VitalTransformation

The impact of health technology made simple

H.R. 3 and Reference Pricing

Total Market Impact

March 22, 2021

Prepared in collaboration with

CSBA Council of State Bioscience Associations

BIOCOM

CLSA California Life Sciences Association

Executive Summary

- Numerous proposals are being considered that would use the average of pricing in other countries to control US drug prices. Proponents argue that this can be done with little impact on innovation.
- Using the Lower Drug Costs Now Act ("H.R. 3") as an example, we find that implementation of international reference pricing in the United States would:
    - Reduce earnings by 62% on average for impacted companies, with one third (32%) of affected companies having reductions larger than 95% of earnings (using conservative assumptions about the impacts on prices).
    - In turn, markedly reduce biopharmaceutical companies' investments in smaller company R&D through M&A, partnerships and other arrangements.
    - Reduce by 90%+ the number of medicines developed by small and emerging biotechs -- 61 fewer medicines over 10 years.
    - Disproportionately impact new treatments in rare diseases, oncology, and neurology.
    - Create large investment ecosystem losses to smaller companies in 19 states.
    - Eliminate nearly 200,000 biopharmaceutical industry jobs, and nearly 1 million jobs across the economy.

Introduction

- **What is an "international pricing index"?**
  - Sets a maximum US price based on the prices for medicines paid in foreign markets, this is called a price ceiling.
  - Price ceilings generally create supply shortages, as they limit the ability of producers to meet market demand; EU payers regularly use delayed access to justify lower prices.
  - The delay in access to new therapies in France, according to the French Government, is nearly two years (540 days); the US market and EU markets are very different in how they provide access.

Overview: What does H.R. 3 do?

- HHS Secretary would be empowered to directly negotiate prices of up to 250 single-source, non generic drugs – 125 drugs in Part D with the highest net spending, or 125 "other drugs" with high net spending across the U.S. in Medicare Parts D and B.
- The H.R. 3 price is determined by a negotiation process that would be available to all purchasers, i.e. **the entire US commercial market** - not just Medicare beneficiaries.
- To control price hikes, price increases are held to the rate of inflation.
- The bill has a minimum inclusion of 25 drugs in 2023, and 50 drugs in 2024.
- H.R. 3 sets a maximum price for any negotiated drug based upon the average international price (AIM) of the weighted average of the drug's price in Australia, Canada, France, Germany, Japan, and the United Kingdom.
- The maximum allowed price is 120% of the AIM price; the 'target price' or goal of the negotiation in terms of HHS, is the lowest price included in the AIM.
- The negotiated "maximum fair price" is determined by CMS to be between the target and the maximum allowed price.

H.R. 3 Pricing

- The ‘target price’ for a drug will be 1.2 times (or 120 percent) of the volume-weighted average International Price Index in the six benchmarking countries.
- The “maximum fair price” will be set by HHS and is negotiated downward from the target price, which cannot be exceeded.
- If a manufacturer refuses negotiations, they will be charged an excise tax between 65-95 percent of annual gross sales.
- H.R. 3 includes all brand-name drugs without two or more generic, biosimilar, or interchangeable biologics up to 125 Medicare Part D therapies, and 125 “other drugs” that have high net spending across the U.S.
- The Secretary would also be empowered to negotiate the price of any newly-launched drug with a wholesale acquisition cost above the median household income.
- Insulin products are also negotiated under the same procedures as H.R. 3 products, and are separate from the 125 drug limit.

Study Objectives:

- We developed a model that measures the impact of H.R. 3 on the biopharmaceutical industry assuming several scenarios:
  - A 'minimum' implementation of 25 drugs in 2023 and 50 drugs in 2024
  - Mandatory Insulin negotiations under H.R. 3 in all cases
  - A 'full' implementation of the top 125 drugs by spending, plus 26 insulin drugs, under H. R. 3
- We model H.R. 3's impacts for the entire commercial market, including globally
- We calculated the impacts of H.R. 3 on the investment ecosystem and drug development under the above scenarios, both for the entire US and for key states.

H.R. 3 Methodology

- Current drug prices for included H.R. 3 therapies were obtained with current pricing listed in the WHO National Medicine Price Sources, UK Monthly Index of Medical Specialties, Japan Ministry of Health, Labor and Welfare, Canada Ontario Drug Benefit Formulary, Australia Pharmaceutical Benefits Schemes, Portugal National Authority of Medicines and Health products, France Ministry of Health, Netherlands College voor Zorgverzekeringen, Germany Lauer-Taxe, Denmark Medicin Priser, Sweden Dental and Pharmaceutical Benefits Agency (TLV), and Switzerland Federal Office for Public Health.
- H.R. 3 revenue reductions were modeled at the drug level based upon per dose data obtained from the Medicare Part D & B Drug Spending Dashboard, audited SEC financial statements, and Biomedtracker by Informa.
- GDP, country growth, population/demographic shifts and Purchasing Power Parities were modeled and included within price elasticity calculations to estimate the long-term economic impacts of H.R. 3.
- The investment/partnering activity over the previous 10 years for H.R. 3 impacted companies was measured using the Biocentury IQ Portal, and then statistically reduced based upon the calculated H.R. 3 impact at the firm level.
- The impact of revenue losses caused by H.R. 3 was statistically modeled to determine the revised probability of approved products entering the market from 2009-2019.

H.R. 3 Key Findings I

- If enacted, H.R. 3 pricing is projected to:
  - reduce US biopharmaceutical industry annual earnings, assuming no defensive measures, from $183 billion to $81 billion in the year 2024 minimum - a reduction of 56%. On average, this is a loss of $102 billion in revenue per year, best case.
- Several companies, many with multiple successful products in H.R. 3, are projected to see revenue reductions larger than their current annual earnings (EBIT), -121%. A third of all affected companies have reductions larger than 95% of net earnings.
- H.R. 3 “penalizes” companies producing the most effective and innovative treatments, many in Oncology, Neurology, Pulmonology and Rheumatology.
- Given its breadth, if enacted, we expect companies will likely avoid developing many Medicare Part D & B therapies altogether, given the punitive H.R. 3 penalties and disincentives.
- It is likely that upwards of $22 billion in revenue from our cohort is being ‘trapped’ by PBMs and not being passed through to patients in terms of savings.

H.R. 3 Key Findings 2 – Ecosystem impacts

- Over the last 10 years, companies that would be affected by H.R. 3 have invested $487 billion into 215 venture partnerships, the majority in the US, leading to 68 approved therapies (this total removes M&A's by J&J/Actelion, AbbVie/Allergan, and BMS/Celgene, Pfizer/Wyeth, Merck/Schering-Plough; if included the total is in excess of $700 billion).
- The potential reduction of $100 billion a year in revenue under H.R. 3 is more than twice the annual $48.7 billion a year in partnership investments from 2009 -2019.
- Controlling for all other factors, the revenue reductions under H.R. 3 would be expected to lead to radical US industry consolidation, and shrink market entry of new drugs from the 68 new assets approved during 2009-2019 in our research cohort to 7 under the most optimistic modeling scenarios
- California alone accounts for 25% of total inward & outward investments of $122 Billion into small emerging biotech companies and for 17 of the 68 US drug approvals in our emerging biotech cohort (roughly 25% of the total), it is the largest in the US.
- Under H. R. 3, only 2 of the 17 medicines produced in California from venture partnerships would have come to market, an 88% reduction.

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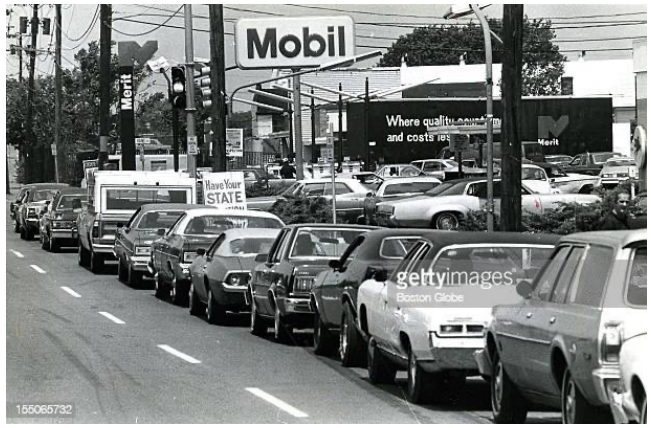
Modeling the impact

H.R. 3 in practice

HR3 is a Price Ceiling, Price Ceilings Limit Access

"A price ceiling occurs when the government puts a legal limit on how high the price of a product can be. . .when a price ceiling is set, a shortage occurs."

USSR & Venezuela
price ceilings on food



"History 101: Price controls don't work"

"Price controls on oil, gasoline and petroleum products. . .were disastrous."
https://www.chicagotribune.com/news/ct-xpm-2007-06-07-0706061080-story.html

Price ceilings limit access in healthcare too

POLITICO

January 27, 2021

How Europe fell behind on vaccines

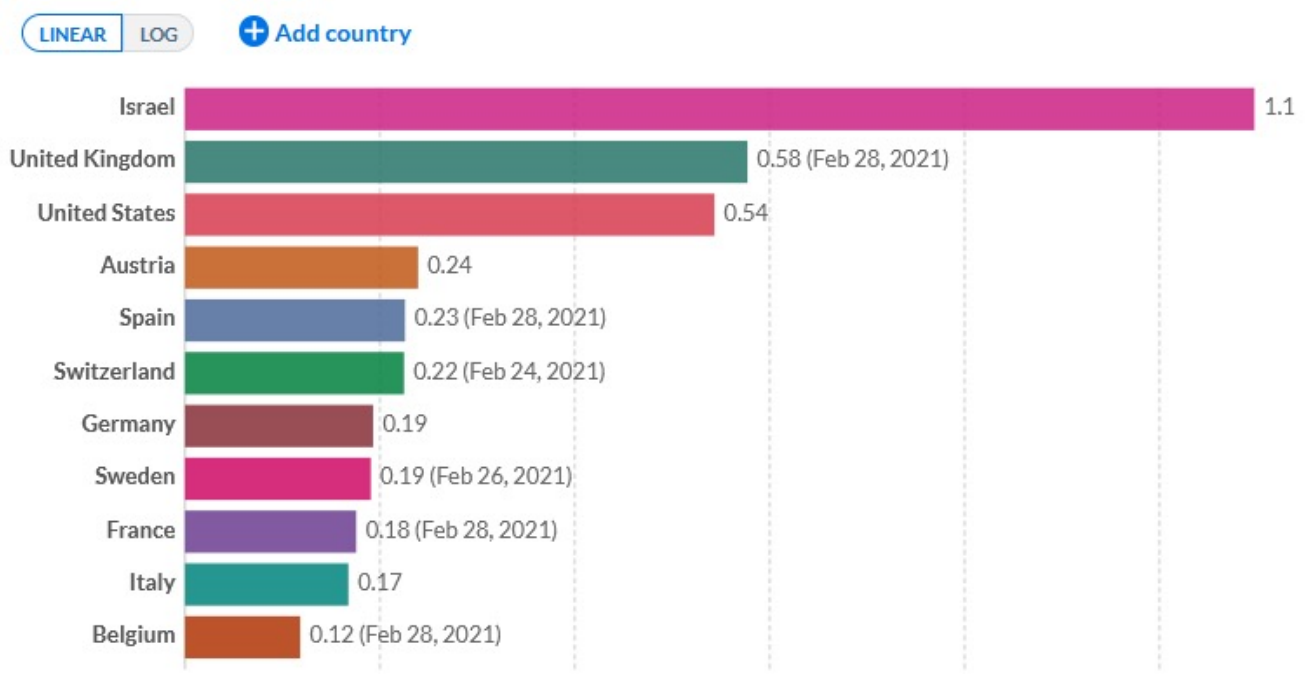
The EU secured some of the lowest prices in the world. At what cost?

