UNIVERSITY of WASHINGTON
SCHOOL OF PHARMACY
The Comparative Health Outcomes, Policy, & Economics (CHOICE) Institute

July 31, 2023

VIA ELECTRONIC FILING - REGINFO.GOV Office of Management and Budget (OMB)

725 17th St NW
Washington, DC 20503
Attn: OMB Desk Officer

Re: ICR Reference Number: 202306-0938-013. Information Collection Request for Negotiation Data Elements under Sections 11001 and 11002 of the Inflation Reduction Act (CMS-10847).

To the OMB Desk Officer:

We are submitting this letter as independent health economists with a long history of collaboration on pharmaceutical policy analysis. In the interests of transparency, we declare that much of this work has been funded by pharmaceutical companies. We appreciate the opportunity to submit comments on the Information Collection Request for Negotiation Data Elements under Sections 11001 and 11002 of the Inflation Reduction Act (CMS-10847). Of course, the views here are our own, and are not meant to reflect the views of the organizations with which we are affiliated.

We submitted a similar letter on April 14 as a comment on the Medicare Drug Price Negotiation Program: Initial Memorandum. We have since published an article in Health Affairs Forefront (June 5, 2023), which is attached; thus, we will only re-iterate the key points in this cover letter.

We would like to comment in particular on Section 1193(e)(1) on "Manufacturer-specific data." This section requests information on a number of items related to research and development (R&D) costs, production and distribution costs, recoupment, and related revenue items. We believe this request reflects a fundamental misunderstanding of the economics of the regulated U.S. and global pharmaceutical marketplace. Even if compliance with this request for R&D costs were possible (which is highly questionable), the submitted estimates would be irrelevant to the determination of the Maximum Fair Price (MFP) for a specific product. This is not to say that evidence and value do not matter. Indeed, in determining MFP through negotiation, the statue does specify what we see as the critical factor: ''(A) The extent to which such drug represents a therapeutic advance as compared to existing therapeutic alternatives and the costs of such existing therapeutic alternatives."

The current market for innovative medicines is regulated through a combination of intellectual property protection (patents and exclusivities) and regulatory (Food & Drug Administration; FDA) statutes and regulations. The result is what economists call a "market design" that incentivizes medical innovation by offering potentially high (but uncertain) rewards for high-risk investments, but then uses competition to keep down prices at later stages of the product life cycle.

The Inflation Reduction Act (IRA) does not directly or explicitly propose to move from this high-risk/high-reward market design to an alternative market design that is an essentially "cost-plus" marketplace with a regulated rate of return. But this may be the consequence of the proposed negotiation

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process for a MFP. While there can be an argument for such a cost-plus regulation in some markets where monopoly power exists — such as parts of the utility sector — it makes little sense in the complex life sciences industry with many competitors: many of whom will fail due to the complexity of the science, and with government granting of temporary market power only for successful products. We assume that CMS is not seeking to change the fundamental life sciences R&D market design which is based on incentives to reward medical advances with such temporary market power. In which case, these historical R&D costs are irrelevant to the value that patients and payers place on any specific product.

In order to explore the challenges of estimating R&D costs, consider the estimates of drug development costs that have appeared in the literature. As the 2021 Congressional Budget Office report (CBO, 2021) makes clear, success rates vary by therapy area, reflecting the diverse scientific challenges, but also making an attribution of relevant failure costs even more difficult. The literature—Cutler (2020);Prasad and Mailankody (2017); Wouters et al. (2020); DiMasi et al. (2016); Wong et al. (2019)— indicates the challenges of estimating R&D costs attributable to one product, and the difficulty of taking account of failures at the level of one company.

Questions about the current costs of the manufacturing and distribution of a product near the end of its exclusivity could conceivably be answered. Companies do have some idea of what is called the current "cost of goods": indeed, many put effort into reducing them. Again, however, this ignores the fact that the current market design aims to promote generic and biosimilar competition at the end of the exclusivity period. With competitive market forces, entrants will compete on price, thereby reducing product prices to a point that will sustain competition among multiple entrants, thus, approximating the social marginal cost of manufacturing and distribution (including marketing costs). In other words, as long as the end of exclusivity is enforced and the transition to generic and biosimilar competition promoted, there is really no need to collect information on the cost of goods of specific products. The reality is that market competition will generate a market price that approaches the marginal cost of production and distribution. No further negotiation is needed.

