A black and white photograph of the U.S. Capitol building in Washington, D.C., featuring its iconic dome and classical architecture. The image is partially obscured by a dark vertical bar on the left side, which serves as a background for the title text.

# Limitations of CBO's Simulation Model of New Drug Development as a Tool for Policymakers

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JUNE 2022

Graham Cookson  
Jake Hitch

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**Graham Cookson**

Office of Health Economics, London

**Jake Hitch**

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**Corresponding Author:**

Graham Cookson  
[gcookson@ohe.org](mailto:gcookson@ohe.org)

For further information please contact:

**Professor Graham Cookson**

Chief Executive, OHE  
Honorary Visiting Professor in Economics at City, University of London

**Tel** +44 (0)207 747 1408

**Email** [gcookson@ohe.org](mailto:gcookson@ohe.org)



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# Executive Summary

In recent years, US policymakers have been considering reforms to reduce drug spending, including those which would allow the government to directly set prices for branded medicines. Such policies would reduce global pharmaceutical revenues, leading to a reduction in research and development (R&D) expenditure and ultimately to lower levels of innovation. To support policymakers in evaluating the impact of such proposals, the Congressional Budget Office (CBO) has developed models to quantify the loss in pharmaceutical industry revenues and the reduction in the number of new drugs expected to reach the US market.

To date, CBO has taken two different approaches to estimating the impact of pharmaceutical pricing policies on new drug development. The initial approach was to estimate a top-down, industry-wide relationship between revenues and new drug development based on historical estimates from the empirical literature (CBO, 2019). Second, in a subsequent working paper (CBO, 2021), CBO modelled the investment decision-making process of a representative pharmaceutical company from the “bottom up” in a product-level simulation. CBO has since updated their simulation model to incorporate more features of biopharmaceutical investing (CBO, 2022).

This OHE report evaluates CBO’s simulation model of new drug development and assesses whether this methodology provides policymakers with accurate estimates of the impact of lower US drug prices on future pharmaceutical innovation. We conclude that while the model is novel and has academic merit, it is too limited to guide policymaking as it inadequately represents the reality of investment in new drug development. Despite revisions published in early 2022, CBO’s modelling of the pharmaceutical R&D landscape is highly incomplete and continues to underestimate the true losses in innovation that would result from drug price setting policies. The estimates produced by the model are also subject to considerable uncertainty. Policymakers should therefore exercise caution in relying on these findings for evaluating potential real-world policy changes.

## Key limitations of the CBO simulation analysis

- The model makes the unrealistic assumption that pharmaceutical companies make investment decisions about individual drugs based solely on those drugs, with no consideration for their wider drug development portfolios
- The model applies an oversimplified decision rule which states that even a very minimal positive expected return on investment is sufficient to incentivise drug development
- The model assumes that the number of drugs approved each year would be constant in the absence of any policy shock. Recent figures suggest this would not be the case
- The model does not reflect that pharmaceutical companies differ in characteristics such as size and development costs which influence R&D decisions
- Signals about a drug candidate’s likelihood of success are unrealistically assumed to be independent across different phases of development
- CBO relies on a narrow conception of pharmaceutical innovation. The only measure of innovation that CBO considers is the quantity of new drugs coming to market, but it is the value not volume of innovation that ultimately matters



# 1 The cost of getting it wrong

While policies that reduce drug spending by allowing the government to set prices may initially sound attractive, a focus on poorly targeted short-term savings could have major adverse consequences for patients in the future by causing an immediate decline in R&D spending, resulting in fewer new drugs coming onto the market in subsequent decades.

Two bills recently passed by the US House of Representatives would require the government to directly regulate the prices of certain prescription drugs. First, in December 2019, the House approved the Lower Drug Prices Now Act (H.R. 3), which would cap the prices of many high-expenditure prescription drugs based on prices in other countries. Second, in November 2021, the House passed the FY 2022 reconciliation package, the Build Back Better Act (BBBA), which would impose government-set ceiling prices for certain brand medicines covered by Medicare, amongst other drug pricing provisions. Both bills would require manufacturers to accept the government's prices or face an excise tax of up to 95% of the medicine's total sales.

