Melissa Barber, Ph.D.
Postdoctoral Fellow
Yale School of Medicine, Yale Law School, and
Yale Collaboration for Regulatory Rigor,
Integrity, and Transparency (CRRIT)
email: melissa.barber@yale.edu
https://scholar.harvard.edu/melissabarber

U.S. Senate Committee on Health, Education, Labor & Pensions (HELP)
428 Senate Dirksen Office Building
Washington, DC, 20510

February 5, 2024

Statement for the record for hearing Why Does the United States Pay, by Far, the Highest Prices in the World for Prescription Drugs?

Background:
I thank the Committee for their continued work in seeking to understand and address the problem of high drug prices in the United States.

I am a health economist based at Yale University. I completed my PhD at Harvard University in 2023 have served as a consultant on pharmaceutical issues for the World Health Organization (WHO), Médecins Sans Frontières (MSF), the Global Fund to Fight AIDS, Tuberculosis, and Malaria, and the World Bank. In September 2023 I testified before the House Committee on Energy and Commerce on *Legislative Proposals to Prevent and Respond to Generic Drug Shortages*. I represent only myself in this submission.

In this statement for the record, I will briefly outline the results of my research on the production costs of pharmaceuticals that the Committee may find useful in their investigation.

Summary of methods used to estimate the cost of production of medicines:
I have worked to develop and refine methods for estimating the cost of production of medicines since 2016. The core costing algorithm was commissioned by WHO for the Fair Pricing Forum in 2017,[1] and has since been expanded and further developed and applied to hundreds of medicines. The costing methods included herein have been extensively peer reviewed in a range of journals (*British Medical Journal (BMJ) Global Health, BMJ Open, Journal of Virus Eradication,* and *The Lancet Oncology*) and presented at numerous international conferences (International AIDS Society, European Society for Medical Oncology, and the European Society of Clinical Microbiology and Infectious Diseases). My co-authors and I have published cost estimates for all tablets/capsules and injectable medicines on the WHO Essential Medicines List (where permitted by available data),[2-3] insulin including insulin analogues,[4] HIV medicines and treatments for opportunistic infections,[5-6] direct-acting antivirals for hepatitis C,[7] cancer medicines,[8] and antihypertensive medicines.[9] Our 2018 *BMJ Global Health* paper was recently included as a reference for cost of production by Novartis researchers, giving us further confidence that our methods, developed in academic contexts, are also regarded as accurate within industry.[10]

Analysis
Sample selection: I include cost of production estimates for drugs (where permitted by available data) covered under Medicare Part D selected for negotiation as part of the Inflation Reduction Act. This sample of drugs was chosen as they were identified by CMS as significant cost drivers in Medicare expenditures, amounting to 20% of total Part D gross covered prescription costs.[11]

Table 1. Estimated cost of production for medicines subject to Medicare negotiation

		Cost (unit)		**Cost (annual)**	
Drug	**Unit**	**Estimated cost of production**	**NADAC**	**Estimated cost of production**	**NADAC**
Eliquis *apixaban*	5mg tablet	$0.02	$9.50	$18	$6935
Entresto *sacubitril / valsartan*	97mg/103mg tablet	$0.16	$11.00	$130	$8030
Farxiga *dapagliflozin*	10mg tablet	$0.04	$18.62	$16	$6796
Fiasp Flextouch *insulin aspart*	3 mL 100unit/mL disposable pen	$1.26	$107.13	$61	$5214
NovoLog FlexPen *insulin aspart*	3 mL 100unit/mL disposable pen	$1.26	$26.85	$61	$1307
Imbruvica *ibrutinib*	140mg capsule	$0.75	N/A	$1091	N/A
Januvia *sitagliptin*	100mg tablet	$0.06	$18.32	$23	$6687
Jardiance *empagliflozin*	10mg tablet	$0.04	$19.53	$16	$7128
Stelara *ustekinumab*	45 mg/0.5 mL in syringe	$2.82	$12,760	$12	$55,293
Xarelto *rivaroxaban*	20mg tablet	$0.03	$17.37	$12	$6340

In the interests of brevity for this submitted statement, I have submitted summary results. The methods are described in detail in the technical appendix and publications linked in the endnotes.

Should Committee members have further inquiries, including questions about cost of production methods and their application, I am available to support as may be helpful.

Sincerely,

Melissa Barber

Technical Appendix

1. Cost comparison to NADAC prices methodology

    1.1 NADAC costs: National Average Drug Acquisition Cost. Most recent price reported as of 31 Jan 2024.

    1.2 Many drugs have multiple indications. See Table A1 for assumptions about the indications and other considerations used in calculating annual treatment costs. Note: Unit costs are rounded to the second decimal point, but were not rounded in calculating annual costs.

