for price negotiation until at least 2036. If many Medicare patients switch from using the intravenous to the subcutaneous hyaluronidase version of Keytruda, this could effectively undermine the savings Medicare might expect from negotiating a lower price for Keytruda. However, under the new guidance, CMS could combine the intravenous and subcutaneous versions of Keytruda for the purposes of price negotiation.

To ensure that manufacturers of drugs like Keytruda cannot "hyaluronidase hop" to delay the effects of price negotiation, CMS should specify a clear operational distinction between active ingredients/moieties that provide therapeutic benefit and those that function solely to facilitate delivery. Thus, we propose that CMS should define "therapeutically active" ingredient as independently conferring benefit for the treatment of the indicated disease state. Therapeutically active should not include ingredients such as excipients and enzymes that alter absorption or tissue permeability, such as hyaluronidase, which actively depolymerizes hyaluronan to enhance the dispersion of co-administered agents in subcutaneous tissue. Hyaluronidase and its recombinant variants (e.g., rHuPH20, berahyaluronidase alfa), while biologically active, function solely to facilitate subcutaneous delivery of other therapeutically active ingredients.

If a therapeutically inactive ingredient is included in a fixed combination drug, this product should be combined for the purpose of drug price negotiation with other products that contain the therapeutically active ingredient(s). CMS should clarify in the final guidance that the presence of a therapeutically inactive ingredient or moiety in a fixed combination drug does not warrant classification as a distinct drug for the purposes of selection.

This definition would affect more than just hyaluronidase co-formulated products, because there are several other examples of therapeutically inactive ingredients that are part of fixed combination products. In the Parkinson's disease treatment carbidopa-levodopa, levodopa—a precursor to dopamine—is therapeutically active, while carbidopa reduces the peripheral metabolism of levodopa and thus enhances its bioavailability in the brain. Buprenorphine, an effective treatment for opioid use disorder, is often co-formulated with naloxone, an opioid antagonist that has essentially no absorption when the product is used orally or sublingually as directed; instead, naloxone serves as a deterrent and prevents overdose if the product is injected or inhaled**.** Several HIV antiviral treatments include ritonavir

[2] https://www.reuters.com/business/healthcare-pharmaceuticals/merck-plans-us-launch-subcutaneous-version-keytruda-october-1-2025-03-27/

or cobicistat, which boost the pharmacokinetic effects of other antivirals by inhibiting cytochrome P450-34A. In each of these cases (carbidopa, naloxone, and ritonavir or cobicistat), the therapeutically inactive ingredients are not used alone to treat the disease.

One argument against CMS combining drugs along with their counterparts co-formulated with therapeutically inactive components for the purposes of qualifying for negotiation is that this could disincentivize the development of new formulations that enhance delivery, efficacy, or safety. However, brand-name manufactures already have substantial financial motivation to pursue such innovations to increase sales of their products, In some cases, manufacturers are able to patent the co-formulated versions, which can delay generic or biosimilar competition. Additionally, any added benefits of the fixed combination version over the original version or any other therapeutic alternatives can be considered by CMS as part of the negotiation process. By negotiating products that include therapeutically inactive ingredients alongside products that contain only therapeutically active ingredients, CMS can preserve incentives for meaningful innovation while preventing opportunities for manufacturers to strategically undermine the negotiation process.

One additional change that CMS should incorporate in its new guidance is necessary to ensure that manufacturers are unable to delay or defer price negotiation by introducing new formulations, including fixed combination drugs that include therapeutically inactive ingredients. The IRA specifies that drugs with generic or biosimilar competition are ineligible for price negotiation. Under current operating procedure, CMS determines whether "*a generic drug or biosimilar biological product has been approved or licensed for any of the strengths or dosage forms for the potentially qualifying single source drugs"* (30.1). Thus, if there are multiple dosage forms available but only 1 has generic competition, the entire product is excluded from negotiation, even if the newer version(s) alone would qualify.

This could prevent CMS from negotiating in cases when there is generic or biosimilar competition for an older version of a drug even while the new version without competition has substantial Medicare spending.[3] For example, in the case of the antipsychotic paliperidone, the existence of generic competition for the oral formulation would have prevented negotiation of later-introduced long-acting intramuscular formulations that incurred billions of dollars in Medicare spending.

[3] Matthew Vogel, Benjamin N. Rome, Aaron S. Kesselheim, et al. Medicare Negotiation's Drug Reformulation Problem. Ann Intern Med.2024;177:817-819. doi:10.7326/M24-0138

In the case of hyaluronidase or other similar products, manufacturers could avoid price negotiation on blockbuster products by using their marketing resources to convert most patients to the new fixed-dose co-formulations and allowing biosimilar competitors to enter the market for the older, less-used formulations. For example, Darzalex Faspro accounts for the overwhelming majority of Medicare spending on daratumumab products, but this version would be exempt from negotiation if the older, less-used intravenous version faces biosimilar competition.

To close this loophole, CMS should aggregate spending only across formulations that do not face generic or biosimilar competition when evaluating eligibility for price negotiation. If the remaining formulations without a generic or biosimilar account for aggregated Medicare spending exceeding $200 million, they should remain eligible for negotiation. Additionally, if bona fide generic or biosimilar competition begins for a drug that has already been selected and negotiated, CMS should evaluate whether the competition affects all included dosage forms and formulations. If one or more formulations lack generic or biosimilar competition, CMS should retain those versions as selected drugs.

Because of the major financial implications of hyaluronidase hopping for patients and the US health care system, we support CMS's assertion that fixed combination drugs that contain therapeutically inactive ingredients can be combined with other formulations of the active ingredient for the purposes of price negotiation. Doing so will ensure that modified formulations are negotiated alongside the original versions of drugs, fulfilling Congress' intent in the IRA. In addition, CMS should modify its approach to excluding drugs based on generic or biosimilar competition so that competition for one formulation does not prevent negotiation for other formulations. Implementation of both changes will ensure that drugs are not inappropriately excluded from reasonable price negotiation by the Medicare program.