Prior to the passage of H.R. 3, the Congressional Budget Office (CBO) was asked to estimate the likely effects of the policy on federal spending and pharmaceutical innovation. A December 2019 report by CBO (CBO, 2019) found that H.R. 3 would reduce direct federal spending by \$456 billion over the period 2020-29 and result in a 19% drop in the present discounted value of worldwide pharmaceutical revenues. Despite H.R. 3's unprecedented impact on the world's largest pharmaceutical market, CBO estimated that only eight fewer new drugs would be approved by the Food & Drug Administration (FDA) over the first decade of the policy (2020-2029), with up to a further 30 new medicines lost over the subsequent ten years. This is equivalent to a 2.7% reduction in annual drug approvals in the first decade and a 10% reduction in the second decade. These estimates are surprisingly low given the magnitude of the policy, calling into question the methods and data behind the analysis.

CBO had attempted a highly complex task in predicting the long-term impact of H.R. 3, and academic economists and industry analysts concurred that their analysis was hampered by substantial uncertainty surrounding the key parameters, especially the response of innovation to expected revenue and the impact of the policy on expected revenue (Hitch et al., 2021). Whereas CBO's initial analysis of H.R. 3 drew heavily on the peer-reviewed academic literature to estimate the relationship between industry revenues and new drug development, CBO ultimately abandoned this methodology.

In August 2021, CBO released a working paper (CBO, 2021) describing an updated approach to estimating the impact of drug pricing policies likely to affect pharmaceutical revenues and the rate of development of new drugs. CBO has since incorporated three additional features of the biopharmaceutical innovation landscape into their model, which we scrutinise in this report.

## 2 A new method for estimating the impact of drug pricing policies on pharmaceutical innovation

### Motivation for CBO's simulation model

Earlier analysis by OHE and others such as Axelsen and Jayasuriya (2021) have identified several challenges with CBO's original approach to estimating the impact of H.R. 3 on pharmaceutical innovation. In August 2021, CBO released a working paper describing an alternative methodology – a general simulation model that can, in theory, be used to evaluate *any* policy which alters drug prices and therefore expected returns or R&D costs (CBO, 2021).

Rather than relying on estimates of the elasticity of innovation from the literature, this new approach attempts to model the investment decision-making process of a hypothetical pharmaceutical company from the "bottom up" to simulate the relationship between expected net revenues and new drug development. The model described in the working paper has subsequently been updated to include three additional features of biopharmaceutical development: preclinical development, accelerated approval and policy impacts on financing costs.

In November 2021, CBO used this simulation approach to estimate the impact of the drug pricing provisions of the BBBA (CBO, 2021). They estimate that in the absence of the policy, 1,300 new drugs will be approved over the 30-year period 2022-2051. Implementation of the policy would result in only 10 of these medicines being lost, a 0.7% reduction in drug development. The policy would take time to have its full effect. CBO estimates that only one of these ten drugs would be lost in decade one (2022-31), four in decade two (2032-41), and the remaining five in decade three (2042-2051).<sup>1</sup> CBO acknowledges that these estimates are subject to uncertainty.

The CBO simulation model is a novel approach and may have academic merit. However, as the model is intended to be used to inform policymaking, it is critical that it provides as accurate a reflection of the real world as is practically possible, i.e., that it is of policy relevance rather than merely academic relevance. It must also be transparent in terms of its methodology, inputs, and assumptions so that the analysis can be fully understood and evaluated by others.

The purpose of this critique is to evaluate the simulation model as a tool for policymakers who implicitly rely on its outputs when considering drug pricing legislation.

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<sup>1</sup> Although not directly stated by CBO, these estimates imply that BBBA would reduce industry revenues by 2.6%. This is calculated by dividing the percentage long-run revenue impact by the long-run elasticity of innovation. CBO estimates that five fewer drugs will come to market by the third decade of the policy and the same thereafter from an assumed baseline of 1,300 drugs, a loss of 1.154%. Using the long-run elasticity of innovation of 0.45 taken from CBO's white paper (2021a) implies a revenue reduction of 2.6% ( $1.154/0.45=2.564$ ) although nowhere does CBO state their estimated revenue impact of BBBA or how they have arrived at the estimate.

## Simulating the pharmaceutical investment decision

CBO describes a simplified economic model of new drug development, which contains several simplifying assumptions outlined below.

