VitalTransformation

The impact of health technology made simple

Alzheimer's Drug Discovery

Potential Impacts of H.R. 3

April 22, 2021

Prepared in collaboration with

Alliance FOR AGING RESEARCH

35 Years of Patient Advocacy

Executive summary

- By 2050, the number of Americans age 65 and older with Alzheimer's disease (AD) may grow to 13.8 million, a steep increase from the estimated 5.8 million Americans age 65 and older who have AD today.
- Total payments in 2020 for health care, long-term care and hospice services for people age 65 and older with dementia are estimated to be $305 billion.
- Clinical trials for AD have failure rates in excess of 98%.
- Large pharmaceutical companies have downsized their research into AD and other neurological disorders by more than 50% due to the associated high risks and failure.
- Bill H.R.3 sets a maximum U.S. price based on the prices for medicines paid in foreign markets, which is called a price ceiling; our previous analysis of H.R.3 estimated a reduction in the probability of discovered drugs by more than 80% caused by the bill.
- Successful products are increasingly required to underwrite and subsidize the investment into AD; H.R.3 essentially removes that available revenue, likely forcing industry to exit Alzheimer's research completely.

The economic cost of AD and other dementias

- By 2050, the number of Americans age 65 and older with Alzheimer's disease (AD) may grow to 13.8 million, a steep increase from the estimated 5.8 million Americans age 65 and older who have AD today (Alzheimer's Association, 2021).
- Between 2000 and 2018, deaths resulting from stroke, HIV and heart disease decreased, whereas reported deaths from Alzheimer's increased 146.2%.
- Medicare payments for services to beneficiaries age 65 and older with AD or other dementias are more than three times as great as payments for beneficiaries without these conditions, and Medicaid payments are more than 23 times as great (IBID).
- Average total cost per decedent with dementia ($287,038) was significantly greater than that of those who died of heart disease ($175,136), cancer ($173,383), or other causes of death ($197,286) (Annals of Internal Medicine, 2015).
- Total payments in 2020 for health care, long-term care and hospice services for people age 65 and older with dementia are estimated to be $305 billion (Alzheimer's Association, 2021).

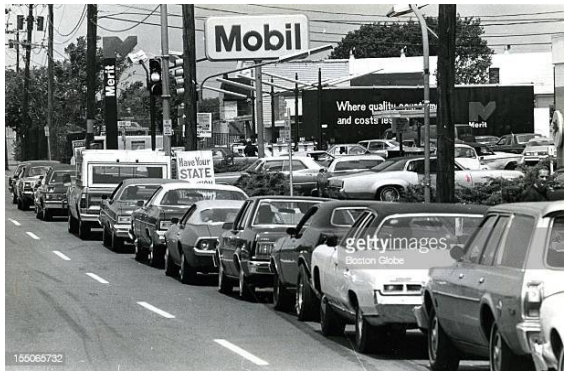
H.R.3 and Alzheimer's Disease

- **H.R.3 - What is an "international pricing index"?**
  - Bill H.R.3 sets a maximum U.S. price based on the prices for medicines paid in foreign markets, which 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.
  - We anticipate that the significantly lower revenues caused by H.R.3 will negatively impact drug discovery in therapy areas such as AD specifically, and neurological disorders more broadly, which have very high failure rates and poor risk versus reward for investors.

H.R.3 is a price ceiling; price ceilings limit access

"When a price ceiling is set below the equilibrium price, quantity demanded will exceed quantity supplied, and excess demand or shortages will result."