Finally, we would like to re-iterate and emphasize that the key factor that should be considered in Medicare Drug Price Negotiation Program to better align price with value is the ''(A) The extent to which such drug represents a therapeutic advance as compared to existing therapeutic alternatives and the costs of such existing therapeutic alternatives." Pursuing that objective would provide better incentives that are more likely to promote dynamic efficiency, i.e., the optimal amount and types of R&D investments to improve population health and well-being. In other words, implementation of the legislation should either focus on an MFP linked to value (driven by comparative effectiveness) or an MFP linked to simulating a post-patent/ post-exclusivity market with potential generic or biosimilar entry. In either case, R&D costs are irrelevant, even if they could be appropriately attributed.

Summary Recommendation:

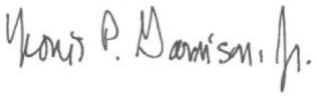
In terms of the implementation of the MFP under IRA, we would recommend: (a) removing any link to use R&D costs to reduce or increase the price derived from the use of comparative effectiveness research; (b) focusing on the estimation of the value that the product is delivering to patients, families, and the health system; (c) avoiding completely the related erroneous notion or calculation of R&D cost "recoupment"; and (d) focusing on ensuring more competitive entry from generic and biosimilar manufacturers.

We appreciate your consideration of our comments as you refine the Drug Price Negotiation Program and its policies. We look forward to continuing to work with CMS to ensure that this program is implemented

to promote more efficient development of and equitable access to innovative medicines for all Americans, while producing knowledge that is beneficial for the health and well-being of all persons globally.

Please contact us if you have any questions regarding our comments.

Yours sincerely,



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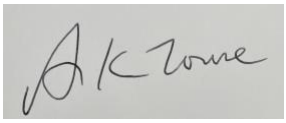

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Attachment:

Garrison LP, Towse A. "The IRA's Request For Product-Specific R&D Cost Information: Short-Sighted And Irrelevant. Health Affairs Forefront. June 5, 2023, DOI: 10.1377/forefront.20230602.550273

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The IRA's Request For Product-Specific R&D Cost Information: Short-Sighted And Irrelevant

Louis P. Garrison, Jr., Adrian Towse

JUNE 5, 2023 **DOI:** 10.1377/forefront.20230602.550273

The Inflation Reduction Act <https://www.congress.gov/bill/117th-congress/house-bill/5376/text> (IRA) of 2022 Section 1193 states that when engaging in drug price negotiation, the Secretary of Health and Human Services should consider, among multiple factors, manufacturer-submitted data on the drug's "research and development costs," as well as "the extent to which the manufacturer has recouped research and development [R&D] costs." And in its initial March 15, 2023, guidance <https://www-cms-gov.offcampus.lib.washington.edu/files/document/medicare-drug-price-negotiation-program-initial-guidance.pdf> for implementation of the Negotiation

Program, the Centers for Medicare and Medicaid Services (CMS) proposes to request detailed information on the costs of R&D and other factors.

We believe this request for R&D cost information reflects a fundamental misunderstanding of the economics of the regulated US and global pharmaceutical marketplace. Writing in this journal in 2004 on the pros and cons of alternative approaches for Medicare drug pricing, Professor Joseph P. Newhouse said: "Large drug companies have many products, and allocating joint costs across those products is arbitrary. … companies must cover the R&D costs of their unsuccessful drugs or go out of business, so reimbursing only those costs that can be directly associated with drugs on the market seems pointless." And more recently in *Forefront*, Henry Grabowski and Richard Manning had the following to say about *hepatitis C* drugs: "The sellers of these drugs did not charge high prices because they had spent a lot of research and development; they were able to set high prices because the products generated remarkable new value to patients."

For these reasons, we believe that any estimated R&D costs submitted under the law would be irrelevant to the determination of the maximum fair price (MFP) for a specific product. This is not to say that evidence and value do not matter. Indeed, in determining MFP through negotiation, the statute does specify what we see as the valid critical factor for the negotiation: "The extent to which the drug represents a therapeutic advance as compared to existing therapeutic alternatives and the costs of these alternatives."

Current Market Design

The current market for innovative medicines is regulated through a combination of intellectual property protection (patents and exclusivities) and regulatory statutes and regulations. The result is what economists call a "market design" that incentivizes medical innovation by offering potentially high (but uncertain) rewards for high-risk investments, but then uses competition to keep down prices at later stages of the product life cycle. Patent-protected Food and Drug Administration-approved products that offer additional patient benefit have some degree of monopoly power through a period of patent and exclusivity protection that averages about 14 years <https://pubmed-ncbi-nlm-nih-gov.offcampus.lib.washington.edu/28892528/> . During this period, the manufacturer has the exclusive right to market their compound: Copies are not allowed to be marketed. This does not mean, however, that they do not face competition in the same drug class: Other compounds with the same biological target and mechanism of action can compete with them.