### Key assumptions behind the CBO simulation analysis

- There is a single pharmaceutical company that is assumed to be representative of the entire industry; there is no analysis of company heterogeneity in terms of size or financing costs, for example.
- As long as the drug candidate is expected to make some positive profit, it will be moved into the next stage of development – the level of expected profit has no impact as long as it is above zero
- In the absence of any policy shock, the number of new drug approvals would be constant over time

CBO uses confidential Medicare Part D reimbursement data to estimate expected industry returns. To estimate expected development costs, CBO uses data from DiMasi, Grabowski and Hansen (2016), a study that surveyed pharmaceutical companies on their aggregate pharmaceutical R&D expenditures for the period 1990-2010. These development cost data are, therefore, relatively old for modelling the impacts of contemporary policy changes.

The mechanics of the simulation model work as follows. In each phase of development – preclinical (phase 0) and clinical (phases I, II and III) – the firm receives a signal (information) about its drug's likelihood of success, returns once on the market, and costs of development. It then decides whether it would be profitable to progress the drug into the next stage of development. It will do so if and only if expected net returns are positive conditional on the information it has received in that phase. The firm continues to follow this decision rule through to phase III and market entry. The model incorporates uncertainty from the perspective of the representative decision-maker, and the decision-maker is also forward-looking.

Importantly, after calibration or estimation of the relevant parameters using the data described above, the model can be used to project the impact of any hypothetical policy which affects expected costs or expected returns.

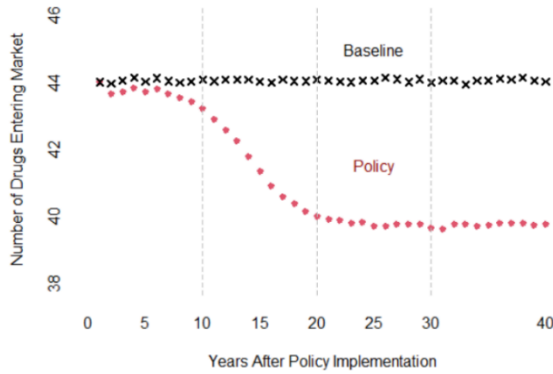
## Evaluating drug pricing policies

To illustrate how the simulation model works, CBO evaluates a hypothetical H.R. 3-like policy that would reduce expected revenues by 15-25% for drugs in the top 20% of drugs ranked by expected returns (CBO, 2021). CBO uses the model to estimate the impact of this policy on the probabilities of a drug candidate moving into each phase of preclinical and clinical development and ultimately on the number of new drugs entering the market (assuming no subsequent policy shock).

The output of the policy evaluation is visualised in Figures 1 and 2. In Figure 1, the black line gives the baseline time path for the annual number of new drugs entering the market in the absence of the policy, and the red line shows the same time path with the policy in place. The baseline is initially set equal to the average number of annual drug approvals by the FDA over the period 2015-2019. The baseline remains around 44 new drugs per year for the entirety of the 30-year policy evaluation window. The full effect of the hypothetical policy, which only occurs after the first ten years, is to reduce the number of new drugs entering the market by 10%.

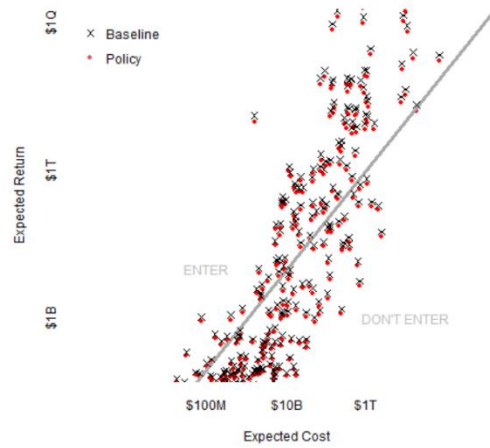


It takes time for the policy to realise its estimated full effect on new drug approvals because drug development timelines are long, and the model assumes that all historical costs are sunk. Therefore, in each phase, the investment decision is based only on the development costs and revenues in the next phase.



**FIGURE 1: ESTIMATED IMPACTS OF THE POLICY ON NEW DRUG DEVELOPMENT OVER TIME**

Source: CBO (2022)



**FIGURE 2: ESTIMATED IMPACTS OF THE POLICY ON ENTRY FROM PHASE II INTO PHASE III**

Source: CBO (2022)

Figure 1 shows the estimated impacts of the hypothetical policy on the number of new drugs entering the market over time. The number of new drugs is initially set equal to the average for the period 2015-2019. The policy has essentially zero impact in the first decade, and the full impact of 10% is only realised from the third decade onwards.

