CURRENT STATE OF THE EVIDENCE RELATED TO FINANCIAL RETURN AND CLINICAL DEVELOPMENT:

how it informs policy for biopharmaceuticals, gaps in existing evidence, thoughts on data, and information needed.

The world's oldest independent health economics research organisation

60+ years old

Founded in 1962 alongside the birth of health economics

Thought leader

Track record of engaging with and informing health policy

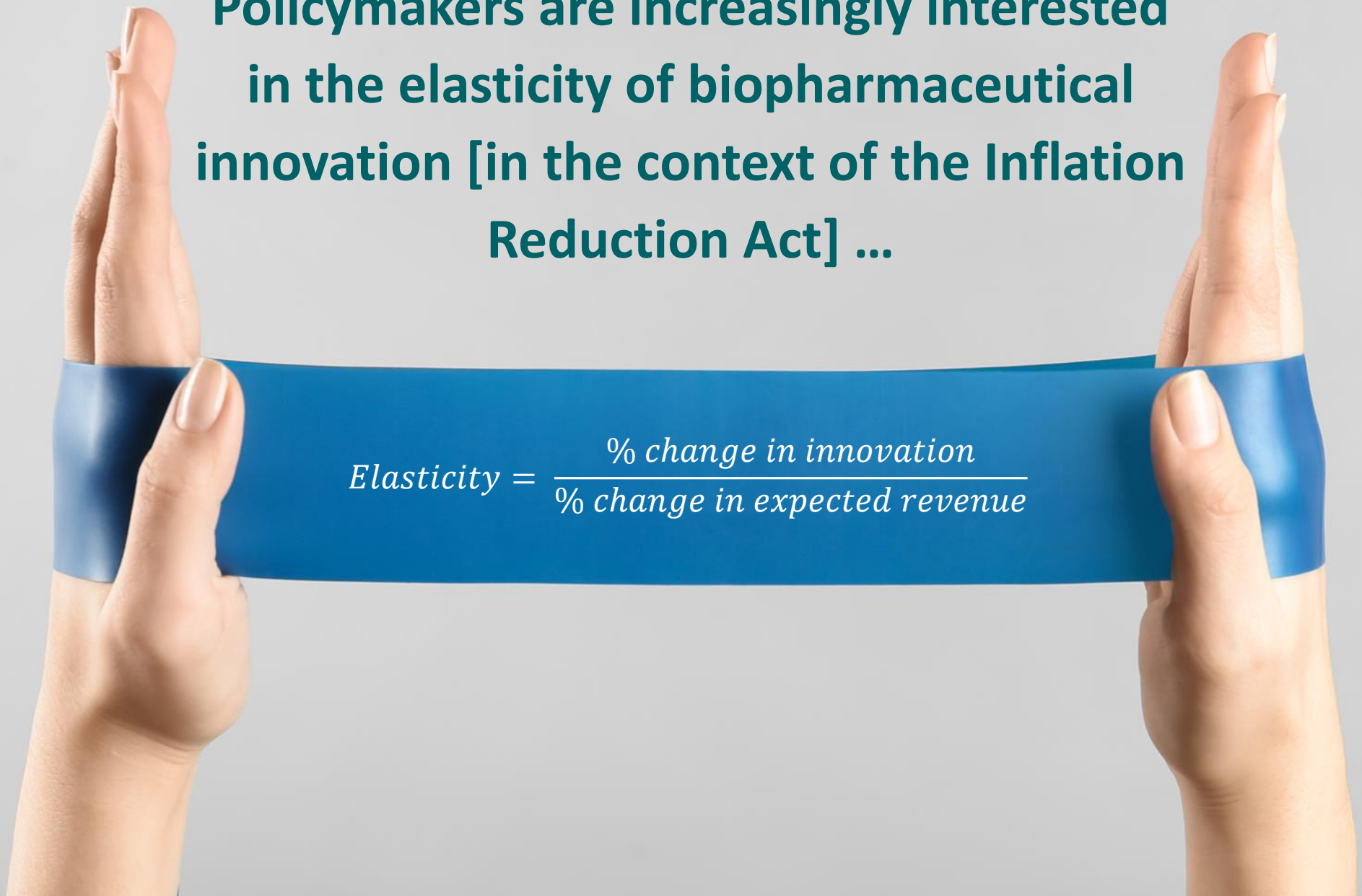
Independent

A non-profit with Independent Research Organisation status

Publisher

Prolific publisher of original research through reports and journal articles

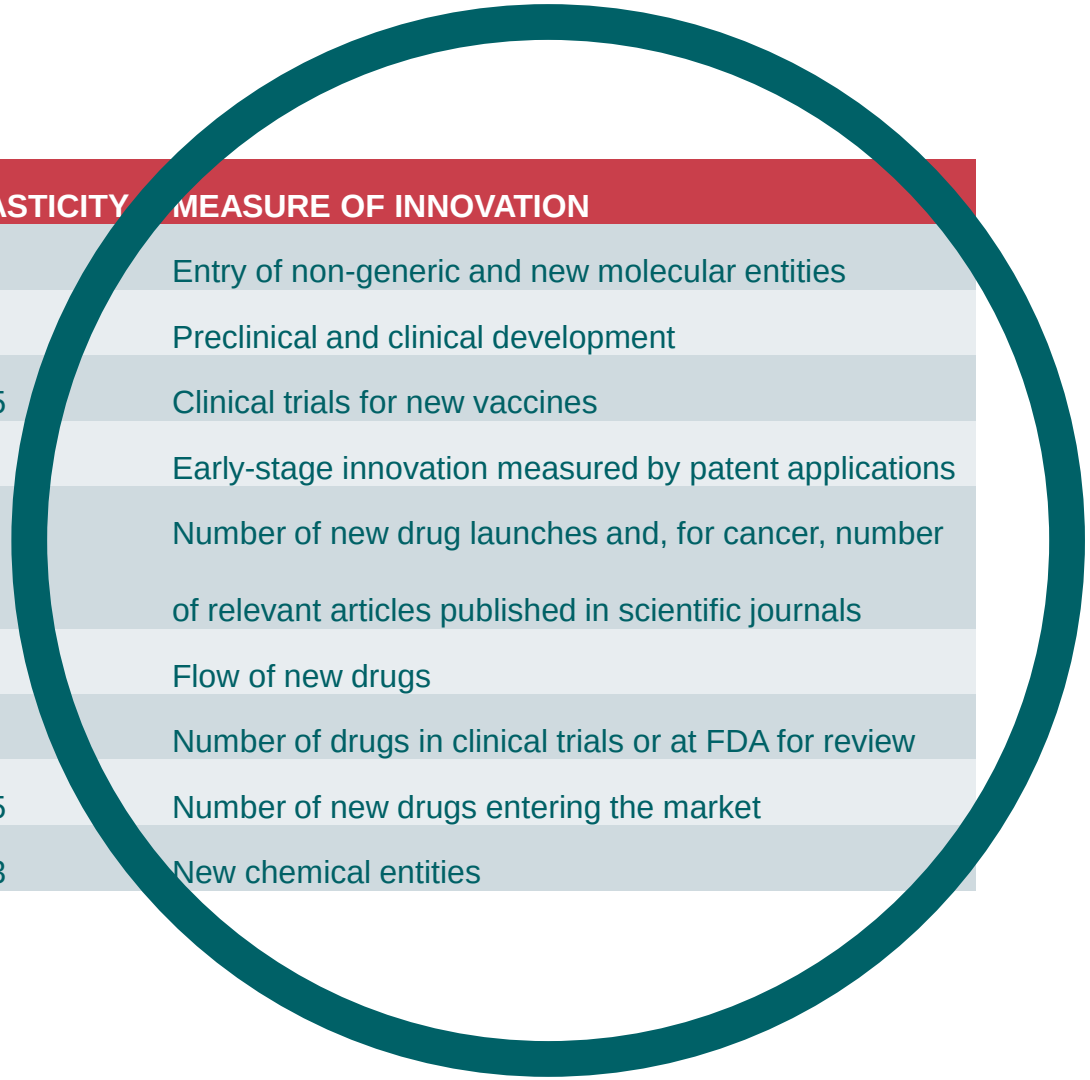
Policymakers are increasingly interested in the elasticity of biopharmaceutical innovation [in the context of the Inflation Reduction Act] …