The market design for innovative medicines is "oligopolistic competition" among single-source products. The best product in the class may receive a premium price and substantial rewards during this period of protection. But, by law, eventually the effective market exclusivity period will end and either generic or, in the case of biologics, biosimilar versions will be allowed to compete with the originator and others in the drug class. The value of this monopoly power is thus limited by market competition and by time.

It is also well known that about nine in 10 products fail during development <https://pubmed-ncbi-nlm-nih-gov.offcampus.lib.washington.edu/29394327/> ; there is no guarantee that their costs are recouped in any way. Rather, the market design is that the rewards to the investors in successful products will have to cover the costs of failures to sustain the market. The rewards to any one product, in fact, should be viewed against the cost of the 10 products needed to yield that one success. Thus, the product-specific R&D costs of any one product are irrelevant to the rewards it does (or does not) earn in the marketplace.

Indeed, imagine that an innovator discovered the cure for Alzheimer's disease based on a brilliant insight into molecular biology with a mechanism of action that was so compelling that it gained approval based on a small, low-cost trial using a surrogate marker that everyone accepted. Would we say that that innovator should only receive a small reward for such a miracle cure because its product-specific development costs were low? Some might say, 'yes, that is exactly what should happen.' But such an approach ignores how the incentives in this investment system have operated for more than 50 years.

For example, many billions of dollars have been spent by the industry on Alzheimer's disease research and thus far very little of this investment has been recouped. This lack of success is, of course, a concern for patients and their families, but it shows the market design is working. Money is going into R&D for diseases that matter even where the science is difficult. That is because companies see high returns if they can deliver treatments that provide additional health benefit to patients.

Moving To Cost-Plus Regulation?

The IRA does not directly or explicitly propose to move from this high-risk/high-reward market design to an alternative "cost-plus" marketplace with a regulated rate of return. But even so, such a shift may result from the proposed negotiation process for a MFP. To be sure, there is a reasonable argument for such a cost-plus regulation in some markets where monopoly power exists—such as parts of the utility sector. But it makes little sense

in the complex life sciences industry with many competitors, many failed products, and the government's granting of temporary market power only for successful products. If we are to assume that CMS is not seeking to change this fundamental market design—and it has not indicated any interest in doing so—then historical R&D costs are therefore irrelevant to the value that patients and payers place on any specific product.

Infeasibility Of Collecting Historical R&D Costs

Add to these challenges the fact that this program will apply to products that have been on the market for at least seven years. We surmise that companies will struggle to accurately account for R&D costs on a product-specific basis. Historically, manufacturers have simply not taken this approach. Although estimates of the cost of specific trials could, in principle, be produced, the costs of all the individuals in the biopharmaceutical organization who are working on multiple products during the pre-launch period—including discovery and pre-clinical phases—are not routinely tracked or allocated to a specific product. Thus, it would most likely be infeasible to provide this information accurately. Of course, assumptions and estimates could be made, but to what end? They are irrelevant to the value of any specific product to Medicare beneficiaries, and they would not in any case adequately address the cost of failures.

To explore the challenges of estimating R&D costs, consider the estimates of drug development costs that have appeared in the literature. A 2021 Congressional Budget Office (CBO) report <https://www-cbo-gov.offcampus.lib.washington.edu/publication/57126> makes clear that success rates vary by therapy area. This reflects the diverse scientific challenges and makes it even more difficult to attribute relevant failure costs. Identification and attribution of discovery and pre-clinical costs is also challenging. The duration of the R&D process is important as it affects the cost-of-capital component of any estimate of "successful" R&D expenditure.

Specifically, the CBO discussed three studies:

Vinay Prasad and Sham Mailankody (2017) <https://pubmed-ncbi-nlm-nih-gov.offcampus.lib.washington.edu/28892524/> dealt with earlier research (that is, discovery and pre-clinical) expenditures and areas with a large number of failures by including all R&D costs for single-product companies. However, this has a survivor bias: The R&D costs of companies working in the same areas that went out of business were not included.