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 Health Care, Too

POLITICO

How Europe fell behind on vaccines

January 27, 2021

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…

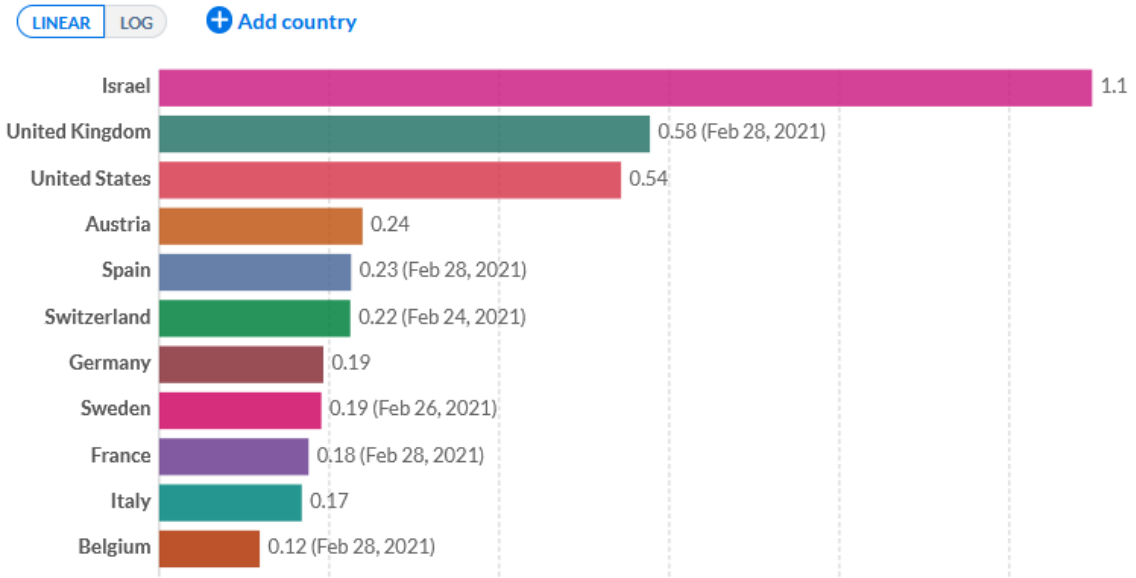
Pfizer committed to delivering 200 million doses for Americans — produced on U.S. soil — by the end of July, while the EU isn't assured that sum until September."

Alliance for Aging Research amicus brief on Most Favored Nation (MFN) model

"[For some medications included in the MFN model] there are no other FDA approved substitutes for patients to access. Thus, the MFN Rule will create conditions akin to drug shortages… research indicates that increased patient mortality, rates of adverse drug reactions, and hospitalization are frequently observed in shortage situations."

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

H.R.3 - 125 Therapies Enrolled

Impact on industry revenues and R&D

H.R.3 will impact the majority of leading companies

H.R. 3 Impacted Companies – 125 Drugs Included in Pricing Model	
Companies 1 – 23	**Companies 24 - 46**
AbbVie	Horizon Therapeutics
Acadia Pharmaceuticals	Incyte Corporation
Alexion	Ipsen
Allergan	Ironwood Pharmaceuticals
Amarin	Johnson & Johnson
Amgen	Mallinckrodt
Anika Therapeutics	Merck
Astellas Pharma	Neurocrine Biosciences
AstraZeneca	Novartis
Bausch Health Companies	Novo Nordisk
Bayer	Otsuka Holdings
Biogen	Pfizer
Boehringer Ingelheim	Regeneron
Bristol Myers Squibb	Riogen
Coherus BioSciences	Roche
Daiichi Sankyo	Sanofi
Dendreon	Seagen
Eagle	Sumitomo Dainippon Pharma
Eisai	Takeda
Eli Lilly and Company	Takeda Pharmaceuticals
Exelixis	Teva Pharmaceutical Industries
Gilead	UCB
GlaxoSmithKline	Viatris

2023 full H.R. 3 revenue impact by clinical area

125 therapies ($U.S. Million)

Clinical Area	H.R. 3 Therapies	2023 Estimated Revenue	H.R. 3 Revised Revenue	H.R. 3 Reduction ($US thousands)	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 are included under H.R.3.

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**

- The 2023 estimated earnings before interest expense and tax (EBIT) for all H.R.3 impacted companies is $204 billion
- H.R.3 with 125 therapies, including insulin reduces earnings by -$143 billion, a 70% reduction.

Revised H.R.3 revenues on Alzheimer's R&D

H.R.3 – Impact on AD Research

What is the impact of a 70% earnings reduction on Alzheimer's research?

- Investors are sensitive to the need of new therapies to return their investment, and dedicate the most capital to those assets with the greatest probability of successfully creating profits.
- A future cut in net revenues from free cash flow due to H.R.3 would have substantial negative implications for their willingness to invest in higher-risk clinical areas with high rates of failure.
- We anticipate that the lower revenues caused by H.R.3. will negatively impact drug discovery, particularly therapy areas such as Alzheimer's Disease (AD) which have a ***very high failure rate over 98%.***
- Our previous analysis of H.R.3 estimated a reduction in the probability of discovered drugs by 80%; given Alzheimer's clinical trials currently have a failure rate in excess of 98%, this means the industry will likely exit AD research completely.
- The estimated relationship explained by the regression between investments and revenues accounts for 77% of our investment model's variability (R^2=0.773) – i.e. this is a highly robust statistical relationship that accurately anticipates the likely behavior of investors.