… but how can innovation decision-making in the biopharmaceutical industry be modelled?

We can’t even agree on what we mean by innovation

PUBLICATION	ELASTICITY	MEASURE OF INNOVATION
Acemoglu and Linn (2004)	5	Entry of non-generic and new molecular entities
Blume-Kohout and Sood (2013)	2.8	Preclinical and clinical development
Finkelstein (2004)	2.75	Clinical trials for new vaccines
Kourouklis and Gandjour (2022)	2.2	Early-stage innovation measured by patent applications
Lichtenberg (2005)	1.3	Number of new drug launches and, for cancer, number of relevant articles published in scientific journals
Filson (2012)	1	Flow of new drugs
Civan and Maloney (2009)	0.5	Number of drugs in clinical trials or at FDA for review
CBO (2021a)	0.45	Number of new drugs entering the market
Dubois et al. (2015)	0.23	New chemical entities



Key empirical estimates are very far apart

PUBLICATION	ELASTICITIES		Identification strategy	Innovation data	Period covered
Acemoglu and Linn (2004)	New drugs Non-generics New molecular entities	6.0 4.0 **4.0-6.0**	Exploit variation in market size across drug categories due to US demographic trends	FDA drug approvals	1970-2000
Blume-Kohout and Sood (2013)	Phase I All phases US FDA approvals (proxied by worldwide market launches)	2.4-4.7 3.3 **2.8**	Exploit variation in Medicare Part D policy exposure across drug categories	Pharmaprojects data on drugs entering different phases of development (public press releases, patent filings etc.)	1998-2010
Dubois et al. (2015)	New chemical entities	**0.23**	Economic and demographic instrumental variables analysis	IMS Health data on product launches and sales in 14 countries.	1997-2007

0.53 (CBO, 2019)[1]

Criticisms[2]

- Based on smaller, price-regulated markets
- Focusses only on average effects
- Based on historical data

Acemoglu, D. and Linn, J., 2004. Market size in innovation: theory and evidence from the pharmaceutical industry. The Quarterly Journal of Economics, 119(3), pp.1049–1090. doi.org/10.1162/0033553041502144.

Blume-Kohout, M.E. and Sood, N., 2013. Market Size and Innovation: Effects of Medicare Part D on Pharmaceutical Research and Development. Journal of Public Economics, 97, pp.327–336. 10.1016/j.jpubeco.2012.10.003

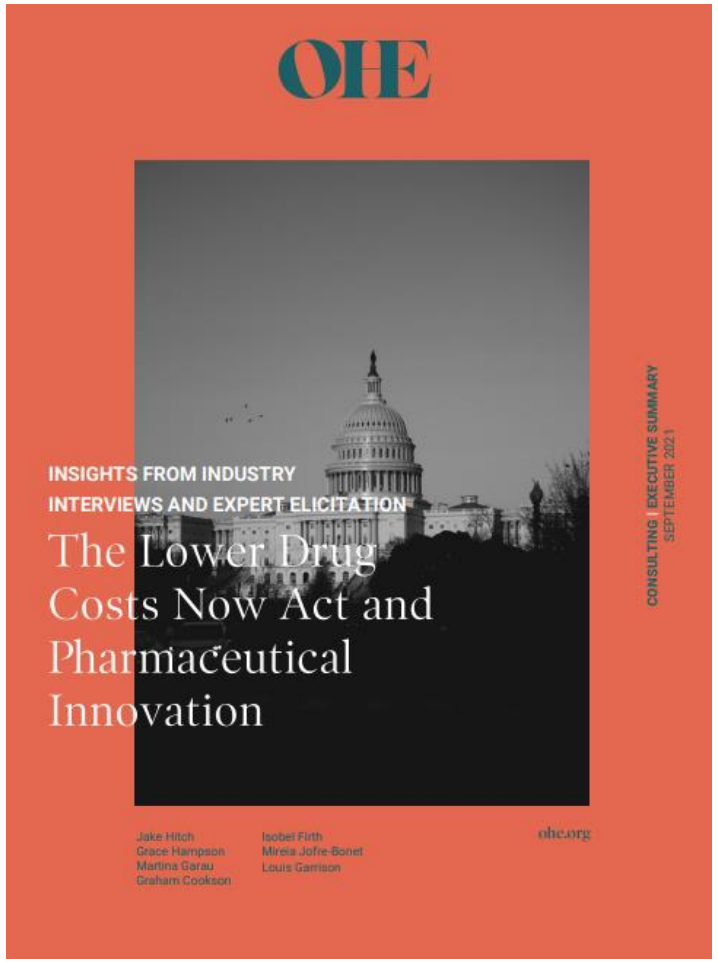
Dubois, P., Mouzon, O. de, Scott-Morton, F. and Seabright, P., 2015. Market size and pharmaceutical innovation. The RAND Journal of Economics, 46(4), pp.844–871. 10.1111/1756-2171.12113.

CBO, 2021. CBO's Simulation Model of New Drug Development: Working Paper 2021-09 | Congressional Budget Office. Available at: https://www.cbo.gov/publication/57010 [Accessed 18 Apr. 2023].

