Government Scorekeepers Likely Underestimate the Impact of Lower Drug Costs Now Act (H.R.3) on Investment in Innovative Medicines

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Executive Summary

In 2019, the U.S. House of Representatives passed the "Lower Drug Costs Now Act" (H.R.3), which would require the federal government to set the price of many prescription medicines. The Congressional Budget Office (CBO), which is charged with calculating the costs of potential legislation to guide policymaking, estimated that if H.R.3 were enacted, government-set prices for medicines would reduce direct federal spending by nearly $500 billion between 2023 and 2029.[1] H.R.3 would also significantly impact biopharmaceutical industry revenues. Research suggests that industry revenues could decline by $1,275 billion to $1,655 billion between 2020 and 2029, which translates to a reduction in U.S. brand drug revenue of 34 percent to 44 percent across the Medicare and commercial markets.[2]

Despite H.R.3's unprecedented impact on the U.S. market, the world's leading market for biopharmaceuticals, CBO projected that only 8 to 15 fewer new medicines would be developed over the next 10 years, with an additional 30 new medicines failing to reach the market in the following decade. Given the challenges inherent in forecasting the impact of a policy change of this magnitude on future innovation—and the potentially serious implications for drug development and consequently the health of the U.S. population—Charles River Associates (CRA) was retained by the Pharmaceutical Research and Manufacturers of America (PhRMA) to review CBO's approach to estimating the impact of H.R.3.

Following a review of the methods and related literature along with expert interviews, CRA concludes that there is no sufficient analogue to estimate the effect of a policy of H.R.3's magnitude and that CBO likely underestimates the true impact of H.R.3 on future incentives for innovation. Therefore, policymakers have not been provided with sufficiently reliable estimates to adequately assess the risk of such a decision. In particular, CRA concludes that CBO's estimate:

- **Undervalues the impact of the U.S. market as the single largest source of industry revenue due to lack of reliable, analogous evidence:** The US represents 41 percent of global biopharmaceutical revenue[3] and is a significant force for stimulating investment in new medicines. CBO relies on estimates of the effect of a change in market size on investment in new medicines from countries with far smaller market sizes. In contrast, investors and developers are significantly more likely to be responsive to changes in U.S. demand. Extrapolation from smaller, price-regulated markets may underestimate the effects of a policy change on the U.S. market.

- **Ignores the likely disproportionate impact of the policy on high risk, high unmet need disease areas:** CBO computes an average effect across all drugs and fails to recognize the differentially large impact of the policy on particular disease states, specifically oncology and rare disease, which would be de-facto targets of the policy. These drugs have distinct development cost profiles and challenges and would treat many diseases for which there are no current options.

- **Underestimates the impact of industry revenue reductions on R&D incentives by failing to make needed mathematical adjustments:** CBO applies a revenue impact estimate from an

academic study which is dependent on a specific magnitude of change in revenue. To accurately estimate the impact of a policy change as large as H.R.3, the impact estimate must be adjusted for market size before being applied. In other words, CBO should have replicated the academic study's model to compute an impact estimate that is relevant to H.R.3, rather than simply applying an average estimate, which would understate the impact.

- **Ignores the complexity and mobility of the investor market which could readily shift to more profitable industries:** In relying on studies which use old data, CBO fails to consider that drug investment is increasingly dynamic, and capital is mobile. Today, smaller biotechnology firms make a sizeable contribution to the development of new medicines.[4] These smaller firms rely to a large extent on venture capital (VC) and on deals and partnerships with large biopharmaceutical companies. In the face of an expectation of lower returns on what are typically highly uncertain investments, venture capital could easily shift to other portfolios offering greater expected returns. At the same time, large biopharmaceutical companies with significantly reduced free cash flow will have less to invest in acquiring or partnering with venture-backed start-ups. These dynamics are ignored in evidence relied on by CBO, which are reflective of an era less reliant on small biotechnology companies and outside investors.