Neuroscience research requires incentives due to high risks

H.R.3 will radically increase risk and depress rewards

CNS Program Portfolios in Large Pharma

Company	2009	2014
Abbott/AbbVie	17	10
AstraZeneca	21	7
Bristol-Myers Squibb	12	2
GlaxoSmithKline	40	14
Johnson & Johnson	18	17
Lilly	16	9
Merck/Schering-Plough	32	7
Novartis	14	15
Pfizer/Wyeth	46	15
Roche/Genentech	22	21
Sanofi/Genzyme	29	12
Total Programs	**267**	**129**

- Large pharmaceutical companies have downsized their neuroscience research even before the impacts of H.R.3.
- Developing drugs to treat brain diseases is more difficult and often more time-consuming and expensive than developing drugs for other therapeutic areas

Neuron, Volume 84, Issue 3, Medicines for the Mind: Policy-Based "Pull" Incentives for Creating Breakthrough CNS Drugs; Dennis W. Choi, Robert Armitage, et al.; 2014, Pages 554-563; ISSN 0896-6273, https://doi.org/10.1016/j.neuron.2014.10.027. (https://www.sciencedirect.com/science/article/pii/S0896627314009477)

The Challenge of Alzheimer's R&D

- Current AD drugs only treat cognitive symptoms, and do not arrest the state of the disease.
- The leading hypothesis for the cause of AD, the amyloid hypothesis, i.e. the assumption that accumulation of the peptide amyloid-β is the main cause of the condition, may be incorrect, thus setting aside 25 years of research.
- Of the 120 molecules for AD we can identify entering RCTs since 2005, only 2 have been approved.
- Given the risks of investing in AD, successful products are required to underwrite and subsidize the investment into new areas of this research; H.R. 3 essentially removes that available revenue to subsidize AD R&D.

The overwhelming majority of global trials for AD are in the U.S.

H.R.3 will impact U.S. leadership in neurological sciences

Location of AD Trials	Total
United States	151
Japan	29
Switzerland	27
United Kingdom	14
Ireland	12
Spain	8
Italy	6
France	5
Australia	5
India	4
Germany	3
Denmark	3
Austrailia	2
Cyprus	2
Singapore	2
Israel	1
China	1
Austria	1
Grand Total	**276**

Location of AD Trials	Total
New York	33
Massachusetts	28
Indiana	19
New Jersey	18
California	14
Florida	10
North Carolina	10
Salt Lake City	7
Pennsylvania	6
Michigan	2
Texas	2
Connecticut	1
Illinois	1

Clinical trials for AD launched since 2005

Trial Type	Total
Approved	4
Development Outside U.S.	6
Generally Recognized As Safe (GRAS)	1
I	33
II	97
III	89
NDA/BLA	3
Preclinical	6
Suspended	37
Grand Total	**276**

- While 276 trials is an impressive number, many of them are multiple trials of the same drug with different formulations/variations and at different stages
- 4 successful trials from 276 launched represents a 98.5% rate of failure

Trials of Individual Alzheimer's Drugs Launched Since 2005

120 drugs, highest point of development

Phase	Highest Phase of Development
Approved	2
I	19
II	43
III	19
NDA/BLA	1
Preclinical	3
Suspended	33
Grand Total	**120**

- Only two of 120 unique Alzheimer's drugs have been approved from our cohort of 276 trials
- By molecule, this represents a failure rate of 98.3%
- Reduced by 80% due to H.R.3, this puts the adjusted rate of failure at 100% (99.7%); this likely would translate into the exit of all companies from Alzheimer's research.

Final conclusions

- Alzheimer's disease (AD) is one of the key areas of unmet medical need; in order to support pipelines, the revenues from other therapeutic areas are needed to meet the investment demands of the high failure rates, and clinical trials.
- Large pharmaceutical companies have downsized their research into AD and other neurological disorders by more than 50% due to the associated high risks and failure over the past decade before the introduction of H.R.3.
- Clinical trials for AD have failure rates in excess of 98%, revenue reductions created by H.R.3 will radically impact the investment ecosystem's ability to support these pipelines, leading to most if not all companies focusing on other clinical areas with better risk reward calculations.
- Total payments in 2020 for health care, long-term care and hospice services for people age 65 and older with dementia are estimated to be $305 billion; current existing therapies are not of sufficient quality to arrest the onset of the disease.
- Bill H.R.3 sets a maximum U.S. price based on the prices for medicines paid in foreign markets, this is called a price ceiling; our previous analysis of H.R.3 estimated a reduction in the probability of discovered drugs by >80%.

Disclosure

- Vital Transformation, an international health economics and health care 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 new drug pipeline development in Alzheimer's disease.
- 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.
- The raw data behind this research can be found here.

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