Figure 2 shows the impact of the policy on entry into phase III from phase II for a set of drug candidates drawn from the estimated joint distribution of expected returns and expected costs. The grey line gives the breakeven line, i.e., all points such that expected returns = expected costs. There is one black cross and one red dot per drug. A black cross gives the combination of expected returns and expected costs for a given drug in the absence of the policy, and the respective red dot gives the same combination but with the policy in place. If the drug is located to the left of the grey line, then expected net returns are positive, and the firm will move the candidate into phase III. If the drug is located to the right of the grey line, expected net returns are negative, and therefore, the drug will not enter phase III.

The impact of the policy on innovation is represented as the total number of drugs that cross the breakeven line. Although no exact quantification is possible, the policy affects only a small number of “marginal” high-expected-return products and firms, i.e., those which were already close to the expected breakeven line before the policy. While those candidates with low initial expected returns could be seen as marginal in financial terms, they could be transformative in terms of health impact.

This methodology differs from CBO’s original analysis of H.R. 3 (CBO, 2019), in which CBO used three industry average figures to estimate the policy’s impact: the estimated average impact of H.R. 3 on revenues, the estimated relationship between revenue and the number of new drugs developed (the elasticity of innovation), and a baseline estimate of the future annual number of new drugs in the absence of any policy change. All three of these estimates are subject to considerable uncertainty, and indeed all have been contested (Cookson, 2021a-e).

The simulation methodology put forth in CBO’s August 2021 working paper makes progress on one of these criticisms – estimating the elasticity of innovation. Instead of CBO selecting its own elasticity (0.53) informed by the historic academic literature and applying this at an industry level, the primary purpose of the new methodology is to build a model from the level of the individual drug candidate and link the expected net returns and R&D decision making throughout the clinical trial programme.

CBO has since updated its simulation model to include the effects that a policy would have on financing costs, account for an accelerated approval process in addition to the standard approval process, and model preclinical as well as clinical development. These are welcome improvements, but they do not address the key limitations of CBO’s simulation model or the broader concerns raised in this critique.

Table 1 presents the main estimates from the first iteration of the CBO simulation model of new drug development and compares these with the estimates from the updated model. The three improvements to the CBO model increase the long-term impact of the policy on the number of new drugs entering the market by 25%, from 8% to 10%. The table also shows that the revisions have a relatively large impact on the number of drugs entering phase I clinical trials through standard approval.

**TABLE 1: COMPARISON OF ESTIMATES IN CBO (2021) AND CBO (2022)**

Sources: CBO (2021); CBO (2022)

IMPACT	MODEL 1 (CBO, 2021)	MODEL 2 (CBO, 2022)		DIFFERENCE (PERCENTAGE POINTS)
Long-term number of new drugs entering market	-8%	-10%		-2
Number of drugs entering phase III clinical trials	-0.6%	-0.7%		-0.1
Number of drugs entering phase II clinical trials	-3%	Standard approval	-3.4%	-0.4
		Accelerated approval	-1.2%	N/A
Number of drugs entering phase I clinical trials	-4%	Standard approval	-4.8%	-0.8
		Accelerated approval	-5.1%	N/A
Number of drugs entering preclinical development (phase 0)	N/A	Standard approval	-1.5%	N/A
		Accelerated approval	-2.5%	N/A

## 3 Limitations of the CBO simulation analysis as a tool for policy evaluation

The model makes the unrealistic assumption that investment decisions are based on a single product rather than a given company's entire drug development portfolio

A limitation of the original CBO analysis of H.R.3. is that it combined a single elasticity of innovation and predicted change in global pharmaceutical revenues to estimate an industry-level reduction in the number of new drugs coming to market. CBO's new simulation model goes to the other extreme and attempts to model investment decision-making at the individual product level.

However, this alternative approach is not realistic, as pharmaceutical companies and private equity investors do not make decisions on individual products in a vacuum but rather within the broader context of a portfolio of R&D projects. This was echoed in recent interviews OHE conducted with biopharmaceutical investors (Hitch et al., 2021). Several individuals with experience making R&D investment decisions within large pharmaceutical companies emphasised the importance of conducting a broad portfolio analysis in addition to product-specific analysis. The expected returns across the portfolio are what influence decision-making in a "blockbuster" model of product innovation like biopharmaceuticals. Investment decisions are made within a budget constraint based upon multi-criteria analysis to optimise the expected performance of a portfolio of assets.