Understanding the true impact of H.R.3 on future innovation is not an easy task, but CBO's implicit assumptions based on outdated evidence and simplified modeling could have dangerous unintended consequences if relied upon as conclusive. Even for an organization as sophisticated and adept as CBO, forecasting the impact on innovation of a policy change of unprecedented magnitude, in the world's biggest market for medicines is impossible, as there are no relevant analogues for change on this scale. Given the lack of similar analogues and limitations in CBO's computational approach to estimating H.R.3's impact on future innovation, we conclude that CBO likely underestimates the true impact of H.R.3 and that policymakers have not been provided with a sufficiently accurate estimate of the cost of the policy to adequately balance the risk of such a decision.

Background

The "Elijah E. Cummings Lower Drug Costs Now Act," first introduced in the House of Representatives as H.R.3 on September 19, 2019, would require the government to set prices for certain brand medicines that account for a high share of spending.[5] Government price-setting would represent a significant departure from today's U.S. biopharmaceutical market, where prices are typically negotiated between private payers and biopharmaceutical companies for most people with insurance, and price intervention by the federal government is limited to Medicaid and to defined groups such as individuals insured via the Department of Veterans Affairs.

The upper limit for prices set by the government would be fixed at a maximum of 120 percent of the average prices for brand medicines charged in six designated foreign countries (Canada, Australia, Germany, France, Japan, and the United Kingdom). Biopharmaceutical companies would face steep financial penalties if they failed to accept these prices, which would also be made available to payers in the commercial market. Should a drug manufacturer refuse to abide by the government-set price for a selected medicine, the manufacturer would be subject to an excise tax penalty of up to 95 percent of the medicine's sales.

H.R.3 is expected to have a significant impact on biopharmaceutical industry revenues. Research suggests that industry revenues could decline by $1,275 billion to $1,655 billion between 2020 and 2029, which translates to a reduction in U.S. brand drug revenue of 34 percent to 44 percent across the Medicare and commercial markets.[6]

The Congressional Budget Office (CBO) serves as an advisor to the U.S. Congress on the federal budget impact of proposed legislation. Additionally, CBO may estimate second-order effects such as industry investment in research and development, which can have potential budgetary implications. In analyzing the impact of H.R.3[7], CBO estimated that:

- 8 to 15 fewer drugs would be developed and made available to the U.S. market over the next 10 years, with an additional 30 new medicines failing to reach the market in the following decade;
- Between 2020 and 2029, price negotiation would reduce direct federal spending by $456 billion and restrictions on price increases would reduce direct federal spending by another $36 billion; and
- Future global biopharmaceutical revenues from new drugs would be reduced by 19 percent.[8]

H.R.3 was reintroduced in the 117th Congress on April 22, 2021 with few changes to its core provisions.[9] CBO will likely release a new score for the bill, but it is unlikely that CBO's scoring methodology will substantially differ from the last Congress.

Given the challenges inherent in forecasting the impact of a policy change of this magnitude on future innovation—and the potentially serious implications for drug development and consequently the health of the U.S. population—Charles River Associates (CRA) was retained by the Pharmaceutical Research and Manufacturers of America (PhRMA) to review CBO's approach to estimating the impact of H.R.3.

Our Approach

CBO's estimate of a modest innovation impact from H.R.3 stems partly from its likely understated estimate of H.R.3's impact on biopharmaceutical company revenues. For example, CBO assumes that the government set price is most likely to be set at the upper end of the range of possible prices, when it could also be set at the lower end of the range.[10,11] Also, CBO assumes companies can increase their prices outside the U.S. when in reality payers outside of the U.S. are unlikely to accept a higher price and those payers have policies in place such as Health Technology Assessment that may not allow a price increase or support significantly higher launch prices.

The focus of CRA's review, however, is on CBO's assessment of the future **innovation impacts** that result from H.R.3's revenue reductions. We applied a three-step process to examine CBO's estimate of the impact of H.R.3 on future innovation:

1. **Review of CBO's methodology and technical assumptions:** CBO does not provide details on its methodology. Therefore, our conclusions are drawn based on information from interviews with the authors of the report and inference from the report's conclusions.

2. **Review of academic studies:** In addition to the three key papers referenced by CBO, we reviewed six other studies that examine the relationship between price controls, market size and innovation.

