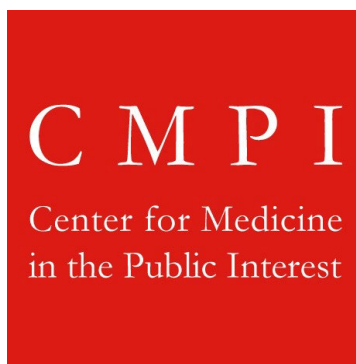




Qualifying Single-Source Drug Policy, Medicare Price Negotiation, and the Incentives for Meaningful Post-Approval Innovation

Peter J. Pitts
Former FDA Associate Commissioner
President, Center for Medicine in the Public Interest

Executive Summary

Medicare has an obligation to get a fair price for medicines. It also has patients who are still waiting for a treatment. Those obligations meet when a company decides whether to finance another clinical trial of an approved drug. CMS's qualifying single-source drug (QSSD) rules help determine the economics of that decision. Grouping an extended-release formulation with the original medicine may make sense. Applying the same rule to a treatment developed for another disease raises a harder question: what happens to the incentive to do the new research?

Manufacturers should not be able to divide Medicare spending among applications to escape negotiation. But preventing that maneuver does not settle how Medicare should recognize a substantial new therapeutic program. CMS needs to explain the distinction, and HHS needs to establish how far the statute allows the agency to act. Where legislation is required, Congress should authorize a narrowly drawn separate eligibility clock for qualifying later products. The case for that treatment must rest on clinical evidence and meaningful development work, rather than the number printed on an FDA application.

The same investment problem arises when a new indication is approved through a supplemental application. Those programs belong in this review. A clinically distinct later product may warrant a separate clock, where the law permits one; a new indication within an existing product requires a different approach. CMS should explain how its negotiation process recognizes the additional evidence and investment. Congress should consider a targeted development incentive if that recognition falls short. Established uses would keep their existing timetable. The purpose is to make worthwhile research financeable while preserving Medicare's ability to negotiate.

The Decision Before CMS

An established molecule can still pose an unanswered clinical question. Will it work in another disease? Can it reach the relevant tissue safely? What dose will help the patient, and what risks come with it? An earlier approval may supply useful knowledge, but it cannot supply those answers. CMS's grouping rules need to account for the work required to obtain them, even where the statute places the resulting products in the same negotiation category.

CMS can begin by making its clinical assessment and reasoning more explicit. HHS should examine the legal basis for a narrowly defined exception and identify any changes Congress would have to make. A separate clock requires lawful authority. Meanwhile, the agency can examine the development decisions its existing rules may discourage. Waiting for legislation need not mean waiting to understand the problem.

The Law, the Clock, and the CMS Grouping Rule

A QSSD designation determines eligibility for negotiation; it does not establish that the grouped medicines are therapeutically interchangeable. The ordinary age thresholds are seven years after approval for drugs under new drug applications (NDAs) and eleven years after licensure for biological products. Expenditure rankings, competition, exclusions, and other statutory provisions then affect selection. The negotiated maximum fair price (MFP) takes effect in a later price applicability year. Seven and eleven years are eligibility thresholds, not automatic starting dates for negotiated prices. [1]

Under CMS's 2028 guidance, dosage forms and strengths sharing an active moiety and an NDA holder are grouped, including products approved under separate NDAs. The group generally takes the earliest applicable approval date. Biological products are addressed through active-ingredient and biologics license application (BLA) holder rules. Application ownership matters here: "same manufacturer" is shorthand, not the complete legal test. Nor does a molecule's scientific description establish its approval pathway or eligibility period. [2]

Orphan-drug history can change that calculation. Beginning in 2028, the 2025 statutory amendments broaden the exclusion to qualifying drugs with one or more orphan designations whose approved indications are confined to designated rare diseases. They also address the timing calculation for former orphan drugs. Section 30.1.1 of CMS's guidance implements these provisions. Any assessment of a particular product must therefore review its designation and approval history before assigning a date. The timing example later in this paper assumes no orphan adjustment. [2,3]

The D.C. Circuit's August 18, 2026, Teva decision rules out an easy answer. The court rejected Teva's challenge to grouping Austedo and Austedo XR, which share an active moiety but have separate NDAs. Its reasoning drew on statutory provisions governing multiple applications, formulation aggregation, and price application across dosage forms.

Separate applications do not entitle a manufacturer to separate QSSD treatment. The dispute concerned an extended-release formulation; it did not assess the investment consequences of every cross-disease development program. The court separately remanded the generic “bona fide marketing” challenge without deciding its merits. [4]

A proposal built around “one NDA, one clock” would collide with that holding and give manufacturers an obvious way to divide spending. The stronger case concerns a demonstrably different therapeutic program. HHS must determine whether the statute leaves room for that distinction. FDA application boundaries, by themselves, cannot do the legal work.