Olivier Wouters and colleagues (2020) <https://pubmed-ncbi-nlm-nih-gov.offcampus.lib.washington.edu/32125404/> used Securities and Exchange Commission filings to estimate discovery and pre-clinical expenditures and the analysis by Chi Heem Wong and colleagues (2019) <https://pubmed-ncbi-nlm-nih-gov.offcampus.lib.washington.edu/29394327/> of success rates by clinical area to multiply up estimates in a way that accounts for failures. In other words, they attempted to estimate the "systemwide" costs associated with bringing an individual product to market. As David Cutler (2020) <https://pubmed-ncbi-nlm-nih-gov.offcampus.lib.washington.edu/32125384/> points out, Wouters and colleagues recognize that they are likely to have underestimated pre-clinical costs because of the difficulty of linking them to a specific molecule.

Joseph DiMasi and colleagues (2016) <https://pubmed-ncbi-nlm-nih-gov.offcampus.lib.washington.edu/26928437/> used aggregate company R&D expenditures to estimate discovery and pre-clinical expenditures along with success/failure rates taken from a broader industrywide database of clinical success rates by stage. Again, this is an attempt to estimate costs including non-product-specific discovery and pre-clinical costs and take account of failures that are not specific to the company concerned. The authors also sought to identify post-launch R&D costs, recognizing that evidence of comparative effectiveness is increasingly collected post-launch.

Each of these studies indicate the challenges of estimating R&D costs attributable to one product, and the difficulty, at the level of one company, of accounting for failures.

Promoting Generic And Biosimilar Competition

Conceivably, one could answer questions about the current costs of manufacturing and distributing a product near the end of its exclusivity. Companies do know their current "cost of goods" and indeed, many strive to reduce such costs. However, elevating such a measure would ignore the fact that the current market design aims to promote generic and biosimilar competition at the end of the exclusivity period. With competitive market forces, entrants will compete on price. This typically reduces product prices to a point that will sustain competition among multiple entrants, thus, approximating the social marginal cost of manufacturing and distribution (including marketing costs). In other words, as long as the end of exclusivity is enforced and the transition to generic and biosimilar competition promoted, there is really no need to collect information on the cost of goods of specific products.

Indeed, using price control to force down the price of the innovator's product will reduce the incentive for generic and biosimilar company entry. Studies of European markets, where pricing policies affect post-patent markets differently in different countries, have shown, [for example <https://pubmed-ncbi-nlm-nih-gov.offcampus.lib.washington.edu/15452754/>](https://pubmed-ncbi-nlm-nih-gov.offcampus.lib.washington.edu/15452754/) : "On the one hand, systems that rely on market-based competition in pharmaceuticals promote a clear distinction between firms that act as innovators and firms that act as imitators after patent expiry. Here, original products enjoy premium prices and exclusivity profits under patent protection, and face fierce price competition after patent expiry. On the other hand, in systems that rely on administered prices, penetration by generic drugs tends to be rather limited."

The "delay request" mechanism in the IRA to allow biosimilar entry and use competition rather than set an MFP—which by implication will make competitive entry harder—supports the view that price control makes entry less attractive for generic and biosimilar manufacturers. The reality is that market competition will generate a market price that approaches the marginal cost of production and distribution. No further negotiation is needed.

Focus On Therapeutic Value To Promote Dynamic Efficiency

Finally, we must emphasize the key factor that should be considered in the Medicare Drug Price Negotiation Program to better align price with value: "(A) The extent to which the drug represents a therapeutic advance as compared to existing therapeutic alternatives and the costs of these alternatives."

Policies aimed at pursuing that objective would provide better incentives more likely to promote dynamic efficiency—in the form of optimizing the amount and types of R&D investments to improve population health and well-being.

In other words, we believe officials implementing the IRA should either focus on an MFP linked to value, driven by comparative effectiveness; or an MFP linked to simulating a post-patent/post-exclusivity market with potential generic or biosimilar entry. In either case, R&D costs are irrelevant, even if they could be appropriately attributed.

In summary, the Secretary should: abstain from attempting to use R&D costs to reduce or increase the price derived from the use of comparative effectiveness research; focus on the estimation of the value that the product is delivering to patients, families, and the health care system; avoid-completely the related erroneous notion or calculation of R&D cost "recoupment"; and focus on ensuring more competitive entry from generic and biosimilar manufacturers.

Authors' Note

Lou Garrison has received personal consulting fees and research support from a variety of life science companies and professional organizations. No funding was received for his contributions to this article. Adrian Towse has received personal consulting fees from pharmaceutical, vaccine, and diagnostic companies, and the Office of Health Economics receives consulting fee income from pharmaceutical, vaccine, and diagnostic companies. No funding was received for his contributions to this article.

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