3. **Interviews with authors of two of the (three) studies referenced and CBO analysts:**[12] Each interview was conducted over 30-40 minutes via teleconference. We discussed how CBO may have used the estimates from the authors' respective studies, as well as the potential limitations and associated implications for forecasting the impact of H.R.3 on the development of new medicines.[13]

CBO's Methodological Approach and Assumptions

In economics, "elasticity" describes the sensitivity of the response in one variable to a change in another. In the context of developing new medicines, elasticity attempts to describe how investors -- biopharma companies; venture capital (VC) firms; or private entities, such as universities-- would react to a change in the expected financial reward from developing a new approved medicine. Typically, there is a greater willingness to invest in developing new medicines where the market is expected to be larger or where development is quicker and less expensive, leading to a greater and/or quicker financial reward. For certain types of medicines that are particularly difficult or costly to develop and lack adequate market size, policymakers have created additional "market-creating" incentives such as tax incentives or additional periods of market exclusivity.

CBO states that it relies primarily on three published studies described in the following paragraphs, which estimate the impact of changes in pharmaceutical revenues on innovation. However, how CBO uses the range of estimates from these analyses is unclear. There is a large range of average elasticities estimated among the three papers cited by CBO -- from 0.23 to six, essentially indicating that a 10percent increase in the expected financial reward from developing a new approved medicine leads to an increase in research and development of between 2.3 percent and 60 percent. An interview with the key CBO report authors confirmed that they primarily relied on the 0.23 elasticity estimate. This estimate is from the most recent study in CBO's sample-- Dubois et al., (2015) -- but they declined to explain their methodology in further detail.[14]

Dubois et al., (2015) measured the relationship between market size and innovation (as measured by new chemical entities appearing on the market for a given disease class) based on data from 13 countries including the U.S.[15] The study estimated the point elasticity of market size to innovation as 0.23, which means that if the market shrinks by 10 percent, the number of new treatments decreases by 2.3 percent.[15] In this study, variation in market size was identified based on demographic variation including income level, population measures and disease mortality in each country.

CBO referenced a second study by Acemoglu and Linn (2004), which estimated the responsiveness of innovation (as measured by new medicine approvals by the FDA in the U.S.) to the expected future market size (as measured by changes in demographics).[16] The study's elasticity estimate ranged between four and six, such that a 10 percent decrease in the potential market size is associated with a 40-60 percent decrease in the number of new medicines.[16] This study only examined the U.S. market.

Industry analysts have found a broad range of estimates of the magnitude of H.R.3's impact.

Avalere estimated that H.R.3 would reduce biopharmaceutical revenues by $1,275 billion to $1,655 billion in 2020-2029. This is equivalent to an estimated reduction in net U.S. brand pharmaceutical revenues across the Medicare and commercial markets of between 34 percent and 44 percent and suggests a decrease in federal spending on drugs approximately 1.4 to 1.9 times larger than CBO's estimate.[17] Other recent assessments of H.R.3 suggest even larger impacts on market size and on new medicines, than estimated by CBO. For example, Vital Transformation estimated that H.R.3 would lead to 61 fewer or a 90% reduction in new medicine approvals over a decade originating from small and emerging U.S. biotechnology firms alone.[18]

Estimates of other policy proposals that would impact pharmaceutical markets are instructive in gauging the magnitude of H.R.3's impact. Giaccotto et al. (2005) estimated the impact of limiting the rate of drug price increases in the U.S. to inflation. This far more modest policy, with a much smaller impact to industry than H.R.3, would have a much larger effect on the introduction of new drugs than CBO's estimate of H.R 3's impact, they found. Furthermore, the authors estimated that the cost to society from losing these drugs would far outweigh the benefits in cost-savings from price controls.[19]

All of these studies suggest a far larger impact of H.R.3 on market size and innovation than the one estimated by CBO.[20] Overall, there is a lack of consensus around the implications of H.R.3.