"A vaccine strategy that was supposed to be a forceful show of European solidarity, an assertion of the single market's buying power and a moral stand against Trumpian "vaccine nationalism" resulted in a rollout that has left the EU lagging behind the United Kingdom and the United States…

Pfizer committed to delivering 200 million doses for Americans — produced on U.S. soil — by the end of July, while the EU isn't assured that sum until September."

Impact of price ceilings on EU vaccine availability

7 day average COVID-19 vaccine doses administered per 100 people - Mar 1, 2021



Country	Days to Vaccinate Population
Israel	91
US	185
Germany	526
France	556
Belgium	833

2023 & 2024 Minimum Revenue Impact by Clinical Area

Clinical Areas	25 H.R. 3 Therapies	2023 Estimated Global Sales ($US Mil)	2023 H.R. 3 Revised Sales ($US Mil)	% Change
Oncology	7	$48,343	$38,205	21%
Rheumatology	4	$27,310	$16,172	41%
Neurology	5	$21,913	$8,503	61%
Other:	9	$35,136	$17,694	50%
Ophthalmology				
Hematology				
Immunology				
Dermatology				
Gastroenterology				
Grand Total	**25**	**$132,702**	**$80,575**	**39%**

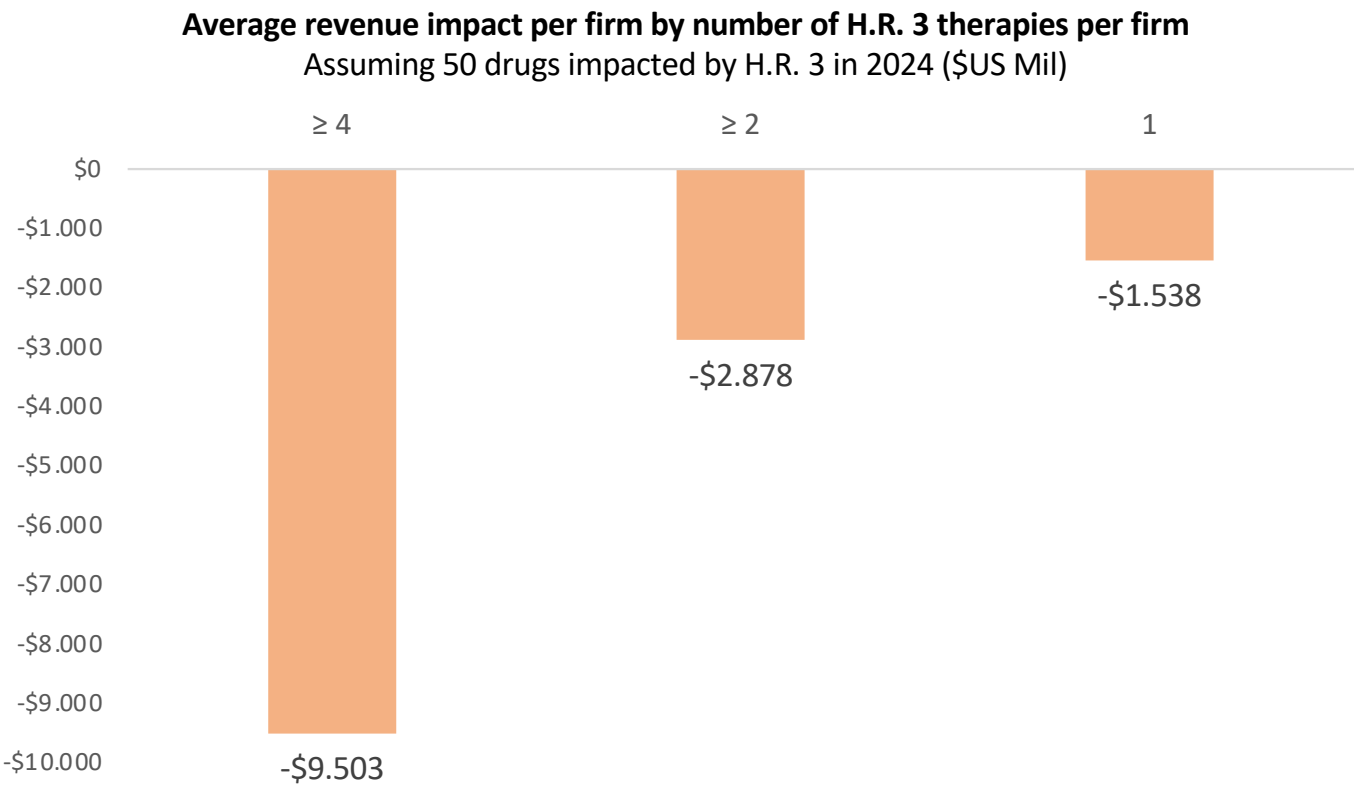
Clinical Areas	50 H.R. 3 Therapies	2024 Estimated Global Sales ($US Mil)	2024 H.R. 3 Revised Sales ($US Mil)	% Change
Oncology	10	$61,875	$51,833	16%
Rheumatology	8	$47,836	$28,302	41%
Immunology	6	$26,655	$14,898	44%
Neurology	9	$31,070	$11,340	64%
Other:	17	$50,600	$26,690	47%
Hematology				
Ophthalmology				
Pulmonology				
Dermatology				
Gastroenterology				
Cardiology				
Urology				
Endocrinology				
Grand Total	**50**	**$218,035**	**$133,063**	**39%**

Estimated H.R. 3 Macro Revenue Impact, 2023 & 2024

- Assumes 25 drugs in 2023 and 50 drugs in 2024 with the greatest total budgetary impact.
- 26 insulin products with the greatest total budgetary impact included in H.R. 3 in both years.

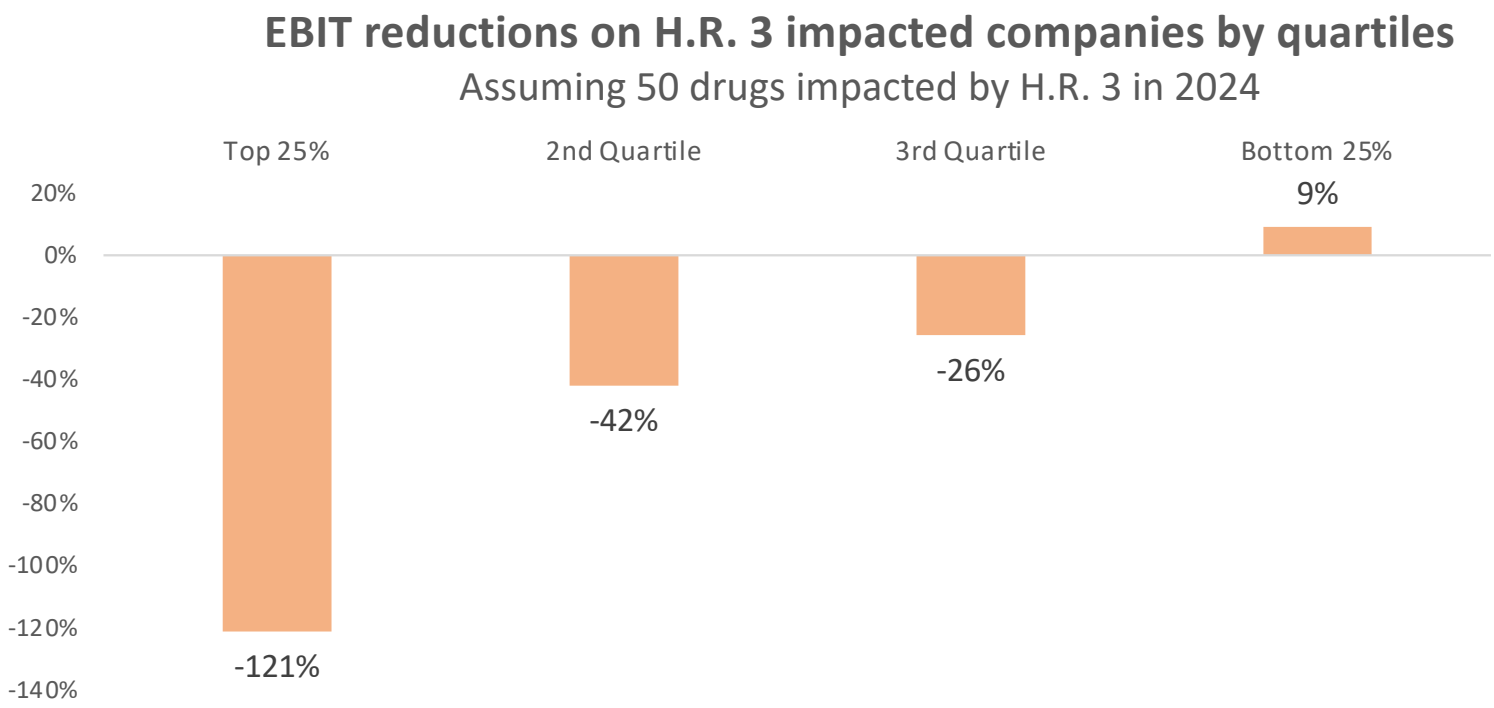
H.R. 3 Impact	2023 Estimated	2023 H.R. 3 Impact	2024 Estimated	2024 H.R. 3 Impact	Revenue Reduction	Total Lost Revenue 2023 & 2024
Diabetes	$33,702	$16,346	$33,702	$16,346	51%	$34,711
2023 25 Drugs	$132,702	$80,575			39%	$52,127
2024 50 Drugs			$218,035	$133,063	39%	$84,972
				TOTAL Revenue Impact 24 Months ($US Mil)		**$171,811**
					TOTAL 2023	$69,483
					TOTAL 2024	$102,328

2024 H.R. 3 Revenue at the company level: 50 Therapies



- H.R. 3 "penalizes" those companies that have invested most in treatments for Medicare Parts D & B.
- The disincentives to product development are additive, in that the more products a company has that are targeted by H.R. 3, the more the firm's cashflow will be impacted.
- The potential cash impacts are major, and would have devastating impacts on innovation and jobs.