[1]Congressional Budget Office (CBO), December 10, 2019. Letter to U.S. House of Representatives "Re: Budgetary Effects of H.R. 3, the Elijah E. Cummings Lower Drug Costs Now Act"

[2]Charles River Associates (CRA) (Axelsen, K. and Jayasuriya, R.), April 2021. White Paper. Government Scorekeepers Likely Underestimate the Impact of Lower Drug Costs Now Act (H.R.3) on Investment in Innovative Medicines: Brief A study for the Pharmaceutical Research and Manufacturers of America (PhRMA)

There is no consensus

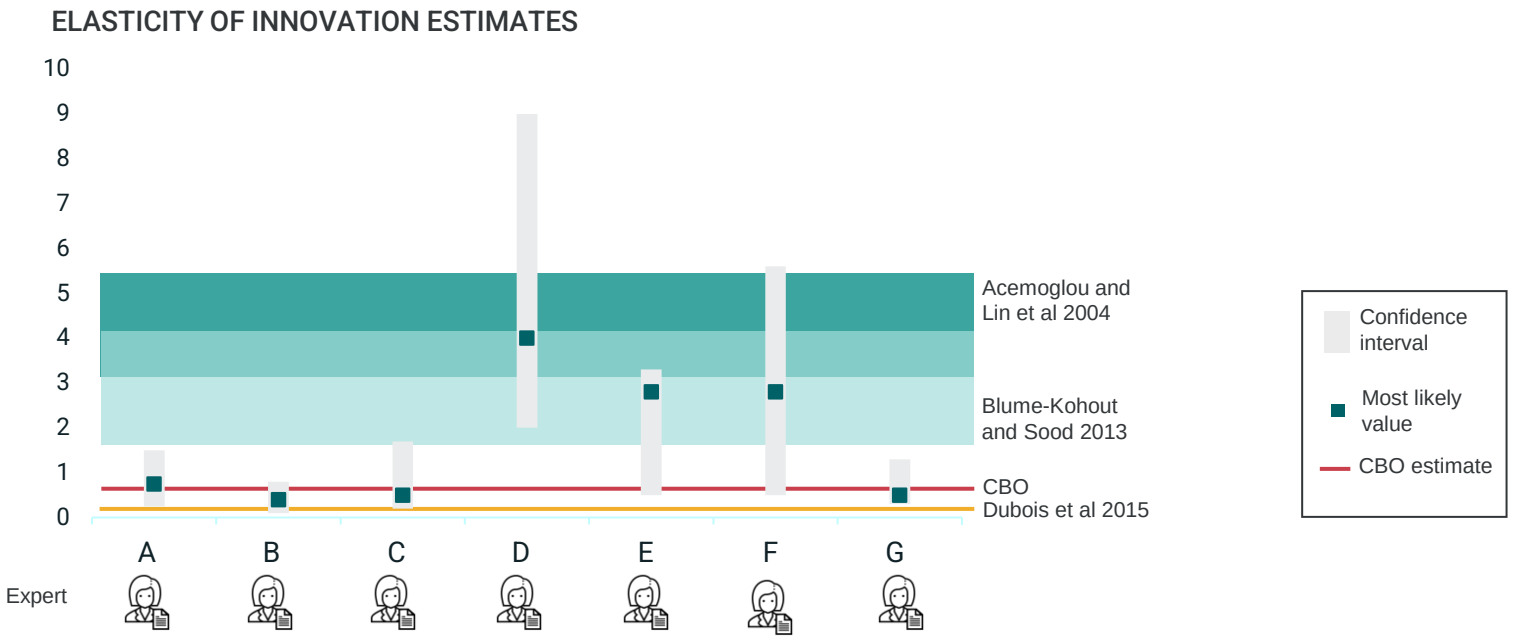


Context: Assess impact of H.R. 3 (proposal predecessor to IRA)

The aim of H.R. 3 was to reduce Medicare Part D expenditure by introducing price controls for high-expenditure drugs based on international reference prices (IRP).

Data collection	*Data collection*	*Analysis*	*Results*
INTERVIEWS	EXPERT ELICITATION	OHE ANALYSIS	CONCLUSIONS
• **10** one-hour virtual **interviews** • Representatives from large pharmaceutical companies (4), biotech (3), and biotech investors (3) (venture capital and private equity)	• 7 expert health economists and analysts were recruited • **2 Delphi survey rounds** were administered over a three-week period	• Quantitative estimates from the Delphi survey • Key insights and areas of **agreement and disagreement** within and across the expert elicitation and interviews.	Agreed to disagree

Experts agree to disagree



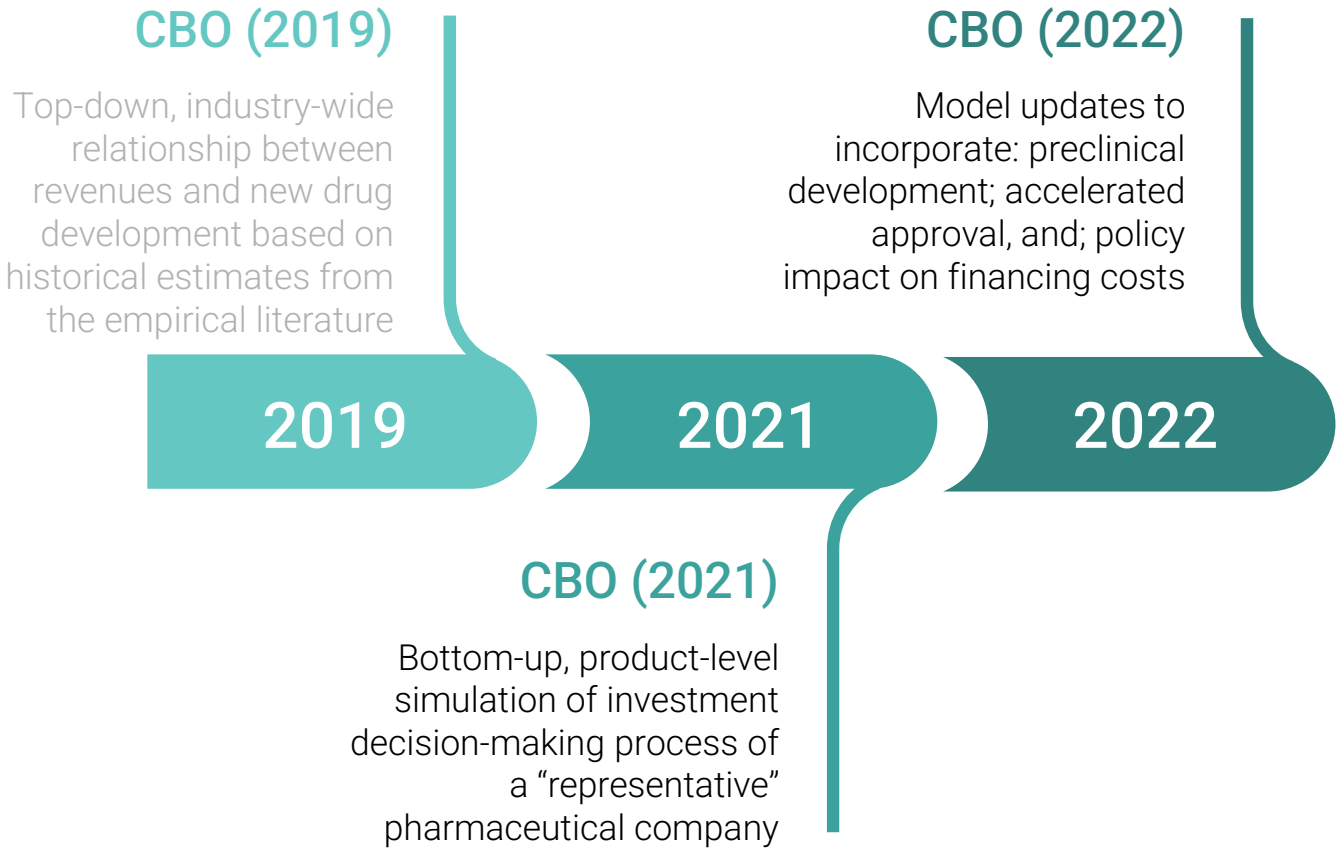
Disagreement on elasticity estimates, which varied across experts and showed a high degree of uncertainty.