The third study CBO references is by Blume-Kohout and Sood (2013) which modeled the expansion of the new Medicare Part D prescription drug benefit in 2006 in the U.S. as an exogenous shock to drug market size and estimated the impact of increased revenue on innovation as measured by clinical trial starts. This study found that investment in R&D, as indicated by the initiation of new clinical trials, was higher for therapeutic areas with higher expected revenues (therapeutic classes with a larger market share in Medicare Part D). They estimated the elasticity of innovation at different phases in the drug development process: The elasticity of Phase I clinical trials was estimated to be between 2.4 and 4.7, and for all clinical trials combined was approximately 3.3. The authors estimated the elasticity of new drugs coming to market with respect to market size as approximately 2.8, meaning a 10 percent reduction in the size of the market would result in a 28 percent decline in new drugs.[21]

Critical Areas of Uncertainty in CBO's Approach to Estimating Impact on New Drug Innovation

Undervalues the impact of the US market as the single largest source of industry revenue due to lack of reliable, analogous evidence

While economists generally agree that market size has an impact on willingness to invest in the development of new medicines, there is broad variation in estimates of the magnitude of the impact. The magnitude of the potential impact of H.R.3 on the biopharmaceutical market would be very significant. In the academic research to date, the change in market size studied has been far smaller than would occur under H.R.3.

There are also significant issues with extrapolating from a small sample of outdated studies to consider a large policy change as CBO has done with H.R.3. This causes considerable uncertainty around the impact of H.R.3 on new drugs, particularly for the types of medicines most affected by the policy.

Principally, there is no policy change in the U.S. or elsewhere to be studied that has a similar magnitude of the effect suggested by H.R.3. In the U.S., when Medicare Part D – the single biggest expansion in drug coverage in U.S. history – was implemented in 2006, annual prescription drug spending growth increased by 9 percent from the previous year,[22] a small estimated difference in spending when compared to the H.R.3 implications estimated by Avalere and Vital Transformation as described below, or even by CBO itself. The lack of such an expansive policy in history to study leaves CBO (and others) with no reliable analog for H.R.3.

Outside of the U.S., there are also no reliable analogs. The U.S. market for pharmaceuticals is larger than any other in the world, is less regulated, representing a significant force for stimulating investment in new medicines. The elasticity of innovation calculated by Dubois et al., (2015) was a critical input to CBO's estimate of H.R.3's impact on pharmaceutical innovation; however, they studied 13 countries in addition to the U.S. Additionally, they analyzed no exogenous shock of a similar magnitude on global revenues, raising questions regarding the study's applicability to the impact of H.R.3.

In 2019, the U.S. accounted for 41 percent of all global drug revenues, or about the same share represented by the EU5 (France, Germany, Italy, Spain, the United Kingdom), Canada, South Korea, China, Japan, Brazil, Mexico, Turkey and Australia combined. The same year, total spending on pharmaceuticals in the 13 ex-U.S. markets studied by Dubois et al. (2015) was $505 billion compared to the U.S.'s $510.3 billion in pharmaceutical spending.[23]

Furthermore, the U.S. is a disproportionately large segment of the market for specialty therapeutic areas such as oncology and rare disease. The U.S. is expected to make up nearly half of the $200 billion global oncology market in 2023.[24] Given the role of the U.S. in the global biopharma market, we expect that biopharma investors and developers – particularly in oncology and rare diseases – will be most responsive to changes in U.S. demand. This suggests that the elasticity of innovation would be lower in ex-U.S. countries, and using ex-U.S. countries to estimate elasticity of innovation would result in an underestimate of the impact in the U.S.

CBO fails to consider that EU markets, and other markets with heavy government intervention, function very differently than the U.S. market. In the U.S., payers competitively negotiate prices in the majority of the pharmaceutical market. Blume-Kohout and Sood (2013) explained that EU pharmaceutical revenues are highly regulated, and prices are controlled, which fosters lower expected profits and greater uncertainty about future profits.[25] In markets where prices are constrained, manufacturers are less likely to be less responsive to changes in expected revenues.

Acemoglu and Linn (2004) and Blume-Kohout and Sood (2013) both focused on the U.S. market alone and found much larger elasticities, although they used a distinct estimation approach. Ultimately this suggests likely lower innovation elasticities in ex-U.S. markets and casts doubt on the use of the Dubois et al., (2015) elasticity estimate in modeling the impacts of H.R.3. Extrapolation from smaller, price-regulated markets may underestimate the effects of a policy change on a market such as the US.