While CBO's assumption of product independence simplifies the model and makes it tractable, it does not reflect the reality that investors make decisions to maximize returns across a portfolio of pipeline investments. Companies that can afford to do so will typically have multiple drug candidates in their pipeline to increase the probability of producing at least one highly successful and profitable product (a blockbuster). In practice, sharply reducing returns on a large share of all commercially successful drugs will sharply reduce returns for the entire portfolio, making it less able to meet return thresholds and attract high risk high reward investment.

The model applies an oversimplified decision rule which states that any positive expected return on investment is sufficient to incentivise clinical development, regardless of magnitude

A crude and almost certainly erroneous assumption is that a drug candidate will be advanced into the next stage of development (e.g., from phase II to phase III) if and only if expected returns exceed expected costs, i.e., if expected net returns are above zero. We refer to this as the decision rule, defined as the mapping from observations of expected development costs and expected returns into a decision about whether to progress the drug candidate into the next phase of development. This implies that the level of (positive) net expected returns is irrelevant. That is, CBO assumes that two

drugs with expected net returns of 0.01% and 15% are equally likely to advance into the next stage of clinical development.

This may make the model tractable, but it does not accord with real-world experience where expected returns are required to be a multiple of investment costs, partly to hedge against future uncertainty in achieving clinical and commercial success. Our findings from recent interviews with industry decision-makers (Hitch et al., 2021) indicate that while thresholds for expected returns are used, these are typically not prescriptive, and committees also consider a range of other factors, such as unmet need and the company's historical areas of success, as well as expectations for the rest of the portfolio. Aside from the level of expected net returns, some investors require that their initial R&D investment will be recovered within a set timeframe to enable this capital to be redeployed. This suggests that projects with lower expected net returns may be preferred over projects which will only offer a positive return on investment after many years.

Decision rules also vary across the different phases of development. In the early phases of clinical development, sophisticated financial and commercial analysis is less important than broader analysis relating to patient populations and level of unmet need. It is on the precipice of phase III that investors typically want to see detailed financial analysis, and thresholds for expected returns may be used. Although commercial considerations may become important earlier in the development timeframe under accelerated approval mechanisms, the factors which determine whether an asset progresses to the next phase of development typically differ across the different stages and are not narrowly commercially focused as the CBO model requires.

## The model does not reflect that pharmaceutical companies have different characteristics such as size and development costs which influence R&D investment decisions

CBO's simulation model only considers a "representative" pharmaceutical company. In reality, biopharmaceutical companies are not homogeneous and differ across many dimensions that may have important implications for R&D investment decisions. One important dimension is size. Due to economies of scale (average costs falling as a company gets bigger), size and development costs may be negatively correlated. A smaller firm would find it more costly to develop the same drug because they must implement more processes and devote a higher share of their budgets to the development. Development costs and timelines may also depend on the company's years of experience in a disease area or in conducting trials.

Another important dimension is the source of financing. In recent years, there has been a trend of increased innovation generated by smaller, venture-capital-based companies. This has many implications, one being that small biotech companies which rely on external investors – who expect a higher return on investment than is needed for traditional in-house financing by large companies – would find it more difficult to secure funding. In the CBO model, a drug candidate with positive expected net returns, no matter how small, will always go ahead into the next phase of development. However, investors in externally funded companies would likely demand higher expected returns than assumed by CBO.

There are many other limitations in assuming homogeneity of firms within the theoretical model presented in the CBO working paper. Firstly, CBO only considers "in-house" drug development. However, in practice, a large share of innovation is produced by small biotech firms, and the drug candidates are then licensed and commercialised by larger pharmaceutical companies. CBO's analysis completely misses this important feature of the innovation supply chain. The representative drug developer is solely responsible for progressing (or not) their drug candidate through the

different phases of clinical development. Again, this choice was likely made for tractability or because CBO is reliant on the DiMasi, Grabowski and Hansen (2016) cost data, which are also based on “in-house” development.

Heterogeneity is a key ingredient that is missing in the CBO simulation model and is further evidence that CBO’s analysis fails to represent the reality of pharmaceutical investment decisions.