The 2029 Proposal and Its Reach

CMS issued its proposed rule for 2029 and subsequent years on June 12, 2026; publication in the Federal Register followed on June 16. Comments closed August 17. At the October 5 source review for this paper, CMS’s policy page still described a final rule as anticipated in fall 2026. The provisions discussed here remain proposals as of that review. [5,6] Proposed §429.125(b)(4)(i) would change the treatment of certain fixed combinations. It addresses products with the same NDA/BLA holder in which an added component enables a different administration route for a shared active component. The preamble gives hyaluronidase as an example. CMS is concerned that separate treatment could divide spending or move utilization away from a product covered by an MFP. It says clinical benefits can be recognized during negotiation and argues that the change would not meaningfully impair innovation incentives. [6]

That concern deserves attention. A manufacturer should not be able to move the same patients into a differently administered product solely to escape negotiation. Yet a route change may reduce treatment burden or solve a delivery problem that matters to patients. CMS should show how the evidence for that benefit enters its negotiation decisions. Even where aggregation is legally required, the clinical contribution remains relevant.

This fixed-combination proposal addresses a different issue from the cross-disease development examined here. EMPAVELI and SYFOVRE illustrate the existing shared-moiety framework. They do not involve adding an ingredient to enable delivery. Each issue requires its own scientific and legal analysis; bundling them together would obscure the choices CMS needs to make.

What Pegcetacoplan Shows

FDA approved EMPAVELI under NDA 215014 for paroxysmal nocturnal hemoglobinuria (PNH) in 2021. Its labeling also includes C3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis in patients aged twelve and older, to reduce proteinuria. SYFOVRE, approved in 2023 under NDA 217171, treats geographic atrophy

secondary to age-related macular degeneration. Both contain pegcetacoplan; EMPAVELI is administered subcutaneously and SYFOVRE intravitreally. Both are NDA products. [7–9]

Clinical dimension	EMPAVELI	SYFOVRE
Illustrative patient population	PNH; labeled kidney-disease populations	Geographic atrophy secondary to age-related macular degeneration
Administration	Subcutaneous infusion	Injection into the vitreous of the eye
Development question	Systemic disease treatment	Effect of local ocular treatment on geographic atrophy
FDA application	NDA 215014	NDA 217171
Policy question	Weight to give shared chemistry versus different clinical development.	Whether the later program warrants distinct recognition under Medicare policy.

SYFOVRE’s FDA review describes two pivotal phase 3 studies assessing reduction in geographic-atrophy lesion growth. It identifies a new dosage form and administration route for pegcetacoplan, while drawing on some nonclinical information from the systemic product. That is how development can work: earlier knowledge supports a later program, which must still establish its own disease-specific evidence. [9,10]

Reusing knowledge is good science. Repeating work that already answers a question wastes time, money, and potentially patients’ participation in research. The important question is what remains to be proved. Evidence supporting a systemic use does not establish the benefit of an ocular treatment. CMS should examine that additional work rather than treating shared knowledge as evidence that little new research was needed.

The comparison raises a classification question. It does not establish that either product has been selected for negotiation or assign either a future MFP date. Those determinations require a product-specific review, including former-orphan provisions. Medicare coverage and payment also depend on the benefit and treatment setting. The comparison should be read within those limits.

The Next Trial Has to Be Financed

The investment decision comes before FDA has an answer. A sponsor considering another use must weigh trial costs, the chance of failure, recruitment time, competing treatments, and the revenue an approval might produce. The fact that a medicine works in one disease can make another program scientifically attractive. It cannot make that program financially viable on its own.

The difficulty becomes acute when a promising use emerges late in a molecule's life. Clinical experience, mechanistic research, or a better understanding of the disease may reveal an opportunity that nobody could have justified at the first approval. If Medicare's clock follows the earlier product, little time may remain between the new approval and negotiated pricing. The fact that a company has recovered its investment in the original product does not pay for the next trial. Those are new dollars committed to a new clinical question.

There need not be a new brand or dosage form for this problem to arise. A company seeking an additional indication through a supplemental application still has to finance new studies while the product's negotiation timetable continues, subject to statutory exclusions. Investors will ask whether the additional return justifies the additional cost and risk. The application route does not make that question disappear.

How Approval Sequence Can Affect a Later Program

Event	Assumed timing	Implication
Original NDA approval	Year 0	Starts the ordinary grouped-drug age calculation.
New-disease program begins	Year 5	The sponsor commits additional capital while the original clock continues.
Grouped drug selected, if otherwise eligible	Year 7 or later	Selection depends on rankings and applicable law; it is not automatic.
New-disease approval	Year 9	The later product may join a group whose selection process is already underway or completed.
Negotiated pricing applies	Applicable future price year	The later approval does not necessarily provide a fresh seven-year eligibility interval.