- Those diverging from the CBO and Dubois et al. values stated the **age of the analysis** and **new technologies** as a reason to believe elasticity would be substantially higher

Agreement that elasticity of innovation would vary by:

- **size of market shock**
- **firm size and type**
- **Therapeutic area**

How it informs policymaking: The CBO has produced models of innovation decision-making…



Modelling approach…

At each stage of development (phase 0,I,II & III), signals on:

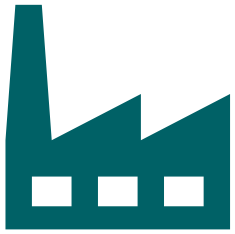
- Likelihood of success
- Returns once on market
- Costs of development

The company decides whether to progress to next-stage if net returns are positive

The model be used to project the impact of any policy that affects expected costs or expected returns

Congressional Budget Office, 2021. *Simulation Model of New Drug Development: Working Paper*.

… but CBO's current model is limited by some key assumptions, including…



Representative pharmaceutical company

Any expected positive return allows for positive decision to continue development

New drug approval remains constant over time

… which hinder the applicability of its findings.

The Fire Alarm Test (TL;DR)

What did we do?

We spoke with investors from across the innovation ecosystem to investigate how credible the assumptions of the model are.

What did we find?

We find that the model's assumptions do not adequately reflect the complex investor decision-making landscape across the life sciences ecosystem.

What are the implications?

Current estimates of innovation elasticity including the CBO's model should not be used to inform policy decision-making. The more extreme the policy proposition under consideration, the higher the risk that this mischaracterisation misinforms policy decisions.

Can we develop a more realistic picture of investor decision-making across the life sciences ecosystem?

OHE collected new data and insights on how investment decisions are made in the complex and diverse biopharmaceutical innovation ecosystem primarily through a series of semi-structured interviews with a range of different investors.

Hypothesis 1

The biopharmaceutical innovation ecosystem is **diverse, complex, and not homogeneous** as depicted in the CBO's simulation model.

Hypothesis 2

Investment capital is **scarce and mobile**, and the current CBO simulation model does not adequately address how investment decisions are made.

Hypothesis 3

The Ceteris Paribus assumption implicit in the CBO's evaluation – that all other things are equal – **does not hold**.

Where are the gaps in our knowledge and data?

1. Ecosystem

Who are the main players and how do they interact and contribute to product R&D?

2. Company vs product

What is the focus of investment for different players - company-focus or product-focus?

3. Risk and capital mobility

What is the attitude to risk when investing and how mobile is capital across markets and portfolios?

4. Investment decision

What are the main factors for decision making and how are they influenced by therapeutic area or type of product.

5. Cost of R&D

Have costs of R&D increased and how is this factored into investment decision making?

6. Impact of IRA

What is the expected impact of the IRA on investors and the ecosystem as a whole? How will this affect the ceteris paribus assumption of CBO?

How did we do this?

1. Literature review on the life sciences and pharma industry investment ecosystem
2. Data on drug authorisations between 2019 to 2024 to understand the major players in R&D and medicines approval
3. 19 semi-structured interviews conducted by one or two analysts

7 Interviews

Early-stage Venture Capital

2 Interviews

Later-stage Venture Capital and Private Equity

3 Interviews

Corporate Venture Capital and investors

4 Interviews

Small BioPharma Company

3 Interviews

Large BioPharma Company

Generating investor insights: *Key Results*

1. Ecosystem

The innovation ecosystem is complex with many diverse sources of investment across the lifecycle of a product.

2. Company vs product

Investors focus on companies and companies focus on products.

3. Risk and capital mobility

Risk tolerance decreases through the development pathway.

Capital is mobile – and it's on the move.

4. Investment decision

Big bets require big returns, and one size does not fit all.

5. Cost of R&D

R&D is more expensive and increases across the development path.