## Signals about a drug candidate’s likelihood of success are unrealistically assumed to be independent across development phases

As well as the assumed independence of drug candidates within a given company’s R&D portfolio, the model features another form of independence. In each phase, the firm receives a random signal about the drug candidate’s type (which encapsulates its likelihood of success, returns once on the market, and costs of development). For modelling simplicity, these are assumed to be independent across phases. This means – for example – that in phase II, a certain drug candidate may have very high expected returns, but expectations could quite easily fall to very low levels upon entry into phase III. In reality, signals received in one phase are likely to be highly predictive of signals received in the next and subsequent phases. CBO admits that this assumption is unrealistic, but again it is employed to simplify the modelling and estimation.

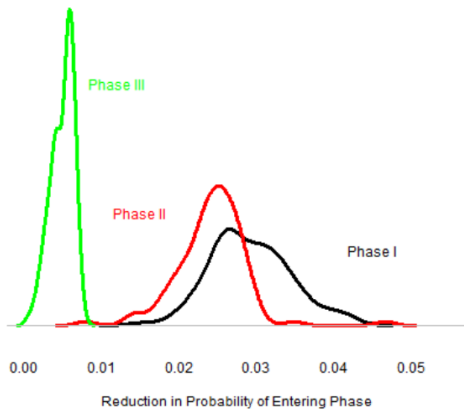
## The significant uncertainty around the estimated impacts mean policymakers should exercise caution in applying them

As CBO acknowledges, uncertainty exists around both the values of key inputs used in the simulation model (which were calibrated or estimated) and around the impact of the illustrative policy. In line with the degree of uncertainty surrounding the point estimates, policymakers should exercise caution in relying on these for the evaluation of potential real-world policy changes.

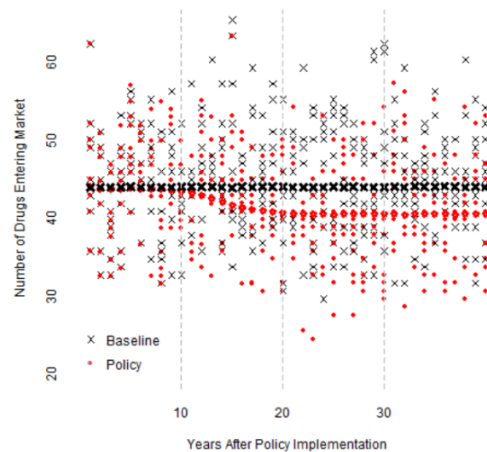
Figure 3 depicts the distributions of CBO’s estimates of the impact of the hypothetical policy on the probability of entering each phase of development. A wider distribution indicates greater uncertainty. Clearly, there is significantly more uncertainty around the impacts on earlier stages of clinical development, as shown by the greater spread in the distributions for phases I and II compared to phase III. Although there is less uncertainty about the impact for phase III, the number of drug candidates in phase III depends on entry into previous phases. More uncertainty around the impacts of the policy on phase I and phase II entry probabilities imply more uncertainty around the impact of the policy on the number of phase III candidates. Policymakers should clearly understand that the findings produced by CBO’s simulation model are subject to considerable uncertainty, which could misrepresent the true impacts of the policy change.

For example, suppose there are 100 potential phase I drugs (successful in preclinical development). Suppose the probability of entering phase I is initially 50%, and it is the same for entering phase II from phase I. We would expect 50 drugs to move into phase I and, consequently, 25 drugs to move into phase II. Twenty-five drugs would therefore be available to potentially enter phase III. If each of these phase entry probabilities is reduced from 50% to 48%, then there would be a 7.8% reduction in the number of drugs available to potentially enter phase III clinical trials. This is despite only a two-percentage-point decrease in the entry probabilities for phase I and phase II. Therefore, small differences in the success rates in early clinical development can have a relatively large downstream and therefore impact the number of new drugs coming to market in a meaningful way.

Figure 4 shows the degree of uncertainty around the time paths of new market entries before and after the hypothetical policy. The figure shows that, on average, the policy reduces the number of drugs entering the market, but for any particular year, the same, significantly fewer, or significantly more drugs could actually enter the market under the policy compared to baseline. This uncertainty is inherent in the model and partially due to the randomness of the signals that the firm receives about its drug candidate.