The example below assumes the same application holder, no marketed generic, no exclusion, and expenditures sufficient for selection. It isolates the effect of the grouped-drug clock. The dates are hypothetical; they establish no guaranteed period of exclusivity, patent protection, or profitability. Negotiation changes the prospective revenue calculation rather than eliminating all revenue.

Some programs will remain attractive under earlier negotiated pricing. A large market, manageable trial costs, or substantial demand outside Medicare may sustain investment. A small population, expensive study, lengthy recruitment, and heavy Medicare exposure can push a different program below the financing threshold. That is the trial CMS should

worry about: scientifically worth pursuing, but no longer worth funding under the expected economics.

CMS should ask sponsors for documented financing decisions and test how much the grouping rule mattered alongside scientific risk, capital markets, and competition. This paper assigns no numerical estimate to programs abandoned because of QSSD policy. The evidence needed for a defensible estimate is precisely what the agency should seek.

Drug Innovation Rarely Arrives as a “Eureka” Moment

Much of drug innovation is incremental. Researchers learn more about a mechanism, an organ system, a dose, or a patient population and discover a use that the original development program never established. Sometimes a delivery method makes treatment practical for patients who could not otherwise receive it. These advances require trials. An untested indication gives the patient neither a reliable answer about benefit and risk nor an additional approved treatment.

The “Eureka” story makes good copy. Drug development requires experiments, failures, financing, and clinical evidence long after the flash of insight. A familiar molecule may open an important therapeutic opportunity; novelty alone tells us little about patient benefit. A pricing rule that makes established molecules progressively less attractive to study risks discouraging the very work that turns accumulated knowledge into another treatment. CMS needs a better yardstick than chemical age.

There is also a commercial reality CMS is right to confront. Manufacturers can change a product to protect an established franchise while adding little for patients. A brand change, another application, or a large expenditure does not establish clinical value. The agency needs to examine what the development program contributed and whether special treatment would support useful research or simply shelter existing sales.

A Standard Grounded in the Development Work

FDA and CMS should assemble a shared record for scientifically complex follow-on programs. FDA can explain what the later approval required, which findings carried over from earlier work, and which questions needed new evidence. CMS would use that record to make the Medicare determination and explain its legal basis. Scientific consultation would give CMS a firmer foundation without asking FDA to endorse a price or an investment return.

The criteria below are a proposed standard. CMS could use them to make clinical assessment and negotiation more transparent under existing authority. Applying them to a separate eligibility clock would require an additional legal determination and, where necessary, legislation.

Criterion	Evidence to examine	Guardrail
Different therapeutic objective	Distinct disease, population, and treatment purpose	A relabeled subgroup or brand change is insufficient.
Substantial new evidence	Pivotal trials, endpoints, and disease-specific benefit-risk evaluation	Application count and trial expenditure alone do not prove value.
Clinically meaningful contribution	Evidence of patient benefit or an important treatment need	Avoid requiring head-to-head superiority where no suitable comparator exists.
Administration or exposure differences	New delivery risks, dosing, tissue exposure, and supporting studies	A route change is supporting evidence, not an automatic exemption.
Investment attributable to the later program	Auditable costs, timing, shared studies, and prospective commitments	Exclude duplicate accounting and unsupported allocation of original costs.
Protection against circumvention	Population overlap, switching strategy, and continuity of the original product	No resetting the older product's clock or sheltering its established sales.

A different disease supported by substantial new evidence should weigh heavily. Delivery improvements should count where the evidence shows a contribution that matters to patients. Head-to-head superiority should not become a universal requirement: an appropriate comparator may not exist, and such a trial may be infeasible. The standard should examine the science consistently across separate and supplemental applications. Meeting it would support consideration for an incentive; it would not automatically award a new clock.

Any statutory exception should attach to the qualifying later product. The original product would retain its timetable. Congress would need to specify how shared indications, supplemental applications, later combinations, and sequential programs are treated. Otherwise, an exception meant to support a valuable development effort could become a succession of clock resets.

What CMS Can Do—and Where Congress Is Needed

CMS should publish worked examples before sponsors commit resources. An ordinary extended-release formulation, a different-disease product sharing an active moiety, a delivery-enabling combination, and a substantial supplemental indication would expose the relevant distinctions. Each example should trace grouping, age calculations, exclusions, selection, and MFP application. Sponsors and the public should be able to follow the agency's reasoning.

A structured FDA consultation would help resolve the scientific questions in difficult classifications. CMS should identify each agency's responsibilities and, where permitted, allow sponsors to correct application histories or supply missing clinical information before the administrative deadlines. The process would have to respect statutory limits on review; it should not be presented as a new appeal right.