H.R. 3 minimum impact on available cash for investments/pipelines



EBIT = earnings before interest expense and tax, i.e. net cash available to a firm at year end

* The $98.4 billion result excludes the H.R. 3 impact upon insulin drugs from the calculation, i.e. this result likely underestimates the full impact on industry

- H.R. 3 reduces the ability of companies to reinvest their free cash flow into their future pipelines.
- The most impacted 25% of companies show **reductions of 121% that exceed their current net annual earnings (EBIT).**
- When applied to 50 therapies in 2024, H.R. 3 implementation is projected to reduce EBIT for all H.R. 3 impacted companies from $183 billion to $98.4* billion, a 46% reduction.

2023 Full H.R. 3 Revenue Impact by Clinical Area

125 therapies ($US Mil)

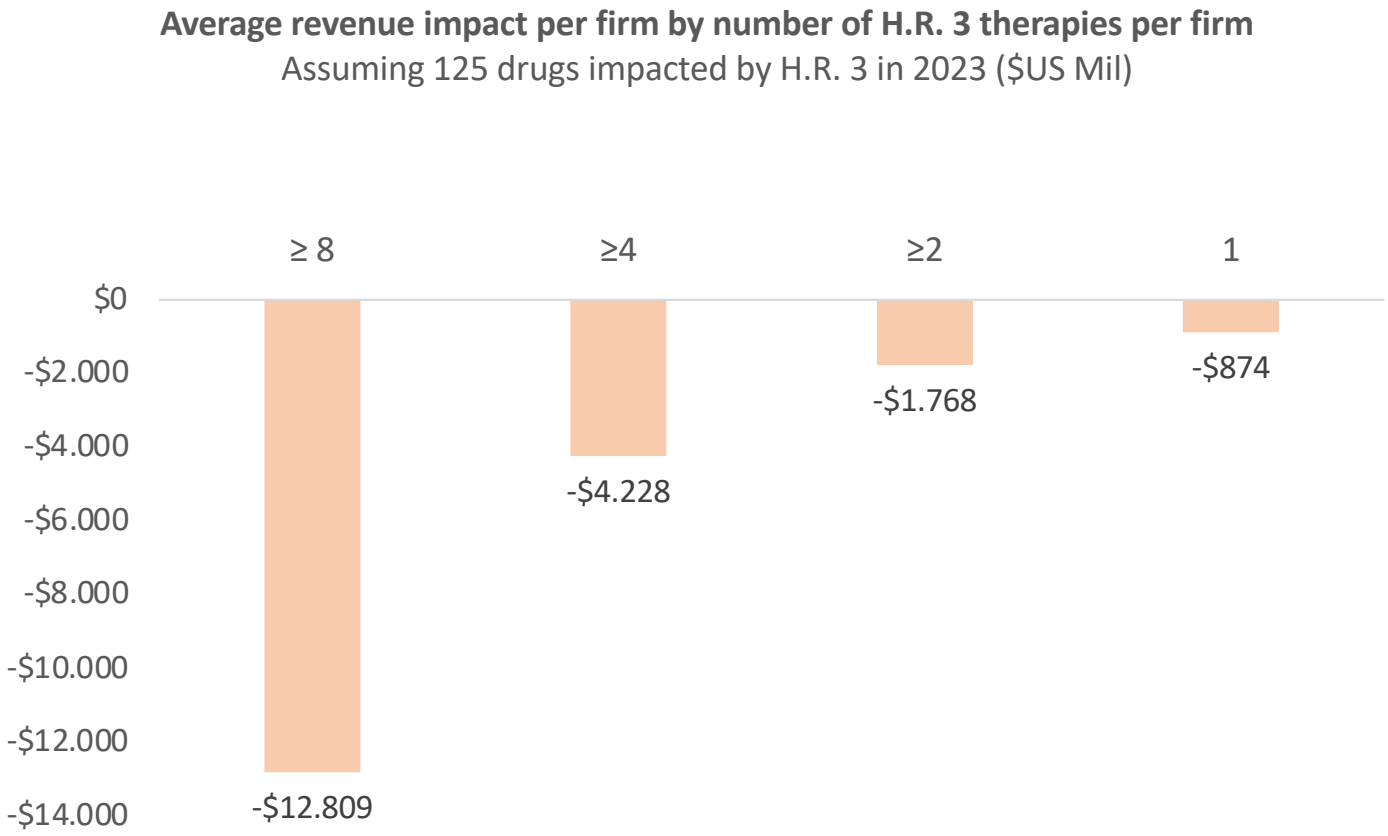
Clinical Area	H.R. 3 Therapies	2023 Estimated Revenue	H.R. 3 Revised Revenue	H.R. 3 Reduction ($US Mil)	Change in Revenue
Oncology	24	$85,345	$70,708	-$14,637	-17%
Neurology	21	$48,311	$20,207	-$28,104	-58%
Pulmonology	17	$20,749	$12,963	-$7,786	-38%
Rheumatology	17	$60,907	$33,993	-$26,914	-44%
Immunology	11	$33,966	$19,239	-$14,727	-43%
Hematology	8	$23,018	$10,856	-$12,162	-53%
Gastroenterology	7	$10,786	$6,020	-$4,766	-44%
Cardiology	6	$5,680	$2,544	-$3,137	-55%
Ophthalmology	5	$13,347	$6,527	-$6,820	-51%
Other:	9	$23,014	$16,848	-$6,165	-27%
Urology					
Dermatology					
Endocrinology					
Grand Total	**125**	**$325,123**	**$199,906**	**-$125,217**	**-39%**

Estimated H.R. 3 Impact, all 125 Drugs and Insulin

- Assumes top 125 priced drugs reviewed in 2023 and 26 insulin products with the greatest total budgetary impact included under HR3.

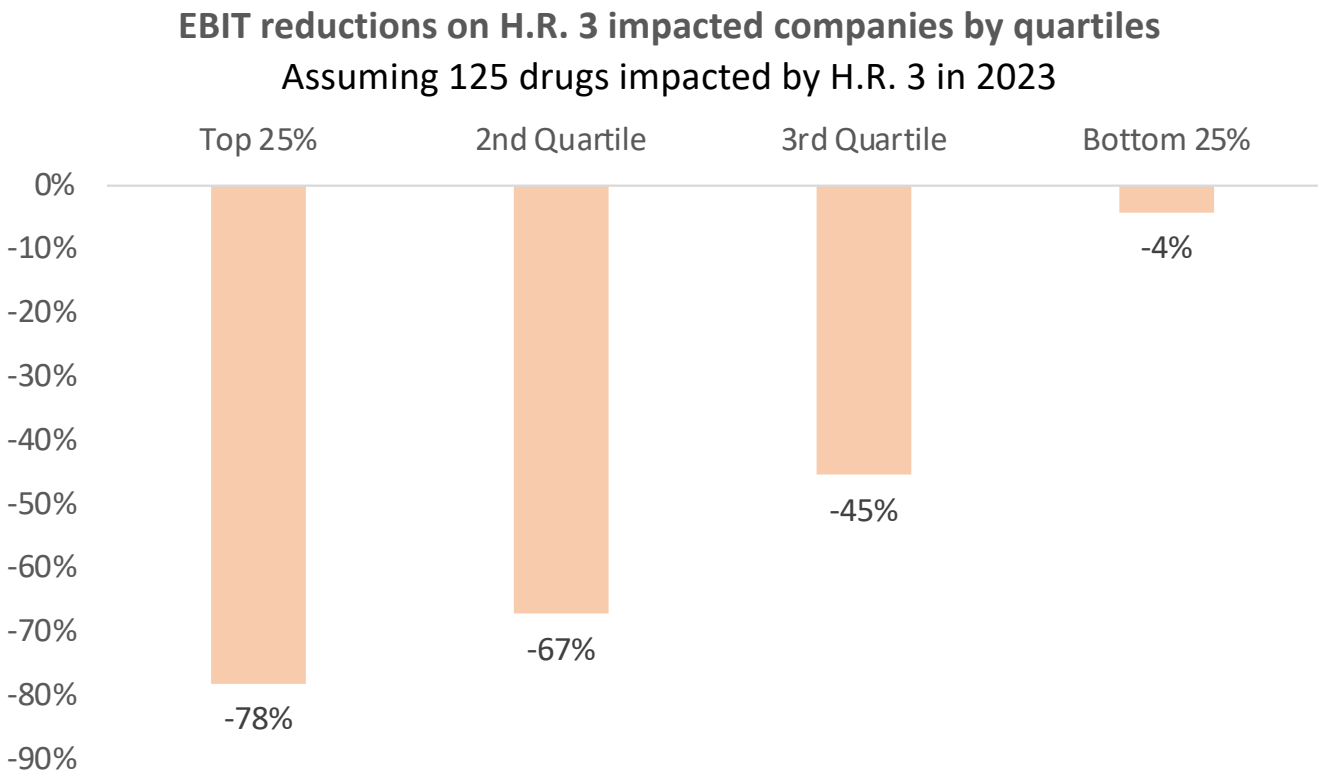
H.R. 3 Impact	2023 Estimated	2023 H.R. 3 Revised	Revenue Reduction %	Subtotal Lost Revenue
Diabetes	$33,702	$16,346	-51%	$17,356
2023 125 Drugs	$325,123	$199,906	-39%	$125,217
			Total 2023 Impact ($US Mil)	**$142,573**

2023 H.R. 3 Revenue at the firm level: 125 Therapies



- H.R. 3 "penalizes" those companies that have invested most in treatments for Medicare Parts D & B.
- The disincentives to product development are additive, in that the more products a company has that are targeted by H.R. 3, the more the firm's cashflow will be impacted.
- The potential cash impacts are major, and would have devastating impacts on innovation and jobs.

