New Combination Drugs: Assessing the Potential Impact of New CMS Draft Guidance on Pharmaceutical Companies and Investors

May 27, 2025

On May 12, 2025, the Centers for Medicare and Medicaid Services ("CMS") issued draft guidance on the Medicare Drug Price Negotiation Program, which sets forth policies that would be implemented for the Initial Price Applicability Year 2028—i.e., the drugs that will be selected for negotiations in 2026, with the capped prices to be put into effect in 2028.[1] CMS asserts that the draft guidance is intended to improve the transparency of the "negotiation program, prioritize the selection of prescription drugs with high costs to the Medicare program, and minimize any negative impacts of the negotiated maximum fair price on pharmaceutical innovation within the United States." The 221-page draft guidance addresses a multitude of issues that we do not address here; the comment period closes on June 26, 2025.

Included in the draft guidance is a proposal that, if implemented, would expand the scope of what counts as the same "qualifying single source drug." This issue may be of critical importance to innovator pharmaceutical companies. If a "qualifying single source" drug is subject to "negotiations" (price controls) and the innovator company subsequently creates a modified version of the drug with the same active ingredient (which CMS treats as a different drug) then the different drug would be on its own timeline for "negotiations. By contrast, if (as CMS apparently intends) the modified drug is treated as the same "qualifying source" drug, then the modified drug would be immediately subject to the above-mentioned price controls (i.e., it would be treated the same as the nonmodified version).

As we discussed here, the Inflation Reduction Act (the "IRA"), enacted in 2022, fundamentally changed how the Medicare program provides reimbursement for prescription drugs. The IRA requires CMS to "negotiate" the price of many of the Part B and Part D drugs that account for the highest Medicare spending, provided they are eligible. Qualifying single source drugs are chosen from a list of drugs with the highest total Medicare Part B spending and/or Medicare Part D spending. Drugs are only subject to negotiations if they are not subject to generic competition and have been on the

[1] This third negotiation cycle of the Medicare Drug Price Negotiation Program would be the first to include Medicare Part B Drugs.

market for a designated period of time—nine years for small molecules and 13 years for biologics.[2] At the conclusion of the "negotiations" process, the drug company has the options of either: (i) accepting the Department of Health and Human Services' ("HHS") offer or (ii) declining to accept the offer—at which point the drug company would face the dire choice of paying a punitive excise tax on the drug selected for "negotiations" or withdrawing from participation in the Medicare and Medicaid programs.

CMS explained that it is generally appropriate to treat different combinations of active ingredients[3] as separate, individually qualifying drugs (i.e., they are treated separately for purposes of determining eligibility for "negotiations"). For example, a combination of active ingredients would be considered a different qualifying drug than those same active ingredients combined with an additional active ingredient. However, CMS stated that there may be circumstances where two drugs are treated as the same "qualifying single source drug," particularly when the modified version has an additional active ingredient but where that additional active ingredient is not "biologically active" against the disease state for which the drug was indicated—and therefore it does not result (according to CMS) in a "clinically meaningful difference." CMS, however, is soliciting comments regarding how it may consider grouping combination drugs where one active ingredient is not active against the disease state for which drug is indicated.

CMS's proposal that a drug qualifies as a separate "qualifying source drug" only if the additional active ingredient is "biologically active" against the disease state for which the drug is indicated would adversely impact many combination drugs where a second ingredient is added for bioavailability or other purposes. For example, as described in public reporting, CMS's proposed guidance—if implemented—could negatively impact innovator pharmaceutical companies that have developed reformulated versions of oncology drugs that are injectable, which allow patients to avoid hours-long intravenous chemotherapy sessions. To effectively deliver the drug to patients while moving from intravenous to injectable form, an active ingredient that increases the bioavailability of the drug must be added. Even though the original version of the drug may be subject to "negotiations" (or will be soon), if an injectable version of the drug is treated as a separate drug, the injectable would not be subject to "negotiations" for years into the future—potentially posing higher overall returns for the innovator company. By contrast, if CMS treats the injectable version of the drug as the same "qualifying source