The negotiation record should show what a substantial later program added. Congress already requires consideration of R&D costs and recoupment, federal support, applications and approvals, and therapeutic evidence. [11] CMS should explain how the later program's attributable investment, additional evidence, and clinical contribution enter that assessment, including when approval comes through a supplement. That recognition must operate within statutory price ceilings. It would neither establish cost-plus reimbursement nor create an indication-specific MFP or separate eligibility period. Sponsors nevertheless need to understand what recognition of their additional work means in practice.

CMS also owes the public an examination of its innovation assumptions. It should seek documented financing decisions and test their sensitivity to negotiation timing, clinical risk, and Medicare exposure. Separate-product and supplemental-indication programs should be analyzed distinctly. The assessment should also measure the risk CMS identifies on the other side: fragmented spending and shifts in utilization that undermine negotiation. Both concerns warrant evidence.

Changes that may require Congress

HHS counsel should answer the threshold legal question: does the statute permit narrower grouping for a genuinely distinct therapeutic program? If the answer is no, CMS should say so and recommend a legislative remedy. Congress should receive proposed eligibility criteria, a budget analysis, and safeguards that preserve the older product's negotiation status. That would turn an innovation concern into a proposal lawmakers can evaluate.

Congress has two different design problems. A clinically distinct later product meeting the evidentiary standard proposed here could receive a bounded separate eligibility clock. A substantial additional indication within an existing product could receive a defined development incentive if recognition during negotiation proves inadequate. The latter would have to attach to the qualifying research and approval without sheltering established sales. Restarting the clock for the entire product after every supplemental approval would defeat that purpose.

Legislation would need to set eligibility, the start date and duration, limits on repeated use, and treatment of existing selections. For supplemental indications, it must also identify how the qualifying use and benefit would be administered. The budget analysis should examine the cost of the incentive and the likelihood of paying for research that would have

proceeded anyway. These choices belong in the legislation, rather than being left for CMS to infer from authority it may not have.

Programs already underway require explicit transition rules. Sponsors need to know how the new standard would apply to committed research, and Medicare needs certainty about existing selections and agreements. Prior development expectations merit consideration, but they do not establish an automatic entitlement to exemption or cancellation of an agreed MFP.

Putting the Review to Work

CMS should put a timetable on this work. The proposed milestones below would produce a legal assessment, a scientific framework, and findings that support administrative action or a recommendation to Congress. They are recommendations for the agency, not commitments it has already made.

Timing after CMS initiates review	Deliverable	Responsible participants
First 60 days	Legal assessment of administrative options; scope and evidence questions	CMS policy staff and HHS counsel
Within 120 days	Clinical assessment framework, worked examples, and targeted evidence request	CMS, FDA, patient and clinician input
Within 180 days	Published findings, implementation steps, and legislative recommendation if needed	CMS and HHS leadership
Annually thereafter	Development, access, spending, and program-integrity review	CMS analytical staff with appropriate external research

Evaluation should begin with trials being started, continued, or stopped. Approvals alone look backward at investment decisions made years earlier. CMS should also track treatment burden, access, Medicare net spending, and movement between older and later products. Apparent savings may reflect costs shifted to another setting or therapy; claimed innovation benefits need evidence that additional development occurred.

The comparisons will require care. Companies pursuing follow-on research differ from those that do not, and investment conditions change for reasons unrelated to Medicare policy. CMS should define comparison groups in advance, disclose the limits of its

analysis, and protect confidential business evidence. A result that can withstand examination is more useful than an impressive headline estimate.

Concluding Thoughts

Medicare can count the savings from a lower drug price. It cannot directly measure the benefit of a trial that never took place. That gap should make CMS careful about declaring a pricing policy successful on the strength of its immediate budget effects alone. Patients waiting for another treatment have a stake in the next investment decision, and their interests belong in the calculation.

The scientific knowledge built around an approved medicine is an asset worth putting to work. A promising new indication still needs evidence, and producing that evidence still requires someone to commit capital before knowing whether the trial will succeed. Washington should want sponsors to ask the next useful clinical question. Making an established molecule progressively less attractive to study risks wasting the knowledge that could bring another treatment to patients.

CMS should demand evidence from manufacturers and be prepared to defend its own assumptions about innovation. Its next step should be to explain how negotiation recognizes substantial new development, examine the financing consequences of its rules, and identify where Congress must act. A new application number deserves no automatic reward. A credible program to answer an important clinical question deserves a policy that gives investors a reason to fund the work. Patients depend on Medicare for affordable treatment today. They also depend on somebody financing the trial that may give them a better option tomorrow.

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