H.R. 3 125 drug impact on available cash for investments/pipelines

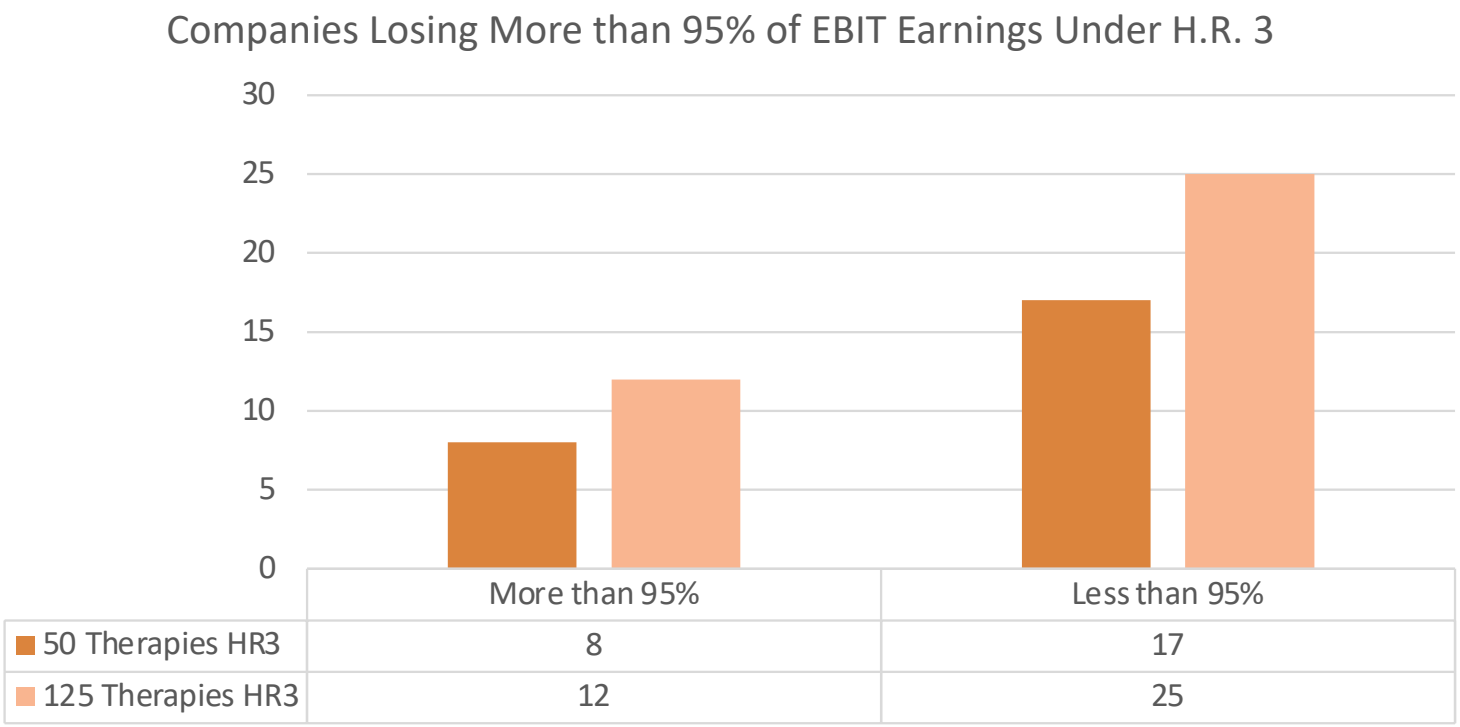


EBIT = earnings before interest expense and tax, i.e. net cash available to a firm at year end

* The $125 billion result excludes the H.R. 3 impact upon insulin drugs from the calculation, i.e. this result likely underestimates the full impact on industry

- H.R. 3 reduces the ability of companies to reinvest their free cash flow into their future pipelines.
- The most impacted 25% of companies show **reductions of 78% of their current net annual earnings (EBIT).**
- The 2023 estimated EBIT for all H.R. 3 impacted companies is $204 billion, H.R. 3 with 125 therapies reduces earnings by $125* billion, a 62% reduction in the cohort.

A third of H.R. 3 affected companies lose more than 95% of their earnings



- H.R. 3 will remove nearly a third of all existing large pharmaceutical companies' earnings, essentially bankrupting a substantial part of the sector

EBIT = earnings before interest expense and tax, i.e. net cash available to a firm at year end

H.R. 3 Direct and Total Supported Job Losses

Total US and 15 most impacted regions/states

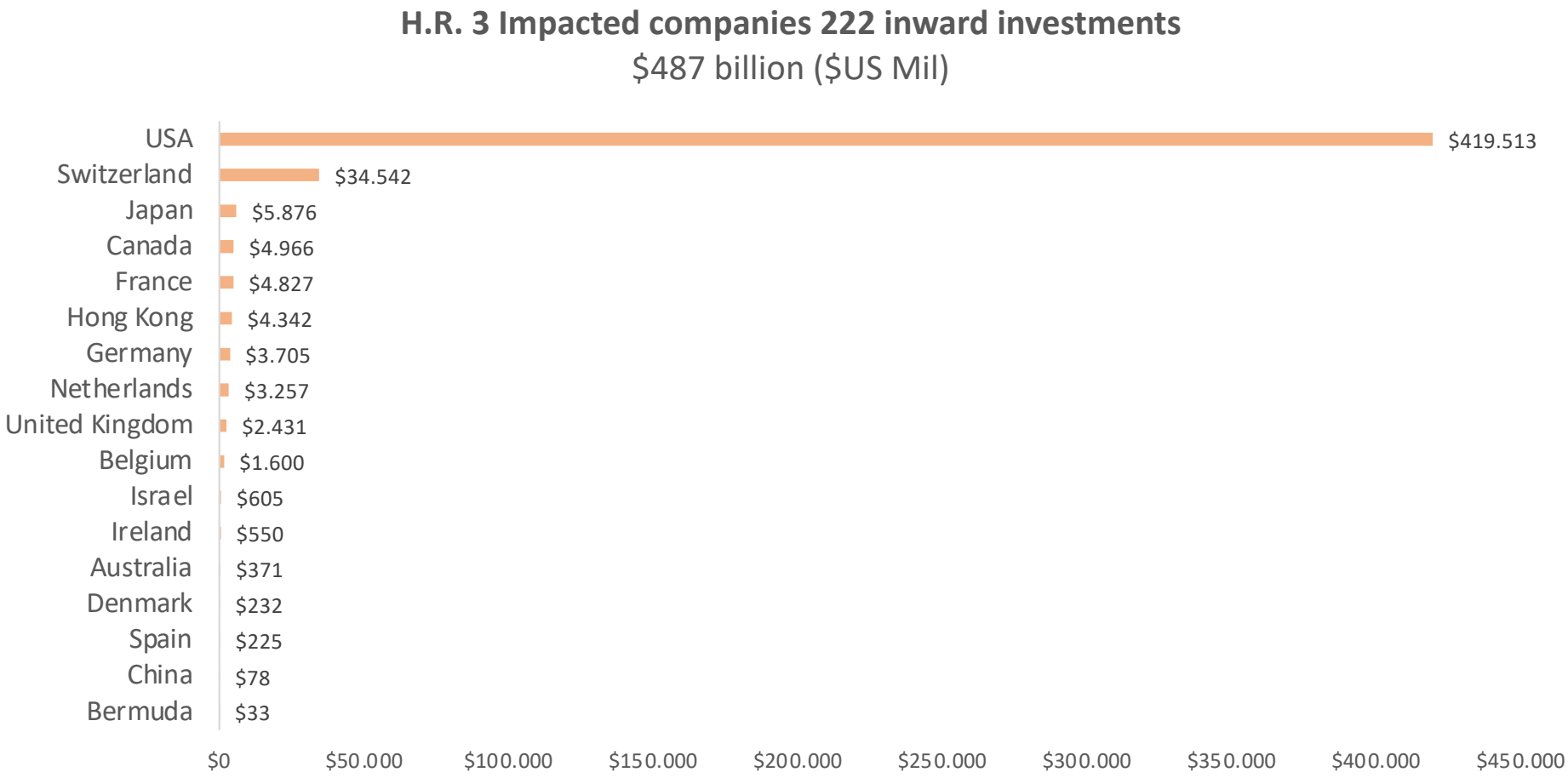
	$132 Billion Annual Revenue Reduction (125 Drugs)			$100 Billion Annual Revenue Reduction (50 Drugs)		
State	Direct Biopharma Jobs Impact	Total Biopharma Supported Jobs Impact	Biopharma Supported Output Impact ($M)	Direct Biopharma Jobs Impact	Total Biopharma Supported Jobs Impact	Biopharma Supported Output Impact ($M)
Totals, U.S. & PR	**-190883**	**-950463**	**-$270,505**	**-144608**	**-720048**	**-$204,928**
California	-32863	-178791	-$54,222	-24896	-135448	-$41,077
New Jersey	-14288	-71834	-$19,635	-10824	-54420	-$14,875
Massachusetts	-14293	-66916	-$16,683	-10828	-50694	-$12,639
Pennsylvania	-11021	-59743	-$15,839	-8349	-45260	-$11,999
North Carolina	-10582	-59078	-$17,523	-8017	-44756	-$13,275
Illinois	-9592	-58065	-$17,177	-7267	-43989	-$13,013
New York	-12981	-54318	-$15,791	-9834	-41150	-$11,963
Texas	-8951	-46183	-$12,660	-6781	-34987	-$9,591
Indiana	-5803	-32933	-$13,089	-4396	-24949	-$9,916
Florida	-6061	-30805	-$6,831	-4592	-23337	-$5,175
Maryland	-7189	-30542	-$7,957	-5446	-23138	-$6,028
Ohio	-4917	-21371	-$5,193	-3725	-16190	-$3,934
Michigan	-3761	-20352	-$5,362	-2849	-15418	-$4,062
Puerto Rico	-4212	-18356	-$13,564	-3191	-13906	-$10,276
Utah	-2901	-17231	-$4,075	-2198	-13054	-$3,087

Source: TEConomy analysis; IMPLAN U.S. 2017 Model, VT adjusted from $100 billion annual reduction of revenue to $132 billion

Ecosystem Impacts of H.R. 3

- Companies impacted by H.R. 3 invested from 2009 – 2019 nearly $487 billion into 215 venture partnerships, the majority in the US, leading to 68 approved therapies.
- H.R. 3 would reduce cashflow available for ecosystem innovation investments by 46% at a minimum.
- Partnerships are not just driven by US companies; all global companies are developing assets in this way. According to VT research, over 70% of global biotech assets are commercialized in the US regardless of the location of the parent company.
- Disproportionately impacts small/emerging companies in 19 states.
  - California alone accounts for 25% of total inward investments into small innovative biotech companies of $122 Billion and for 17 of the 68 US drug approvals in our emerging biotech cohort (roughly 25% of the total).
- H.R. 3 does not impact all companies equally.