---

[2] On April 15, 2025, President Trump issued a drug pricing Executive Order ("EO") that, among other things, attempts to end the four-year disparity between small molecule drugs and biologics. The EO provides: "The Secretary shall work with the Congress to modify the Medicare Drug Price Negotiation Program to align the treatment of small molecule prescription drugs with that of biological products, ending the distortion that undermines relative investment in small molecule prescription drugs, coupled with other reforms to prevent any increase in overall costs to Medicare and its beneficiaries." President Trump issued another drug pricing EO on May 12, 2025, addressing most-favored nation drug pricing. See our discussion of the May 12, 2025 EO here.

[3] CMS uses the term "active moieties" interchangeably with "active ingredients."

drug" as the original—as is suggested by the draft guidance—the injectable drug would be subject to immediate price controls despite the addition of an active ingredient that improves clinical outcomes.

If CMS finalizes its guidance and acts upon it, it will inevitably trigger lawsuits by innovator drug companies. Innovators with drugs impacted by CMS guidance will likely make the following arguments (among others). First, CMS is improperly seeking to regulate through guidance; if CMS wants to set forth rules regarding what counts as a "qualifying single source drug" it must follow the Administrative Procedure Act and issue formal regulations after notice and comment. Second, CMS's position is not statutorily authorized under the IRA. Section 1192(d)(3)(B) of the IRA provides that when CMS is considering whether a drug has sufficient revenue to be qualified for "negotiations," it should use "data that is aggregated across dosage forms and strengths of the drug, including new formulations of the drug, such as an extended release formulation, and not based on the specific formulation or package size or package type of the drug." CMS's draft guidance begins by tracking the statutory language of the IRA—commenting that it is generally appropriate to treat different combinations of active ingredients as separate, individually qualifying drugs—but then creates a new requirement that to be a different drug the additional active ingredient must treat the disease state for which the drug is indicated. While the statute recognizes that one drug may have different dosage strengths, packaging or formulation such as extended release, none of those examples cover a drug that now has an entirely different formulation because it now includes an additional active ingredient. Notably, because of the Supreme Court's *Loper Bright* opinion, CMS's interpretation of the applicable statutory language will not be afforded deference by the courts.

As of this time, it is unknown what position CMS will ultimately take regarding what constitutes a "qualifying single source" drug or whether its position will succeed in court. However, where a pharmaceutical company has a modified version of a drug subject to "negotiations" in its pipeline, the company and/or potential investors will want to carefully assess when that modified drug is likely to become subject to "negotiations."

* * *

Please do not hesitate to contact us with any questions.

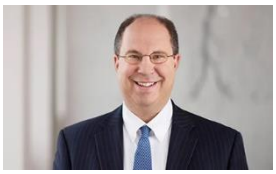
Andrew L. Bab
Partner, New York
+ 1 212 909 6323
albab@debevoise.com

Mark P. Goodman
Partner, New York
+ 1 212 909 7253
mpgoodman@debevoise.com

Maura Kathleen Monaghan
Partner, New York
+ 1 212 909 7459
mkmonaghan@debevoise.com

Winston M. Paes
Partner, New York
+ 1 212 909 6896
wmpaes@debevoise.com

Kevin Rinker
Partner, New York
+ 1 212 909 6569
karinker@debevoise.com



Paul D. Rubin
Partner, Washington, D.C.
+ 1 202 383 8150
pdrubin@debevoise.com

Melissa Runsten
Counsel, Washington, D.C.
+ 1 202 383 8073
mrunsten@debevoise.com

Jacob W. Stahl
Counsel, New York
+ 1 212 909 6874
jwstahl@debevoise.com

Abby Draper
Associate, New York
+ 1 212 909 6509
kadraper@debevoise.com

Zoe Jacoby
Associate, New York
+ 1 212 909 6521
zjjacoby@debevoise.com

Kaitlyn McGill
Associate, New York
+ 1 212 909 6817
kemcgill@debevoise.com

Adriana Kranjac Rielly
Associate, New York
+ 1 212 909 6126
akrielly@debevoise.com