6. Impact of IRA

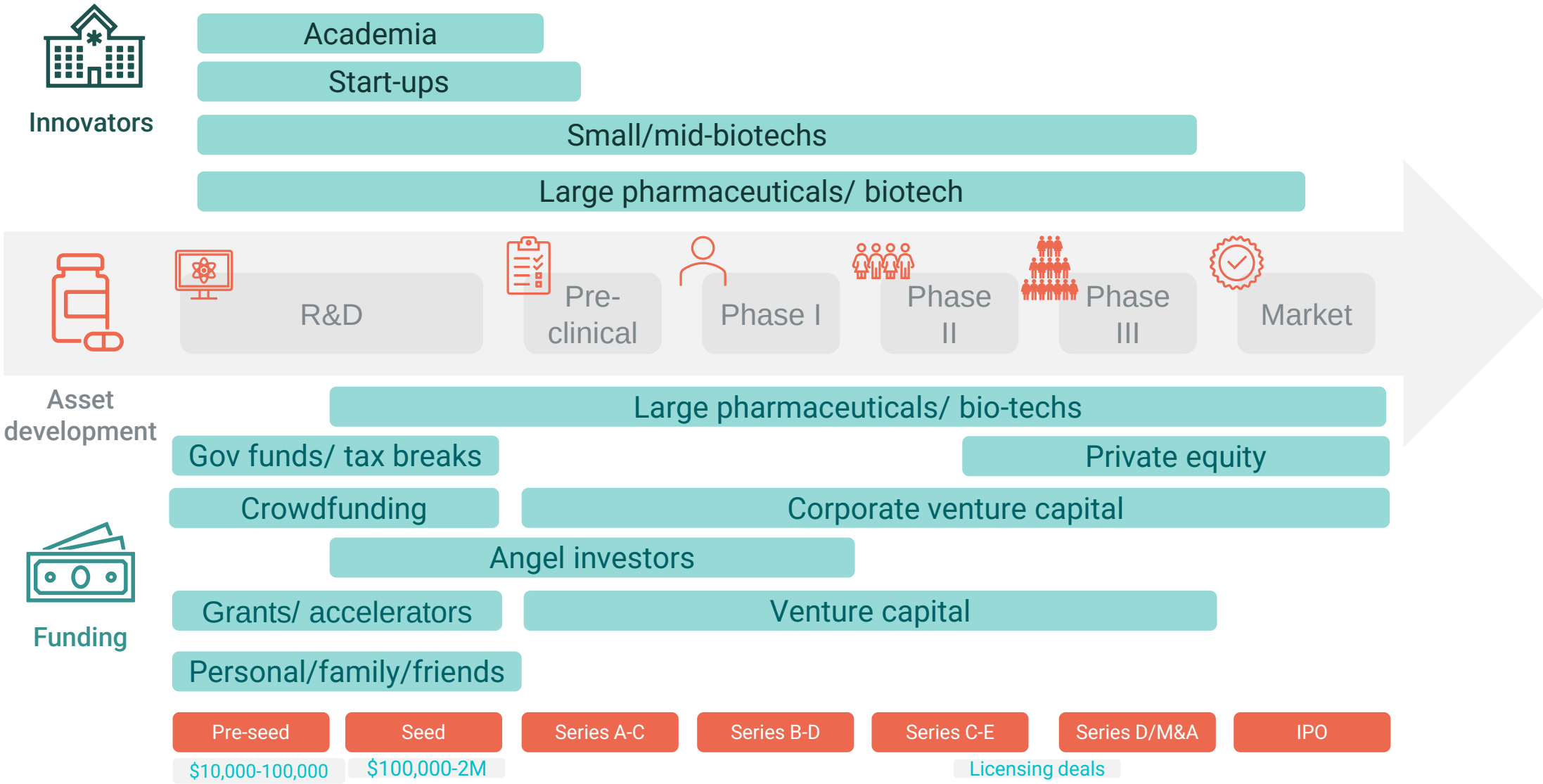
The IRA has already impacted investor behaviour and will spillover to other areas of development.

The IRA is distortionary, reducing interest in small molecules, orphan drugs, and indication extensions.

Future perspectives: The expansion of price regulation is the greatest concern of investors

1. Ecosystem

The innovation ecosystem is complex with many diverse sources of investment across the lifecycle of a product



Data extracted from Carmot homepage (data-cutoff is May 31 2024)

EXAMPLE: Carmot therapeutics

Therapeutics for those living with metabolic diseases including obesity and diabetes

Milestones

Jan 2018 Funding to support early clinical proof of concept for lead type-2 diabetes drug

Dec 2018 Phase 1 initiation for **CT-868**

Sep 2020 Financing to support Phase 2 study for **CT-868** and phase 1/2 studies for **CT-388**

May 2021 IND Clearance for **CT-868**

July 2022 Financing to support completion of phase 2 study for **CT-388**, phase 2 studies for **CT-868** and phase 1 studies for **CT-996**

Jan 2023 Spin-Off launch, Kimia Therapeutics

May 2023 Financing to support pre- and clinical pipeline

Nov 2023 Phase 2 initiation for **CT-868**

Jan 2024 Acquisition by **Roche**

R&D | Pre-clinical | Phase I | Phase II

Asset development

Funding

2009
- **Gov grant** US National science foundation

Grant $200k

2010
- **Venture capital** The column group

Series A

Jan 2018
- **Venture capital** Horizon ventures, The column group
- **Angel investment** Jerome Dahan

Series B $15m

Sep 2020
- **Venture capital** Horizon ventures, The column group
- **Corporate venture** Amgen
- **Institutional investors**

Series C $47m

July 2022
- **Venture capital** Horizon ventures, The column group, RA Capital, Deep Track Capital
- **Family office** Willett Advisors
- **Institutional investors**

Series D $160m

May 2023
- **Venture capital** Deep Track Capital, 5AM Ventures, Venrock Healthcare, RA Capital Management, The Column Group
- **Other funds** Frazier Life Sciences, TCGX
- **Family office** Willett Advisors
- **Asset management** Franklin Templeton, Janus Henderson Investors, Millennium Management