2009 – 2019 H.R. 3 Impacted companies: inward investments, totals by location



Total deal value of the 222 inward investments made 2009 – 2019 by companies impacted by H.R. 3, by US State

Small and Mid Cap Innovative Biotech Only

USA - Emerging Biotech Only	$366,725,490,000
California	$129,079,490,000
New Jersey	$74,641,000,000
Massachusetts	$73,961,400,000
Illinois	$18,855,000,000
Colorado	$11,400,000,000
Washington	$10,833,000,000
North Carolina	$10,130,000,000
Pennsylvania	$9,279,000,000
Connecticut	$8,267,000,000
New York	$4,968,000,000
Maryland	$4,314,500,000
Tennessee	$3,600,000,000
Texas	$3,139,500,000
Georgia	$2,500,000,000
Utah	$780,000,000
Missouri	$472,500,000
Nevada	$318,600,000
Florida	$140,000,000
Minnesota	$46,500,000

Total Investments (2009 – 2019) by H.R.3-Impacted Firms in Small & Mid Cap Biotech Companies in CALIFORNIA

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California Biotech Investments by Firm, 2010-2020			
Companies 1-27	Investments 1-27	Companies 28-54	Investments 28-54
Adheron Therapeutics Inc.	$580,000,000	Impact Biomedicines Inc.	$7,000,000,000
Afferent Pharmaceuticals Inc.	$1,250,000,000	InterMune Inc.	$8,300,000,000
Alios BioPharma Inc.	$1,750,000,000	KAI Pharmaceuticals Inc.	$315,000,000
AliveGen USA Inc.	$562,500,000	Labrys Biologics Inc.	$825,000,000
Allogene Therapeutics Inc.	$2,800,000,000	MabVax Therapeutics Holdings Inc.	$11,000,000
Amylin Pharmaceuticals Inc.	$7,000,000,000	Medivation Inc.	$13,631,000,000
Anacor Pharmaceuticals Inc.	$5,200,000,000	Meritage Pharma Inc.	$245,000,000
Anadys Pharmaceuticals Inc.	$230,000,000	Neurocrine Biosciences Inc.	$2,015,000,000
Apricus Biosciences Inc.	$27,500,000	NextWave Pharmaceuticals Inc.	$680,000,000
Aragon Pharmaceuticals Inc.	$1,000,000,000	Ocera Therapeutics Inc.	$117,000,000
Armo BioSciences Inc.	$1,600,000,000	Onyx Pharmaceuticals Inc.	$10,400,000,000
Arrowhead Pharmaceuticals Inc.	$1,040,000,000	Pearl Therapeutics Inc.	$1,150,000,000
Audentes Therapeutics Inc.	$3,000,000,000	Pharmacyclics Inc.	$21,000,000,000
Auspex Pharmaceuticals Inc.	$3,500,000,000	Pionyr Immunotherapeutics Inc.	$1,740,000,000
Avanir Pharmaceuticals Inc.	$3,560,000,000	Portola Pharmaceuticals Inc.	$1,176,000,000
BiPar Sciences Inc.	$500,000,000	Principia Biopharma Inc.	$3,680,000,000
Cadence Pharmaceuticals Inc.	$1,300,000,000	Quanticel Pharmaceuticals Inc.	$485,000,000
CGI Pharmaceuticals Inc.	$120,000,000	Questcor Pharmaceuticals Inc.	$300,000,000
Corthera Inc.	$620,000,000	Receptos Inc.	$7,321,000,000
Cougar Biotechnology Inc.	$1,000,000,000	Seragon Pharmaceuticals Inc.	$1,725,000,000
CV Therapeutics Inc.	$1,400,000,000	Synthorx Inc.	$2,500,000,000
Delinia Inc.	$777,000,000	TargeGen Inc.	$560,000,000
Denali Therapeutics Inc.	$325,000,000	Tracon Pharmaceuticals Inc.	$155,000,000
Dermira Inc.	$109,500,000	Via Pharmaceuticals Inc.	$22,800,000
Flexus Biosciences Inc.	$1,250,000,000	Vical Inc.	$100,490,000
IDM Pharma Inc.	$66,700,000	Vitae Pharmaceuticals Inc.	$639,000,000
Ignyta Inc.	$1,753,000,000	Xyphos Biosciences Inc.	$665,000,000

Total Investments (2009 – 2019) by H.R.3-Impacted Firms in Small & Mid Cap Biotech Companies in MASSACHUSETTS

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Companies 1-18	Investments 1-18	Companies 19-36	Investments 19-36
Adolor Corp.	$72,000,000	Idenix Pharmaceuticals Inc.	$3,900,000,000
Akebia Therapeutics Inc.	$232,500,000	Kanyos Bio Inc.	$760,000,000
Anthos Therapeutics Inc.	$250,000,000	Karyopharm Therapeutics Inc.	$217,000,000
Ardea Biosciences Inc.	$1,300,000,000	Lexicon Pharmaceuticals Inc.	$106,500,000
Ariad Pharmaceuticals Inc.	$5,200,000,000	Neurovance Inc.	$250,000,000
ArQule Inc.	$2,700,000,000	Padlock Therapeutics Inc.	$600,000,000
Avila Therapeutics Inc.	$925,000,000	Potenza Therapeutics Inc.	$404,700,000
Bioverativ Inc.	$11,600,000,000	Promedior Inc.	$1,390,000,000
BioVex Inc.	$1,000,000,000	Ra Pharmaceuticals Inc.	$2,300,000,000
BlueRock Therapeutics L.P.	$600,000,000	Rhythm Pharmaceuticals Inc.	$80,000,000
Boston Biomedical Inc.	$2,640,000,000	Rodin Therapeutics Inc., Rodin Therapeutics Inc.	$485,000,000
CoLucid Pharmaceuticals Inc.	$960,000,000	Stromedix Inc.	$562,500,000
Corvidia Therapeutics Inc.	$2,100,000,000	Synageva BioPharma Corp.	$9,483,300,000
Cubist Pharmaceuticals Inc.	$9,565,000,000	Tesaro Inc.	$5,100,000,000
Dyax Corp.	$6,546,000,000	Tilos Therapeutics Inc.	$773,000,000
FerroKin BioSciences Inc.	$319,500,000	Verastem Inc.	$130,500,000
Foresight Biotherapeutics Inc.	$300,000,000	Visterra Inc.	$430,000,000
Gloucester Pharmaceuticals Inc.	$640,000,000	Xenetic Biosciences plc	$38,900,000

Total Investments (2009 – 2019) by H.R.3-Impacted Firms in Small & Mid Cap Biotech Companies in OTHER STATES (Pt 1)

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State	Companies	Investments
NJ	Abraxis BioScience Inc.	$3,550,000,000
	Engage Therapeutics Inc.	$270,000,000
	Ikaria Inc.	$2,300,000,000
	Immunomedics Inc.	$21,000,000,000
	Insmed Inc.	$150,000,000
	Medarex Inc.	$2,400,000,000
	NPS Pharmaceuticals Inc.	$5,200,000,000
	Pernix Therapeutics Holdings Inc.	$267,000,000
	Pharmasset Inc.	$11,200,000,000
	The Medicines Co.	$10,224,000,000
	Tobira Therapeutics Inc.	$1,695,000,000

State	Companies	Investments
IL	AveXis Inc.	$8,700,000,000
	Furiex Pharmaceuticals Inc.	$35,000,000
	Stemcentrx Inc.	$9,800,000,000
	TerSera Therapeutics LLC	$320,000,000

State	Companies	Investments
WA	Vanda Pharmaceuticals Inc.	$100,000,000
	Immune Design Corp.	$248,000,000
	Calistoga Pharmaceuticals Inc.	$600,000,000
	ZymoGenetics Inc.	$885,000,000
	Juno Therapeutics Inc.	$9,000,000,000

State	Companies	Investments
NY	Axsome Therapeutics Inc.	$334,000,000
	Elevation Pharmaceuticals Inc.	$430,000,000
	OSI Pharmaceuticals Inc.	$4,000,000,000
	Synergy Pharmaceuticals Inc.	$195,000,000
	Valeant Pharmaceuticals International Inc.	$9,000,000

State	Companies	Investments
NC	Inspire Pharmaceuticals Inc.	$430,000,000
	Cardioxyl Pharmaceuticals Inc.	$2,100,000,000
	Stiefel Laboratories Inc.	$3,600,000,000
	Asklepios BioPharmaceutical Inc.	$4,000,000,000

Total Investments (2009 – 2019) by H.R.3-Impacted Firms in Small & Mid Cap Biotech Companies in OTHER STATES (Pt 2)

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State	Companies	Investments
CT	SpringWorks Therapeutics LLC	$103,000,000
	Achillion Pharmaceuticals Inc.	$930,000,000
	Loxo Oncology Inc.	$7,234,000,000

State	Companies	Investments
MD	Cerecor Inc.	$114,500,000
	Sucampo Pharmaceuticals Inc.	$1,200,000,000
	Human Genome Sciences Inc.	$3,000,000,000