Ignores the likely disproportionate impact of the policy on high risk, high unmet need disease areas

Price setting under H.R.3 would target drugs with higher costs and limited generic competition. As a result, it would have a significant and disproportionate effect on the prices and future revenues of medicines for oncology and rare disease.

CBO's estimate fails to recognize the likely disproportionate impact on select therapeutic areas, often representing areas of unmet medical need. Additionally, CBO fails to note the differential impact of the policy due to variation in the elasticity across therapeutic classes. This is despite the evidence presented in two of the papers cited in CBO report (Dubois et al. (2015) and Blume-Kohout and Sood (2013)), which find differing effects of market size on innovation by therapeutic area.

Variation in elasticity across therapy areas is well documented in the literature and should have been taken into account.**Error! Bookmark not defined.** For example, Dubois et al. (2015) provide estimated elasticities between therapy areas ranging from 0.07 to 0.41 and emphasize that "the assumption that elasticity is the same across disease categories may not be realistic."[15] In Dubois et al. (2015) higher elasticity estimates were found in oncology, nervous system disorders and sensory organ disorders. Pierre Dubois confirmed in an interview that a more accurate estimate would have been reached if elasticities had been computed by therapy area, as was done in his study.[26] Given the lack of transparency, we do not know whether CBO accounted for differences in classes in some other manner, however, the CBO report explicitly "does not predict what kind of drugs would be affected".**Error! Bookmark not defined.** This is particularly inappropriate when estimating the impact of a policy change such as H.R.3, which disproportionately affects drugs for rare disease and oncology. Therefore, there are significant uncertainties surrounding CBO's estimation of 8-15 fewer drugs, and CBO does not attempt to isolate the effects of the policy on a therapeutic area or patient population.

In sum, H.R.3 would increase uncertainty around expected returns and diminish manufacturers' incentives to discover new treatments in certain therapeutic areas.[27] Expected revenues are a key incentive to innovate and several academics have shown that a reduction in revenue in the U.S. would lead to lower R&D investment and fewer new therapies.[28,29,30] In separate conversations with Pierre Dubois and Neeraj Sood, both authors noted that the CBO report does not consider how the reduction in revenues from H.R.3 would shift the research incentives to develop certain classes of medicines.[27,28] Vital Transformation studied which types of drugs are most likely to be affected and found that the biggest estimated impacts were in oncology (16 fewer medicines) and rare diseases, including pediatric conditions (10 fewer medicines).[20]**Error! Bookmark not defined.**

Underestimates the impact of industry revenue reductions on R&D incentives by failing to make needed mathematical adjustments

Dubois et al. (2015) used a computationally involved mathematical approach to develop their elasticity estimates, using market sizes and elasticities to predict the number of innovations in a given disease area. This approach uses markets of varying sizes and varying elasticities, with the 0.23 elasticity estimate representing a point estimate across drug classes at the mean market size.

Dubois et al. (2015) developed an estimate of a "semi-elasticity".[31] While an elasticity describes the response of one variable in percentage terms to a percentage change in another, a semi-elasticity describes the response of one variable in percentage terms to an absolute change in another. A constant semi-elasticity implies that an absolute increase in a variable – here, market size -- delivers a percentage change in innovation. Thus, the response to a market change of 1 million to two million would not be the same percent response to a market change from 10 million to 20 million.

To accurately replicate the Dubois et al. (2015) approach for H.R.3, CBO would have needed to use a similar mathematical model to the one Dubois et al. (2015) used. CBO would have needed to allow for the change in elasticity in relation to the market size and impact of H.R.3. However, it appears that CBO instead applied the average elasticity to a much larger market size change than the one Dubois et al. (2015) evaluated. In our interview with CBO, the interviewees reported that they did not use a mathematical simulation model.[31] Therefore, their approach, which used the elasticity estimate in Dubois et al. (2015) to estimate the impact of a change in U.S. revenues, would incorrectly estimate the impact of H.R.3.[31, 32]

There is a broad range of estimates for the relationship between innovation and industry revenue (elasticities of innovation) for pharmaceutical products. CBO uses one estimate at the low end of the range.