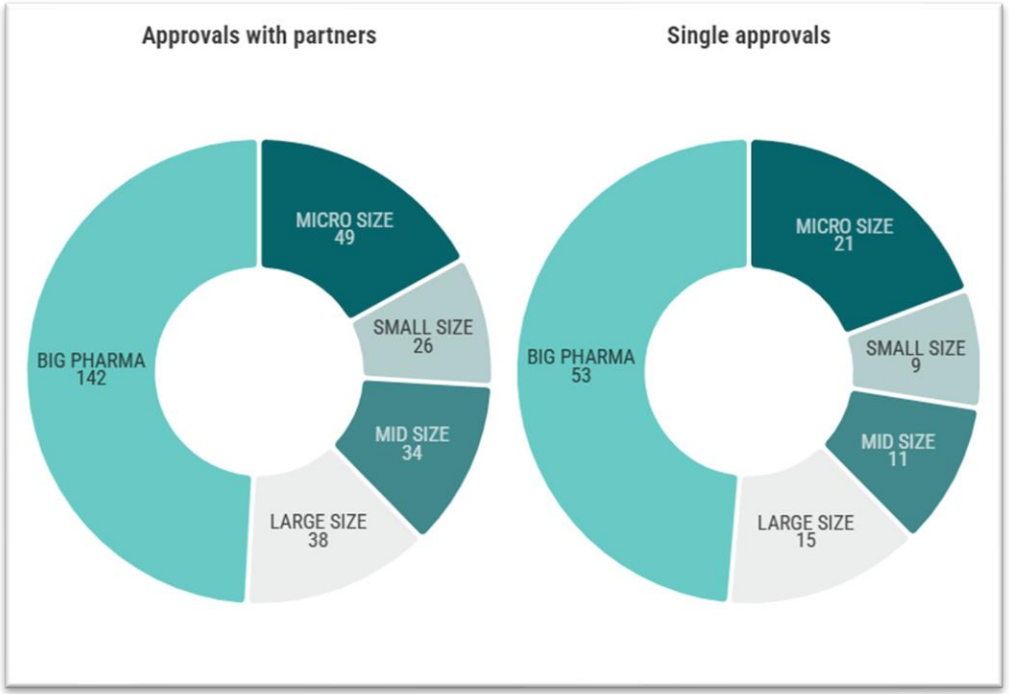
Series E $150m

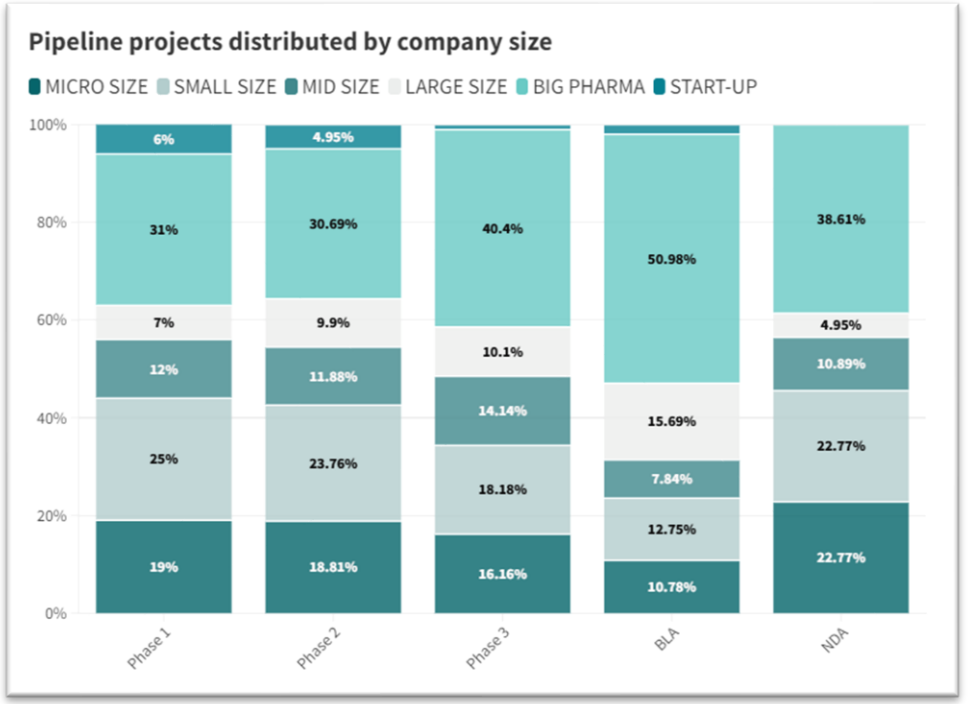
Jan 2024
- **Big pharma** Roche

Acquisition $2.7 billion

There is a rich ecosystem of companies developing and launching products

- Most drugs (~70%) are developed in partnership
- More drugs are brought to market by bigger companies, but preclinical and investigational new drugs are driven by smaller companies.





Data extracted from Citeline PharmaProjects (data-cutoff is May 31 2024)

Illustrate example: Imbruvica (Ibrutinib)

Data extracted from PitchBook (data-cutoff is May 31 2024)

OHE

Innovators & Asset Deals

Celera Genomics

Asset acquisition: ($2M + stocks)

Pharmacyclics

Co-development (up to ~$1 bn)

Company acquisition ($20bn)

AbbVie

Johnson & Johnson

Imbruvica

Discovery — 2005

Pre-clinical

Phase I — 2009: FDA IND

Phase II

Phase III

Market — 2013 First indication

Post-marketing R&D — Multiple Indication Extensions

Company Funding

Celera Genomics (1998)

- **VC Funding:** Flagship Pioneering, Asset Management Ventures
- **IPO** (2008)
- **M&A** (2011) by Quest Diagnostics

Pharmacyclics (1991)

- **VC Funding** (1994): Adams Street Partners, Alloy Ventures, Asset Management Ventures, BB Biotech, Blackstone Life Sciences, Comdisco Ventures, Integral Capital Partners, Kleiner Perkins, ProQuest Investments, Venrock;
- **IPO** (1995)
- **M&A** (2015) by AbbVie

AbbVie (2012)

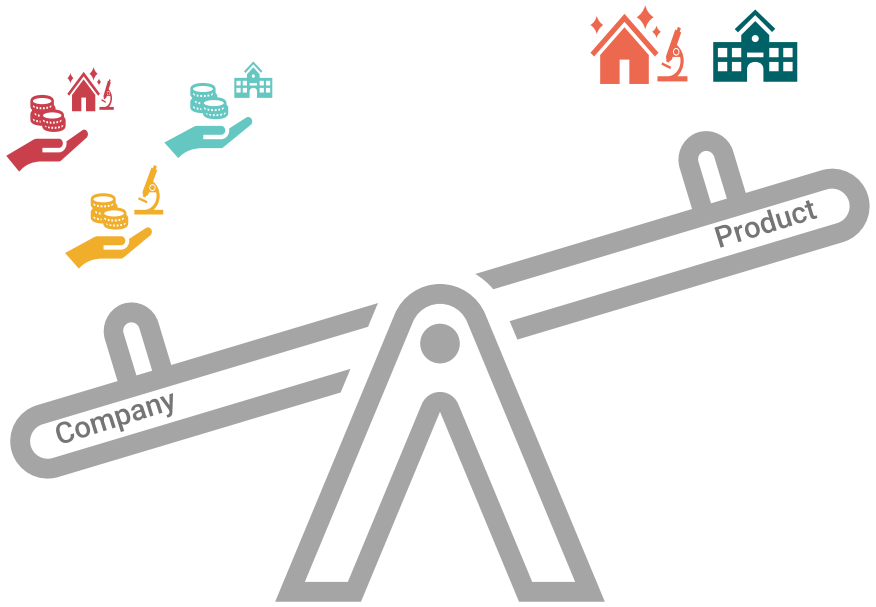
- **IPO**: (2013)
- Financing by **debt** and **VC**

Johnson & Johnson (1887)

- **IPO** (1944)
- Financing by **debt** & **private equity**

Investors focus on companies and companies focus on products

- Financial investors are primarily focussed on company investments. However, companies' individual assets are considered in the decision-making process.
- Small BioPharma normally focus on product-level R&D but requires buy-in from investors throughout the asset progression pathway.
- Large BioPharma can focus on product-level investment (in-house and licensing) with additional M&A activities.