State	Companies	Investments
TN	King Pharmaceuticals Inc.	$3,600,000,000
GA	Inhibitex Inc.	$2,500,000,000
UT	Tolero Pharmaceuticals Inc.	$780,000,000
MN	ANI Pharmaceuticals Inc.	$46,500,000

State	Companies	Investments
CO	Array BioPharma Inc.	$11,400,000,000

State	Companies	Investments
MO	Nabi Biopharmaceuticals	$47,500,000
	InfaCare Pharmaceutical Corp.	$425,000,000

State	Companies	Investments
NV	Spectrum Pharmaceuticals Inc.	$24,600,000
	PDL BioPharma Inc.	$294,000,000

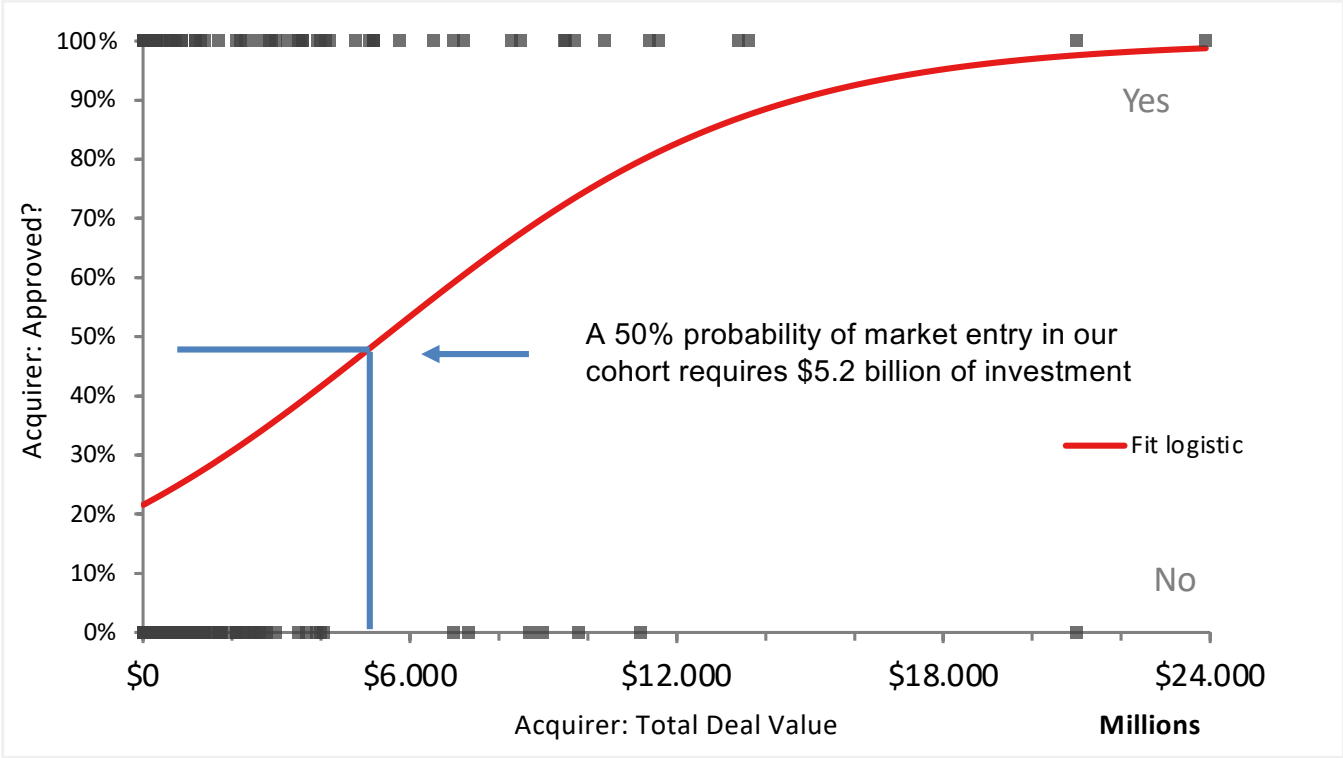
State	Companies	Investments
FL	Envoy Therapeutics Inc.	$140,000,000

State	Companies	Investments
TX	CerSci Therapeutics Inc.	$939,500,000
	Peloton Therapeutics Inc.	$2,200,000,000

State	Companies	Investments
PA	NuPathe Inc.	$279,000,000
	ViroPharma Inc.	$4,200,000,000
	Spark Therapeutics Inc.	$4,800,000,000

Analysis of 215 inward emerging biotech investments

Total Investments Accurately Predict Market Entry



Source	-LogLikelihood	DF	G^2 statistic	p
Difference	12.918	1	25.84	<0.0001
Fitted model	121.25	213		
Null model	134.17	214		

- This chart shows that the total of all cash invested into the R&D of a therapy predicts FDA approvals with high statistical certainty.
- The “p-value” of 0.0001 means that there is less than a 1 in 10,000 probability that this relationship arises by random chance.
- In our cohort of therapies, a 50% probability of market entry requires a cash commitment of $5.2 billion.

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H.R. 3 for 50 therapies - 46% Reduction of EBIT cashflow

Reduction from 68 approved therapies to 7

Indication	Initial Approval 1-17	H.R. 3 50 Impact	Indication	Initial Approval 18-34	H.R. 3 50 Impact	Indication	Initial Approval 35-51	H.R. 3 50 Impact	Indication	Initial Approval 52-68	H.R. 3 50 Impact
MS	99%	86%	Crohn's disease	49%	35%	Hypertension	32%	27%	Migraine	23%	22%
Cancer	98%	80%	Psoriasis	49%	35%	Bacterial infection	32%	27%	IBD	23%	22%
B cell lymphoma	88%	61%	Lymphoma	48%	35%	Hypertension	31%	26%	Hypertension	23%	22%
Psoriasis	87%	61%	Hemophilia	46%	34%	Basal cell carcinoma (BCC)	29%	25%	Migraine	23%	22%
Anemia	81%	55%	Angioedema	43%	32%	Angina	28%	25%	Migraine	23%	22%
Breast cancer	81%	54%	Diabetes	42%	32%	Pain	27%	25%	Constipation	22%	22%
Liver cancer	77%	51%	NSCLC	42%	31%	Alopecia	27%	24%	Meningitis	22%	22%
Cardiovascular	73%	49%	Solid tumors	41%	31%	Lymphoma	27%	24%	Migraine	22%	22%
Post-operative ileus	72%	48%	Fibromyalgia syndrome	39%	30%	Melanoma	25%	24%	Bleeding	22%	22%
Cardiovascular	72%	48%	Psoriasis	39%	30%	Ovarian cancer	25%	23%	HIV/AIDS	22%	22%
Cancer	68%	45%	Pancreatic cancer	39%	30%	Influenza virus	25%	23%	Bone cancer	22%	22%
Pulmonary fibrosis	66%	44%	Neurology	39%	30%	ADHD	24%	23%	Diabetes	22%	22%
Lung cancer	61%	41%	MS	37%	29%	lymphoma (CTCL)	24%	23%	Breast cancer	22%	22%
Lipodystrophy	59%	40%	Lupus	36%	29%	Encephalitis	24%	23%	ED	22%	22%
Autoimmune	57%	39%	MS	35%	29%	Conjunctivitis	23%	23%	ED	22%	22%
Cancer	52%	37%	NSCLC	35%	28%	Bleeding	23%	22%	lymphoma (NHL)	22%	22%
Thyroid cancer	49%	35%	Insomnia	34%	28%	Breast cancer	23%	22%	Hyper-cholesterol	22%	22%
	Bring to Market	**Do Not Bring to Market**		**Bring to Market**	**Do Not Bring to Market**		**Bring to Market**	**Do Not Bring to Market**		**Bring to Market**	**Do Not Bring to Market**

H.R. 3 for 125 therapies - 62% Reduction of EBIT cashflow

Reduction from 68 approved therapies to 2

Indication	Initial Approval 1-17	H.R. 3 125 Impact	Indication	Initial Approval 18-34	H.R. 3 125 Impact	Indication	Initial Approval 35-51	H.R. 3 125 Impact	Indication	Initial Approval 52-68	H.R. 3 125 Impact
MS	99%	70%	Crohn's disease	49%	31%	Hypertension	32%	26%	Migraine	23%	22%
Cancer	98%	65%	Psoriasis	49%	31%	Bacterial infection	32%	25%	IBD	23%	22%
B cell lymphoma	88%	49%	Lymphoma	48%	30%	Hypertension	31%	25%	Hypertension	23%	22%
Psoriasis	87%	48%	Hemophilia	46%	30%	Basal cell carcinoma (BCC)	29%	25%	Migraine	23%	22%
Anemia	81%	44%	Angioedema	43%	29%	Angina	28%	24%	Migraine	23%	22%
Breast cancer	81%	44%	Diabetes	42%	31%	Pain	27%	24%	Constipation	22%	22%
Liver cancer	77%	41%	NSCLC	42%	28%	Alopecia	27%	24%	Meningitis	22%	22%
Cardiovascular	73%	40%	Solid tumors	41%	28%	Lymphoma	27%	23%	Migraine	22%	22%
Post-operative ileus	72%	39%	Fibromyalgia syndrome	39%	28%	Melanoma	25%	23%	Bleeding	22%	22%
Cardiovascular	72%	39%	Psoriasis	39%	28%	Ovarian cancer	25%	23%	HIV/AIDS	22%	22%
Cancer	68%	37%	Pancreatic cancer	39%	28%	Influenza virus	25%	23%	Bone cancer	22%	22%
Pulmonary fibrosis	66%	37%	Neurology	39%	27%	ADHD	24%	23%	Diabetes	22%	22%
Lung cancer	61%	35%	MS	37%	27%	lymphoma (CTCL)	24%	23%	Breast cancer	22%	22%
Lipodystrophy	59%	34%	Lupus	36%	27%	Encephalitis	24%	23%	ED	22%	22%
Autoimmune	57%	33%	MS	35%	26%	Conjunctivitis	23%	23%	ED	22%	22%
Cancer	52%	32%	NSCLC	35%	26%	Bleeding	23%	22%	lymphoma (NHL)	22%	22%
Thyroid cancer	49%	31%	Insomnia	34%	26%	Breast cancer	23%	22%	Hyper-cholesterol	22%	22%
	Bring to Market	**Do Not Bring to Market**		**Bring to Market**	**Do Not Bring to Market**		**Bring to Market**	**Do Not Bring to Market**		**Bring to Market**	**Do Not Bring to Market**