**FIGURE 3: UNCERTAINTY IN THE ESTIMATED IMPACTS OF THE POLICY ON PHASE ENTRY PROBABILITIES**  
Source: CBO (2022)



**FIGURE 4: PATH OF NUMBERS OF NEW DRUGS ENTERING THE MARKET**  
Source: CBO (2022)

Notes: These figures are taken from the first iteration of CBO’s model, which does not account for impacts on financing costs and preclinical development nor for an accelerated approval process. CBO hasn’t provided corresponding figures for their updated model.

## CBO assumes a constant baseline number for annual drug approvals, contrary to recent figures

CBO measures the impact of drug pricing policies on innovation by the change in the number of new drugs coming to the market each year. In their initial analysis of H.R. 3 (CBO, 2019), CBO assumes that 300 new drugs are approved each decade, implying 30 per year on average. This baseline has been disputed, with other evidence suggesting this number is significantly higher. For example, the 10-year average from 2011 was 41 (FDA, 2021), and the median number estimated by the experts we surveyed in our recent study was 45 (Hitch et al., 2021).

As well as understating the level of baseline new drug approvals, CBO uses a constant rate of new drug approvals over the 20-year policy horizon, but the experts surveyed in our study suggested that developments such as genomics will contribute to an increasing rate of new molecular entities (NMEs) approved each year. These enabling technologies give scientists a better understanding of the biology underpinning disease, making drug development much more targeted because scientists know the structure, sequence, and role of so many molecules involved in diseases. Relying on a static baseline is a simplifying but highly unrealistic assumption.

In their August 2021 working paper (CBO, 2021), CBO increases their baseline value for annual market approvals from 30 to 44 (the average annual number of drugs entering the market 2015-2019), a 47% increase, without clear justification. Assuming the same elasticity of innovation (the same percentage change in new drug approvals for a given percentage change in expected revenues/returns), this increase in baseline new drugs should have increased the CBO's estimate of the impact of H.R. 3 in their original evaluation by 50%. However, there have been no updates or revisions to that original work incorporating this higher baseline approval figure.

Despite the greater level of detail in the CBO simulation analysis, there clearly remains a lack of transparency around many aspects of the modelling exercise, including the assumed baseline number or trend in new drug approvals. This is important because the impacts of a pricing policy on innovation depend on what the levels of new drug approvals would have been in the absence of the policy. The sample policy analysed by CBO directly affects drug candidates in the top 20% by expected returns. If the distribution of expected returns stays the same but the number of drugs approved each year increases over time – as there is reason to believe – then more drugs will be lost. In other words, assuming a constant baseline understates the absolute reduction in pharmaceutical innovation as measured by numbers of drugs entering the market.

Another point which requires greater transparency is what exactly is included in CBO's measure of "new drugs". While the working paper does not state this explicitly, it is highly likely that by "new drugs" they mean the number of novel drug approvals by the Center for Drug Evaluation and Research (CDER), including new molecular entities (NMEs) and biologics license applications (BLAs) approved. If this is the case, then the analysis omits biological products which are under the remit of the Center for Biologics Evaluation and Research (CBER), such as vaccines and cell and gene therapies. Excluding biological products in the estimation limits the applicability of the results to policies which might directly or indirectly affect these types of products. The lack of transparency on the types of products considered in the analysis is also a noteworthy limitation in and of itself.

## CBO uses numbers of new drugs coming to market as their only measure of innovation

More fundamental than the assumption of a constant baseline level of new drug approvals, number of new drug approvals alone is too simplistic a measure to capture the true impact of any policy on innovation. It is the value, not the volume of innovation, that is fundamental to patients and wider society. In health care, innovation should generate "value" by (1) improving patients' quality and/or length of life and/or (2) reducing the costs of achieving these health objectives. A simple count of the annual number of new drugs coming to market is, at best, a correlate of meaningful health innovation. Changes in this number also tell us very little about the size or distribution of the impact on innovation across therapeutic areas/diseases/indications.

This may seem intuitive, but drugs generate different amounts of value. The total value a drug delivers depends on how many patients will benefit and how much health gain the drug generates for each patient. Some drugs target diseases with large patient populations; for example, the antiretroviral therapies developed in the 1990s to treat millions of HIV patients worldwide. Others, like orphan drugs, are more specialized and target rare diseases with small populations.

Innovation can also be classified by how much health gain is achieved for each patient, i.e., distinguishing between 'breakthrough' and incremental innovations. A new, lifesaving, curative therapy, such as those for treating a rare disease like spinal muscular atrophy, may provide enormous health gains for each patient. Another innovative treatment may help many patients by preventing unnecessary heart attacks, and hospital stays, for example.