Early-stage Venture Capital

Strong focus on company investment and attention to percentage ownership

Later-stage Venture Capital and Private Equity

Focus on company investment, but mindful of product, considering platforms or later stage assets

Corporate Venture Capital and investors

Strong focus on company investment, including seed, early stage, or clinical stage

Small BioPharma Company

Generally relies on product investment but focus on generating company investment for R&D activities.

Large BioPharma Company

- Product investment: inhouse or licensing
- Company investment: M&A

Results from the Investor Interview Series conducted by OHE Consulting Ltd.

Risk tolerance decreases through the development pathway

- For biopharma companies, risk tolerance decreases as companies advance their assets/innovations through the R&D pathway.
- Financial investors have higher risk tolerance, especially at early stages. They will build portfolios to reduce and spread risks.
- Investors try to ensure that failures are avoided at later stages, where costs for development are higher.

Early-stage Venture Capital

- Investment is heavily driven by risk-reward parameters
- Portfolio of investments to reduce and spread overall risks

Later-stage Venture Capital and Private Equity

Lower technical risk due to later stage investment, but logistics and supply chain can still pose a risk

Corporate Venture Capital and investors

Balancing risk tolerance to create synergy between biotech and big pharma

Small BioPharma Company

Building portfolio with larger (possible acquiring) company in mind to maximise chance of acquisition

Large BioPharma Company

- Larger portfolios to spread risks
- New investment is dependent on previous successes

Results from the Investor Interview Series conducted by OHE Consulting Ltd.

Capital is mobile – and it's on the move

- Across financial markets: investment capital is mobile. Biopharma can be seen as a riskier market due to high inflation of R&D costs and longer-term investment periods.
- More competitive markets like AI and tech have already been considered by some investors as alternatives to biotech.
- Within portfolio: investment decisions are generally made by considering the rest of the portfolio, previous investments, and past successes.

Early-stage Venture Capital

- Capital is mobile
- Investors have already moved away from non-performing sectors to more lucrative ones

Later-stage Venture Capital and Private Equity

- Capital is mobile
- Investors have already exited the biotech market amid risks like IRA

Corporate Venture Capital and investors

- Capital is somewhat mobile

Small BioPharma Company

- Dependent on a functional capital market for R&D investment

Large BioPharma Company

- Less dependent on capital market
- Own capital is not particularly mobile, and disinvesting can be a difficult decision

Results from the Investor Interview Series conducted by OHE Consulting Ltd.

Big bets require big returns

- Investment in companies is different to funding specific product development:
  - Company investment -> return on investment through investment *exit strategies*
  - Product Investment -> return on investment through *revenue.*
- Moderately positive NPV is *not* the sole basis for investment decisions. Different expectations of returns and multiple other factors play a role.
- NPV calculations or revenue estimates may not be accurate at early-stages of investment.

Early-stage Venture Capital	Later-stage Venture Capital and Private Equity	Corporate Venture Capital and investors	Small BioPharma Company	Large BioPharma Company
Potential return on investment required (3x return or higher)	Potential return on investment required (3x return or higher)	Potential return on investment required ▪ Fulfilment of mission - if mission-driven	Might just follow strategy without NPV as core influencing factor	Value could expand into other indications

Results from the Investor Interview Series conducted by OHE Consulting Ltd.

One size does not fit all

- Multiple factors drive decision to invest, including unmet need, therapeutic area, type of asset, preliminary evidence on asset and regulatory requirements.
- Investment appraisals, and therefore relationships between market size and R&D, vary across different therapeutic areas and modes of action.

Modality/Asset

What type of product is it and how much it will cost to get the asset manufactured; e.g., cell therapies are more complex and therefore require more capital than small molecules or proteins which are easier to manufacture.

Therapeutic area

What is the competition and unmet need. Also, what is the population size and size of the clinical trial program. Costs of clinical trials depend on scale, e.g. cardiovascular trials require large populations and longer horizons.

Early-stage Venture Capital

- Unmet need
- Type of innovation

Later-stage Venture Capital and Private Equity

- Focus on product differentiation

Corporate Venture Capital and investors

- Unmet need
- Fulfilment of mission (if mission-driven)

Small BioPharma Company

Focus on smaller markets and smaller clinical developments with unmet need

Large BioPharma Company

- Focus on larger indications and high unmet need.
- Strategy depends on portfolio and therapeutic area

Results from the Investor Interview Series conducted by OHE Consulting Ltd.

R&D is more expensive and increases across the development path

- Cost of R&D has increased, driven by factors including inflation, medicines being more complex to manufacture and clinical trials becoming increasingly logistically difficult.
- Cost of R&D increases over the asset development process, making it difficult to support full clinical developments for smaller companies backed by investment only. Exit strategies for investors and small companies take this into account.
- VC investors often also help their companies to reduce R&D costs and increase efficiencies at early stages.

Early-stage Venture Capital

- Clinical costs can end up being too high
- Exit strategies earlier in clinical development or partnering

Later-stage Venture Capital and Private Equity

- Clinical costs can end up being too high
- Exit strategies earlier in clinical development or partnering

Corporate Venture Capital and investors

- Clinical costs can end up being too high
- Exit strategies earlier in clinical development or partnering

Small BioPharma Company

- Clinical costs can end up being too high
- Exit strategies earlier in clinical development or partnering

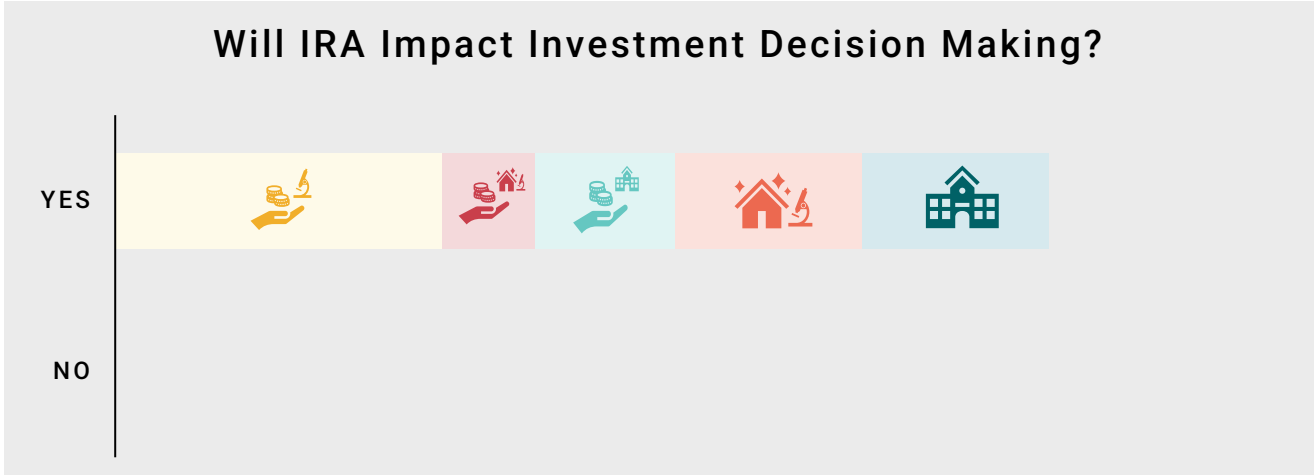
Large BioPharma Company

Time to market is becoming increasingly important because of IRA, so trial duration is an important factor determining investment

Results from the Investor Interview Series conducted by OHE Consulting Ltd.