New therapies not coming to market with 50 drugs under H.R. 3

VitalTransformation

61 Therapies Losing Marketing Access - 46% EBIT Reduction

Indication Lost	Quantity		Indication Lost	Quantity
Migraine	4		Encephalitis	1
Hypertension	3		Conjunctivitis	1
Non-small cell lung cancer (NSCLC)	2		Basal cell carcinoma (BCC)	1
Bleeding	2		Lung cancer	1
Erectile dysfunction (ED)	2		Fibromyalgia syndrome	1
Breast cancer	2		Bone cancer	1
Lymphoma	2		Post-operative ileus	1
Cancer (unspecified)	2		Meningitis	1
Multiple sclerosis (MS)	2		Pulmonary fibrosis	1
Cardiovascular (unspecified)	2		Attention deficit hyperactivity disorder (ADHD)	1
Diabetes	2		Thyroid cancer	1
Psoriasis	2		Non-Hodgkin lymphoma (NHL)	1
Lipodystrophy	1		Angina	1
Neurology (unspecified)	1		Ovarian cancer	1
Melanoma	1		Inflammatory bowel disease (IBD)	1
Constipation	1		Pancreatic cancer	1
Pain	1		Influenza virus	1
Crohn's disease	1		Insomnia	1
Lupus	1		Hemophilia	1
Cutaneous T cell lymphoma (CTCL)	1		Solid tumors	1
Angioedema	1		HIV/AIDS	1
Bacterial infection	1		Alopecia	1
Autoimmune (unspecified)	1		Hypercholesterolemia	1

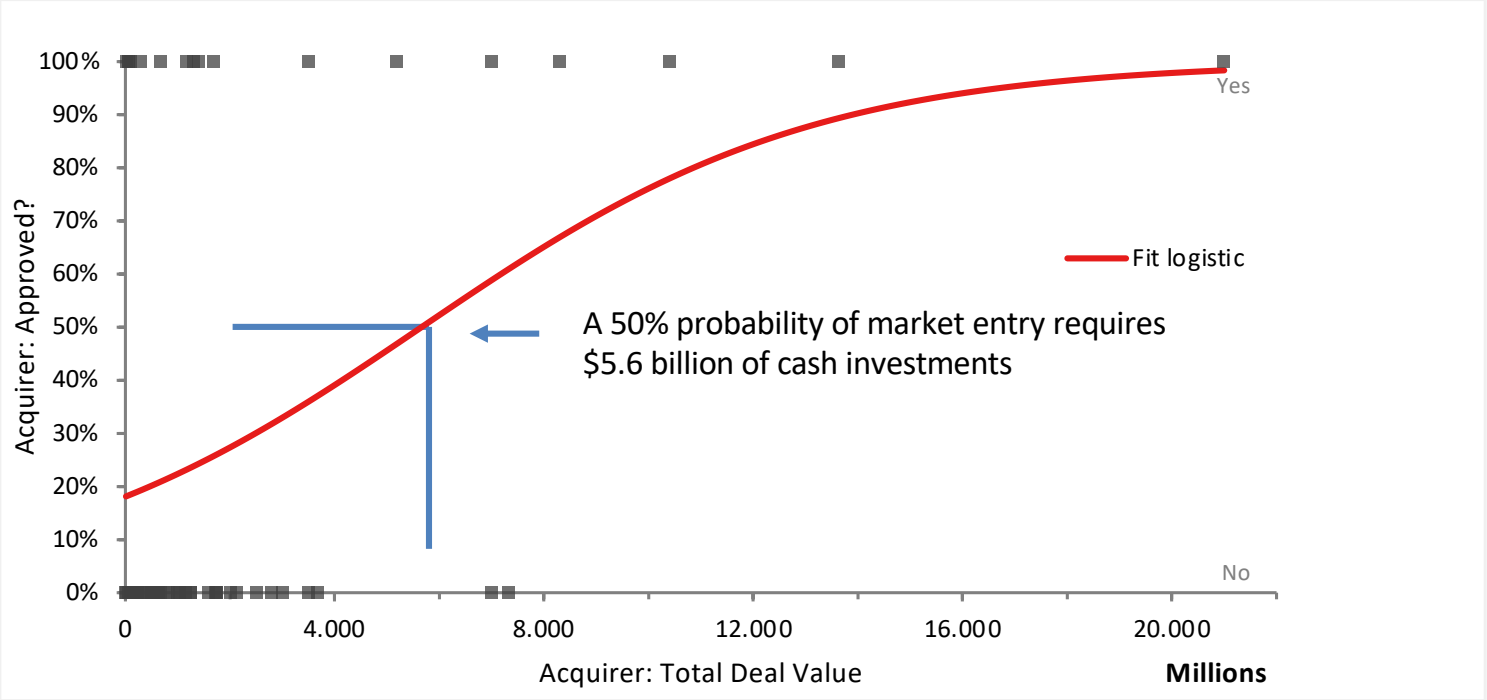
New therapies not coming to market with 125 drugs under H.R. 3

VitalTransformation

66 Therapies Losing Market Access - 62% EBIT Reduction			
Indication Lost	Quantity	Indication Lost	Quantity
Migraine	4	Autoimmune (unspecified)	1
Hypertension	3	Insomnia	1
Psoriasis	3	Encephalitis	1
Breast cancer	3	Liver cancer	1
Non-small cell lung cancer (NSCLC)	2	Pain	1
Bleeding	2	Lupus	1
Lymphoma	2	Pancreatic cancer	1
Cancer (unspecified)	2	Melanoma	1
Multiple sclerosis (MS)	2	B cell lymphoma	1
Cardiovascular (unspecified)	2	Anemia	1
Diabetes	2	Solid tumors	1
Erectile dysfunction (ED)	2	Neurology (unspecified)	1
Influenza virus	1	Alopecia	1
Meningitis	1	Angina	1
Lung cancer	1	Bacterial infection	1
Attention deficit hyperactivity disorder (ADHD)	1	Angioedema	1
Non-Hodgkin lymphoma (NHL)	1	Inflammatory bowel disease (IBD)	1
Conjunctivitis	1	Post-operative ileus	1
Lipodystrophy	1	Fibromyalgia syndrome	1
Constipation	1	Pulmonary fibrosis	1
Basal cell carcinoma (BCC)	1	Hemophilia	1
Crohn's disease	1	Thyroid cancer	1
Bone cancer	1	HIV/AIDS	1
Cutaneous T cell lymphoma (CTCL)	1	Hypercholesterolemia	1
Ovarian cancer	1		

Analysis of 58 CA Investments Into Emerging Biotech Products

Total Investments Accurately Predict Market Entry



Source	-LogLikelihood	DF	G^2 statistic	p
Difference	4.2540	1	8.51	0.0035
Fitted model	30.831	56		
Null model	35.085	57		

- This chart shows that the total of all cash invested into the R&D pipelines of California therapies predicts FDA approvals with high statistical certainty
- The "p-value" of 0.0035 means that there is less than a 1 in 250 probability that this relationship would arise by random chance
- In our cohort of therapies, a 50% probability of market entry requires a cash commitment of $5.6 billion

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A 46% reduction of EBIT (50 drugs in H.R. 3) reduces CA therapies approved from 17 to 2
A 62% reduction of EBIT cashflow (125 Drugs in H.R. 3) reduces CA therapies approved from 17 to 1

Indication	Current Probabiliity	46% Reduction	62% Reduction
Cancer (unspecified)	98%	82%	65%
B cell lymphoma	89%	61%	47%
Liver cancer	78%	49%	39%
Pulmonary fibrosis	67%	42%	34%
Diabetes	59%	38%	31%
Psoriasis	47%	32%	27%
Neurology (unspecified)	36%	27%	24%
Basal cell carcinoma (BCC)	26%	22%	21%
Angina	24%	21%	20%
Pain	24%	21%	20%
Lymphoma	23%	21%	20%
Attention deficit hyperactivity disorder (ADHD)	21%	20%	19%
Inflammatory bowel disease (IBD)	19%	19%	19%
HIV/AIDS	18%	18%	18%
Bone cancer	18%	18%	18%
Diabetes	18%	18%	18%
Erectile dysfunction (ED)	18%	18%	18%
BRING TO MARKET		**DO NOT BRING TO MARKET**	

H.R. 3's impact upon the market access of new products

- With 50 drugs included in H.R. 3 and a 46% reduction of EBIT cashflow, we predict a reduction from 68 approved therapies to 7 in the US, and a reduction from 17 to 2 approved products specifically from emerging California biotech companies.
- With 125 drugs included in H.R. 3 and a 62% reduction of EBIT cashflow, we predict a reduction from 68 approved therapies to 2 in the US, and a reduction from 17 to 1 approved products specifically from emerging California biotech companies.
- Therapies lost include those in the treatment of migraine pain, hypertension, psoriasis, breast cancer, non-small cell lung cancer (NSCLC), bleeding, lymphoma, multiple sclerosis (MS), diabetes, and others.
- A 50% probability of market entry in our 10 year cohort of 215 therapies requires total investments of $5.2 billion dollars per therapy.

Additional Implications and Conclusions

- The impact of an H.R. 3 roll out would, on average, exceed the annual earnings of a quarter of impacted companies as measured by EBIT.
- H.R. 3 will reduce overall earnings for all impacted companies between 46% -62%, thus leading to the destruction of the majority of US biopharma shareholder value for the majority of large biopharmaceutical companies
- Industry likely would accelerate movements towards China, Singapore, Korea, and other growth markets.
- The following are possible responses to H.R. 3:
  - The industry will be unable to significantly raise prices in countries dragging down the average AIM price, and would likely stop selling to those markets as a defensive measure.
  - Europe is more price sensitive than the US, and price increases may be met with aggressive roll backs in access and volumes, and/or regulatory responses including compulsory licenses and greater use of the hospital exemption for advanced therapies
  - For H.R. 3 to have the 'teeth' to create the desired end results (lower US costs, higher European costs), countries where US patents and access are challenged will need to be met with reciprocal US government access threats against foreign-owned companies operating in the US; this seems highly unlikely.
  - H.R. 3 may force a single transparent price in the US and impacted markets. Price segmentation increases revenues and access (utilization); both will be substantially lower under H.R. 3.