There is broad variation in the innovation elasticity estimates in academic research and the approach to creating the calculation. For example, Dubois et al. (2015) highlight how prior studies consider the elasticity of market size to innovation to be "in the vicinity of 0.6, though there are exceptions".[15] Furthermore Dubois et al. (2015) find a range of estimates within their own research (elasticities between 0.03 and 0.32), depending on the mathematical model used.[15]

Blume-Kohout and Sood (2013) also describe how differences in the way innovation is measured (clinical trials, new molecular entities) can lead to varying elasticity estimates.[23] They estimated an overall elasticity estimate of 2.8 for pharmaceutical innovation. Acemoglu and Linn (2004) estimated an elasticity of between 4 and 6. Both studies found much higher estimates of the elasticity of pharmaceutical innovation than Dubois et al. (2015), and CBO used only the lower estimate to attempt to quantify the innovation impact of the H.R.3. This necessarily results in an estimate of reduced innovation on the low end of what would be suggested by the full range of the literature.

Ignores the complexity and mobility of the investor market which could readily shift to more profitable industries

Small companies developing specialized medicines are a hallmark of the biopharmaceutical market today, resulting in a different market structure than existed at the time of the studies referenced by CBO. Retrospective analyses necessarily use historical data, but analysts must be careful to ensure that data used for their models are not obsolete. The papers cited by CBO use data from as early as 1996.[15] Since then, drug development has evolved significantly. For example, new drug launches in oncology have grown to account for a higher proportion of all new drug launches, increasing from 11 percent in 1996-2000 to 28 percent in 2011-2016. Looking ahead, further growth in specialty medicines and treatments for oncology and rare diseases are expected, absent a policy change such as H.R.3.[33] Finally, Blume-Kohout and Sood (2013) emphasize the risk of relying on outdated data, as events and policy changes may have altered the estimated relationship between expected revenue and innovation (e.g. from declining R&D

success rates, increasing clinical trial costs).[Error! Bookmark not defined.] The use of data predating fundamental changes to market conditions is inappropriate to understand today's pharmaceutical market.

Today's drugs are far more likely to originate in small companies which depend on investment from venture capital or larger biopharmaceutical companies. In 2018, 77 percent of the late-stage drug pipeline was in small to emerging companies compared to 58 percent in 2003.[3] The biotech industry and small companies in particular rely on investments from VC (the value of deals supported by venture capital reached over $23 billion in 2018, a 200 percent increase since 2010.[3]**Error! Bookmark not defined.**). A significant reduction in the size of the U.S. biopharmaceutical market may motivate VC to redirect investment to other industries with higher returns on investment if there were a significant change in the expected return from investment in biopharmaceuticals.

Conclusion

H.R.3 poses a significant risk to the resilience of the innovation system and to the availability of future treatments for the thousands of diseases that currently have no treatment options. Following a review of the methods and related literature along with expert interviews, CRA concludes that CBO likely understates the impact of H.R.3 on the development of new medicines, for the following reasons:

- CBO undervalues the impact of the US market as the single largest source of industry revenue due to lack of reliable, analogous evidence;
- CBO ignores the likely disproportionate impact of the policy on high risk, high unmet disease areas; [3]
- CBO underestimates the impact of industry revenue reductions on R&D incentives by failing to make needed mathematical adjustments; and
- CBO ignores the complexity and mobility of the investor market which could readily shirt to more profitable industries.

Understanding the true impact of H.R.3 on future innovation is not an easy task, but CBO's implicit assumptions based on outdated evidence and simplified modeling could have dangerous unintended consequences if relied upon as conclusive. Even for an organization as sophisticated and adept as CBO, forecasting the impact on innovation of a policy change of unprecedented magnitude, in the world's biggest market for medicines is impossible, as there are no relevant analogues for change on this scale. Given the lack of similar analogues and limitations in CBO's computational approach to estimating H.R.3's impact on future innovation, we conclude that CBO likely underestimates the true impact of H.R.3 and that policymakers have not been provided with a sufficiently accurate estimate of the cost of the policy to adequately balance the risk of such a decision.

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