The IRA has already impacted investor behaviour

- IRA has changed signals for what will be valued. Hence, IRA impacts investment decision making for all investors in the ecosystem.
- Extent of price reductions currently unknown, but investors model it as earlier “genericization”.
- Investors and biopharma companies are already actively taking IRA into account in their investment decision making models. Investors already actively discuss IRA with their invested companies.



Early-stage Venture Capital

IRA increases risk of assets and hence affects company investment decision making especially for companies operating in areas affected by IRA regulation

Later-stage Venture Capital and Private Equity

IRA increases risk of assets and hence affects company investment decision making especially for companies operating in areas affected by IRA regulation

Corporate Venture Capital and investors

IRA increases risk of assets and hence affects company investment decision making especially for companies operating in areas affected by IRA regulation

Small BioPharma Company

- Affected by devaluing of assets by investors
- Changing development strategies with view on large companies as exit strategy

Large BioPharma Company

- Adjustment of revenue forecasts
- Carry-over effect onto other assets in development
- Broader considerations on indications and sequences

Results from the Investor Interview Series conducted by OHE Consulting Ltd.

The impacts of IRA will spillover to other areas of pharma development

IRA will reduce revenue of top selling drugs. Investors describe that up to 75% of revenue is derived from the US, hence the IRA will significantly and disproportionately reduce the total return on investment and revenue of drugs. This will have spillover effects on the early investment ecosystem, R&D activity, commercialisation, generic/biosimilar market, and the job market.

- **Early investment ecosystem:** Investors will try to consolidate and work in syndicates to create smaller but better-financed company pool, because of higher risk and financing is hard to get.
- **R&D activity:** Investors highlight that when the revenue of the top-selling drugs is reduced, it will affect the investment into other assets in the R&D portfolio. The most profitable drugs are considered outliers and important profit centres for the biopharma industry to compensate for other less profitable assets and R&D investments. R&D in biopharma is risky there is not an option to *not* invest into promising early-stage assets that may not end up succeeding.
- **Commercialisation**: Investors outlined that commercialisation of assets is risky and hard, as exemplified by companies often losing value after drug approval. IRA will make commercialisation of assets not acquisitioned before phase 2 even harder as it reduces the economic incentives.
- **Generic/biosimilar market**: Investors highlighted that they are not generally interested in the biosimilar/generic market, but they predict that IRA will also lead to a devaluation amid the devaluation of branded products before patent expiration.
- **Job market:** Investors stressed that IRA may impact the biopharmaceutical industry's ability to create jobs, skills and opportunities.

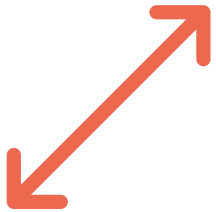
The IRA is distortionary reducing interest in small molecules, orphan drugs, and indication extensions

IRA won't affect all products and developments equally. Especially hit are small molecule developments, orphan medicines and indication extensions, and certain therapeutic areas affecting the population covered by Medicare.

- **De-prioritisation of small molecule assets**: distorted signal, leading to not all drug targets being incentivised equally. There is no scientific rationale as to why intracellular therapeutic drug targets that are best addressed by small molecules should be deprioritised.
- **De-prioritisation of orphan medicines:** while orphan medicines are excluded for their first indication, IRA will be applicable in case the indication is extended. The orphan medicines incentive is the main driver behind the biotech business model and this is likely to be impacted by IRA.
- **Strategic rethinking of sequencing of indications:** since the time to pricing reductions starts ticking from the first indication, investors are re-thinking the sequencing of indications and marketing authorisations. Generally, medicines are first studied in smaller populations before expansion of indication. IRA could change this paradigm and lead to delays in access.
- **De-prioritisation of indication extensions**: since the time to pricing reductions starts ticking from the first indication, investors are re-thinking the value of extending indications to novel patient populations. One investor even thought about developing multiple me-too drugs with the same mechanism of action to treat different conditions rather than developing one molecule and extending the indication.

The expansion of price regulation is the greatest concern of investors

Investors shared some perspectives regarding the future of price regulation in the US:



Expansion

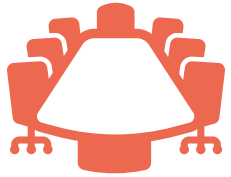
Investors shared their concerns regarding the possibility of expansion of price regulation, like in other areas of the world which may not pay their “fair share” of medicines development

Protection of Small Molecules

In the current scheme, investors believe that the protection period of small molecules needs to be extended to 13 years to allow for higher recuperation of investment

Better Information

Investors call for a more informed policy debate and would like to see more education and information on the benefits of pharmaceutical innovation and how medicines are developed.



Other Actors

Innovators highlighted that any US pricing policy should also consider other actors in the USA supply chain that can have an impact on drug pricing for example pharmacy benefit managers (PBM)

Results from the Investor Interview Series conducted by OHE Consulting Ltd.

CBO model assumptions do not adequately reflect the complex investor decision-making landscape

1. Ecosystem

The innovation ecosystem is more complex than the assumptions in the CBO models. It features many diverse sources of investment across the lifecycle of a product, which differ in risk, capital, and other factors that affect investment decisions.

2. Company vs product

Investors do not make product by product decisions. Instead, investment decisions are often made at the company or product portfolio level. CBO doesn't consider the capital investment market.

3. Risk and capital mobility

Capital is mobile and risk tolerance decreases along the development path. Biopharmaceutical investments are more sensitive than CBO models predict.

4. Investment decision

Big bets require big returns. CBO models assuming any marginally positive expected NPV is sufficient to incentivize investment will understate investment impacts.

5. Cost of R&D

R&D costs have increased. CBO models that use historical estimates of R&D costs will understate impacts.

6. Impact of IRA

The IRA will spill over to other areas of drug development. In addition, the distortionary impact (on small molecules, orphan drugs and indication extension) is not captured by CBO models that only consider impact on the "number of drug approvals."

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Are we even asking the right question?

Shouldn’t policymakers care about the “quality” rather than the “quantity” of innovation?

To enquire about additional information and analyses, please contact:

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