CBO does not explore the impact of fewer drugs coming to market on patient health, when clearly scientific advances are affecting both the number and distribution of the types of new medicines across disease areas. New drugs that CBO estimates will be lost may include the fifth treatment on the market for migraines or a cure for Alzheimer's. The former society may be willing to forgo, while the other would be a significant loss because it has so much value for patients and wider society.

## 4 Conclusion

Projecting the impact of drug pricing policies on future innovation is a challenging task. The simulation model developed by CBO is highly interesting, and the level of effort invested demonstrates the importance of the debate. However, the model suffers from several serious flaws and ultimately fails to adequately represent the reality of biopharmaceutical investing. The model may be of academic interest, but it cannot be reliably used to inform policymaking, at least not without a better accounting of the uncertainty around the point estimates.

It is encouraging to see that CBO has updated their simulation model to account for additional features of the biopharmaceutical development process, including preclinical development, impacts of policies on financing costs, and an accelerated approval process. However, there is currently insufficient detail about the new modelling to judge whether these features have been incorporated in an appropriate way. Also, besides the new features, many criticisms of the analysis remain. In particular, it is not at all clear how CBO models the link between potential drug pricing policies and pharmaceutical revenues, and the impact on the number of new drugs entering the US market will be sensitive to the size of the revenue reduction assumed by the analysts.

Although it does not claim to, CBO's model cannot project the impact of legislative changes on population health, which would be required for a complete and thorough policy evaluation. The CBO analysis is rich, but we still do not know what types of innovation would be lost due to the passage of government price setting policies for prescription drugs, nor what the ultimate impact on the average length and quality of life will be for the US and global populations. Buxbaum et al. (2020) find that 35% of the US life expectancy gained over the period 1990-2015 was due to pharmaceuticals which suggests that the health losses from binding price-setting policies will not be negligible.

While policies that reduce drug spending by allowing the government to set prices may initially sound attractive, a focus on poorly targeted short-term savings could have major adverse consequences for patients in the future by causing an immediate decline in R&D spending, resulting in fewer new drugs entering the market in the next few decades. Policymakers should clearly understand that the estimates produced by CBO's simulation model are subject to considerable uncertainty and should exercise caution in relying on these findings for evaluating the potential impact of real-world policy changes.



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## Appendix 1: Key criticisms of CBO's evaluation of H.R. 3 (CBO, 2019)

1. **Important features of biopharmaceutical investing are ignored:** CBO does not closely model the real decision problems facing biopharmaceutical investors
2. **Implausibly low elasticity of innovation used:** the value assumed by CBO is too low and as highlighted by experts, there is substantial uncertainty around its value.
3. **Upward trend in number and composition of NME approvals ignored:** CBO assumes a constant baseline number of NMEs approved but experts in our original study (OHE, 2021a) suggested that developments such as genomics will contribute to an acceleration in NME approvals.
4. **Wrong measure of innovation:** measuring innovation in terms of total NMEs is misleading as there is no link between NMEs and the health improvement lost.
5. **Uncertainty around parameters makes precise and reliable estimates hard to achieve:** the lack of consensus on parameter values in our expert elicitation exercise demonstrates this uncertainty, which should reduce confidence in the final point estimates.



### About us

Founded in 1962 by the Association of the British Pharmaceutical Society, the Office of Health Economics (OHE) is not only the world's oldest health economics research group, but also one of the most prestigious and influential.

OHE provides market-leading insights and in-depth analyses into health economics & health policy. Our pioneering work informs health care and pharmaceutical decision-making across the globe, enabling clients to think differently and to find alternative solutions to the industry's most complex problems.

Our mission is to guide and inform the healthcare industry through today's era of unprecedented change and evolution. We are dedicated to helping policy makers and the pharmaceutical industry make better decisions that ultimately benefit patients, the industry and society as a whole.

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- The costs of treating, or failing to treat, specific diseases and conditions
- Drivers of, and incentives for, the uptake of pharmaceuticals and prescription medicines
- Competition and incentives for improving the quality and efficiency of health care
- Incentives, disincentives, regulation and the costs of R&D for pharmaceuticals and innovation in medicine
- Capturing preferences using patient-reported outcomes measures (PROMs) and time trade-off (TTO) methodology
- Roles of the private and charity sectors in health care and research
- Health and health care statistics