Appendix A

Distribution of Part D and B Medicines in the Analysis

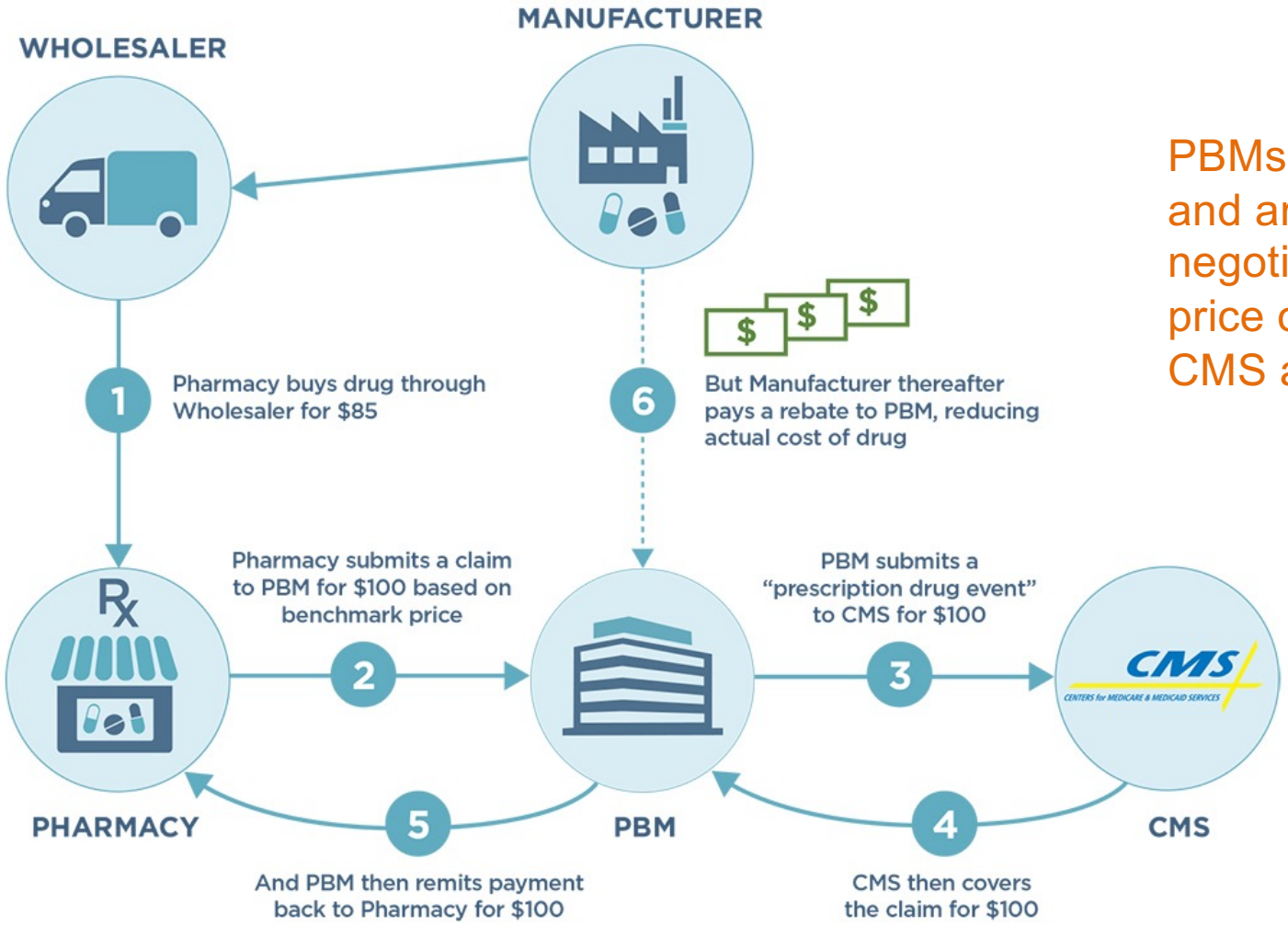
Distribution of Part D and B Medicines in the Analysis

- Of the top 25 drugs by spending, 5 are Part B and 20 are Part D
- Of the top 50 drugs by spending, 9 are Part B and 41 are Part D
- Of the top 125 drugs by spending, 21 are Part B and 104 are Part D
- Of the entire cohort of the top 175 drugs by spending, 50 are Part B and 125 are Part D

Appendix B

The Role of Pharmacy Benefit Managers (PBMs)

What is a PBM, and why does it matter in H.R. 3?



PBMs act as brokers, and are supposed to negotiate the best price on behalf of CMS and consumers

Insulin prices and pharmacy benefit manager rebates: pin the tail on the patient

STAT *By* Duane Schulthess March 19, 2020

All told, the unallocated insulin sales [for the six insulin products we investigated] that were reported in Medicare Part D but not booked on the corporate balance sheets . . . total a bit over $2 billion.

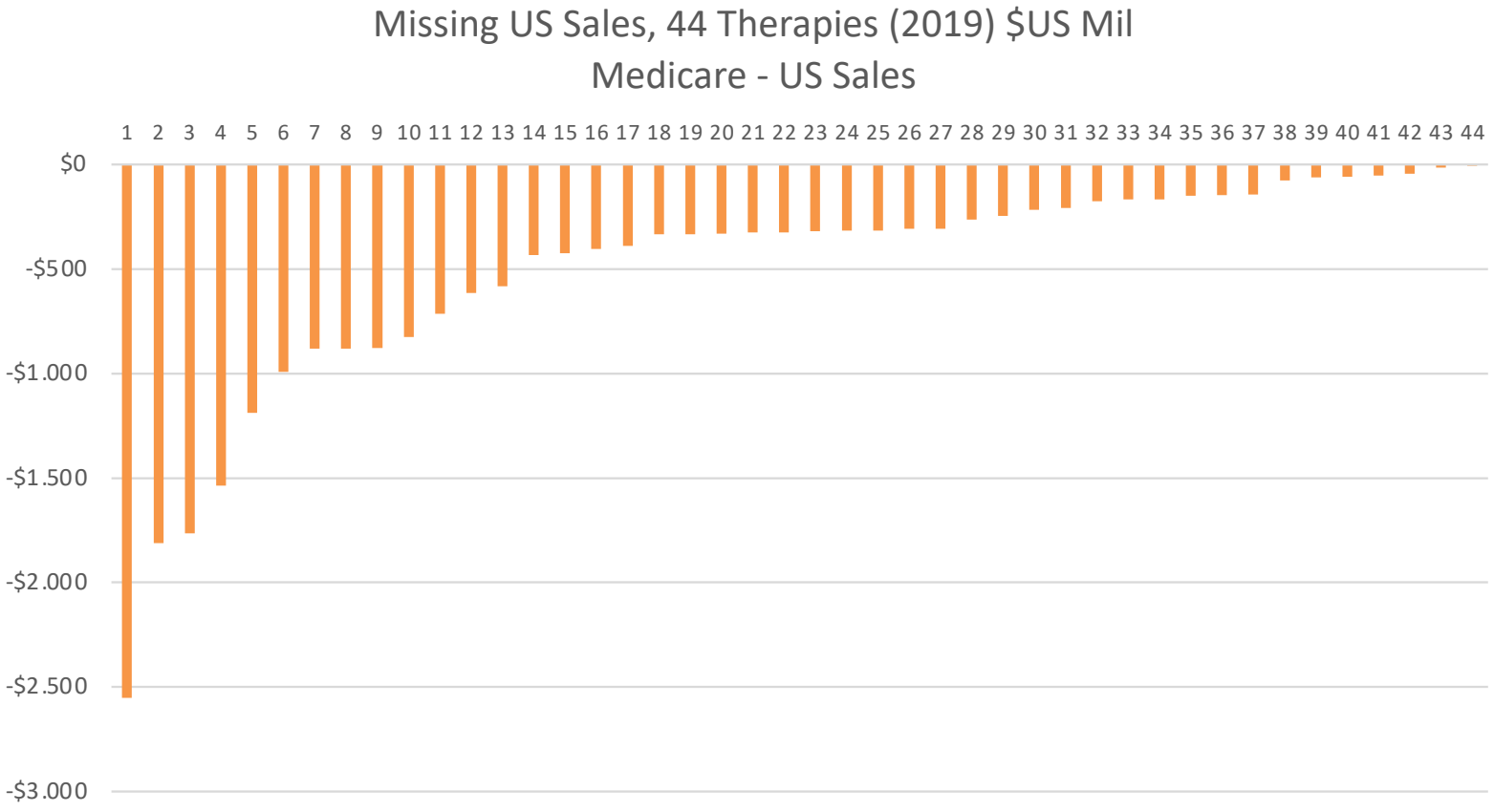
How could $2 billion in [insulin] sales simply vanish into thin air?

While our data aren't proof that pharmacy benefit managers are gobbling up some, if not all, of this insulin margin, it is possible, even probable, . . .the missing sales . . . might be sitting in PBM bank accounts.

One thing for certain is that it isn't coming back to consumers as discounts and it isn't going to the pharmaceutical companies that make the products.

44 therapies where Medicare sales exceed all audited US sales

$22.2 billion of missing sales



- We find 44 instances in our 175 drug cohort where Medicare CMS sales exceed total audited US sales in the annual SEC filings.
- The amount of 'missing' revenue, lost in the supply chain, is roughly $22 billion of missing sales in 2019.
- This money is not ending up on the company balance sheets, nor as discounts to patients.
- We suspect the majority is being paid as discounts to PBMs.

Appendix C
Disclosure

Disclosure

- Vital Transformation, an international health economics and healthcare real world evidence strategy consultancy, was asked to conduct an analysis of the impact of international reference pricing, as proposed in H.R. 3, on the biopharmaceutical innovation ecosystem, and specifically the impact on investment and small company capital formation and new drug pipeline development.
- The opinions included in this work are those of Vital Transformation, LLC, and not necessarily those of the project sponsors.
- The analysis was performed by Vital Transformation Consulting Economist Dr Harry Bowen, and Vital Transformation Managing Director Duane Schulthess.

VitalTransformation

The impact of health technology made simple

H.R. 3 and Reference Pricing

Total Market Impact

March 22, 2021

Prepared in collaboration with

CLSA

California Life Sciences Association

BIOCOM

CSBA

Council of State Bioscience Associations