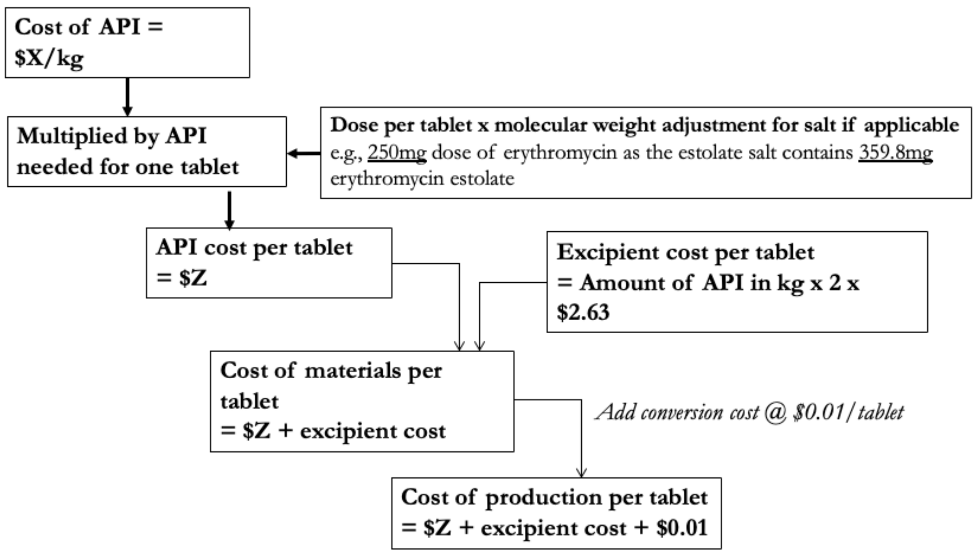
Table A1. Indication and treatment assumptions in calculating annual costs

Drug	Unit	Treatment regimen	Representative indication used for comparison (FDA label)	Notes / assumptions
Eliquis *apixaban*	5mg tablet	5mg x 2 daily	reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation	
Entresto *sacubitril / valsartan*	97mg/103mg tablet	97mg/103mg x 2 daily	to reduce the risk of cardiovascular death and hospitalization for heart failure in adult patients with chronic heart failure. Benefits are most clearly evident in patients with left ventricular ejection fraction (LVEF) below normal.	target maintenance dose as recommended in AHA/ACC/HFSA 2022 guidelines
Farxiga *dapagliflozin*	10mg tablet	10mg daily	adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus	Typical dose
Fiasp Flextouch *insulin aspart*	3 mL 100unit/mL disposable pen	40 units/day	Improve glycemic control in adults with diabetes mellitus	WHO DDD 40 units/day
NovoLog FlexPen *insulin aspart*	3 mL 100unit/mL disposable pen	40 units/day	Improve glycemic control in adults with diabetes mellitus	WHO DDD 40 units/day
Imbruvica *ibrutinib*	140mg capsule	140mg x 4 daily	Mantle cell lymphoma (MCL) who have received at least one prior therapy	
Januvia *sitagliptin*	100mg tablet	100mg daily	adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus	
Jardiance *empagliflozin*	10mg tablet	10mg daily	reduce the risk of cardiovascular death in adults with type 2 diabetes & established cardiovascular disease	
Stelara *ustekinumab*	45 mg/0.5 mL in syringe	45 mg/0.5 mL in syringe every 12 weeks	moderate to severe plaque psoriasis (Ps) who are candidates for phototherapy or systemic therapy.	Maintenance dose, assumed weight <100kg
Xarelto *rivaroxaban*	20mg tablet	20mg daily	reduce risk of stroke and systemic embolism in nonvalvular atrial fibrillation	

2. Cost of production methodology:

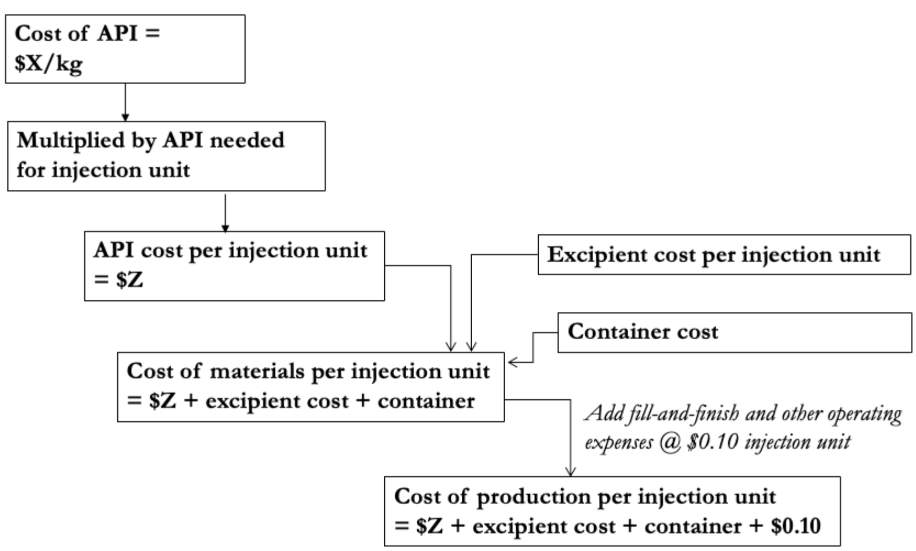
The costing algorithm includes costs of materials (active pharmaceutical ingredient, excipients), and formulation costs. This technical appendix briefly summarizes the methodologies of peer-reviewed publications to describe how different parameters were sourced. This summary is not comprehensive. Please see referenced publications and their supplementary appendices for a full description of data source, data cleaning algorithms, and costing considerations.

Figure A1. Cost of production algorithm for solid oral dosage formulations



Algorithm as published in Hill A, Barber MJ, Gotham D. Estimated costs of production and potential prices for the WHO Essential Medicines List. BMJ Global Health 2018; 0: e000571.

Figure A2. Cost of production algorithm for injectable formulations



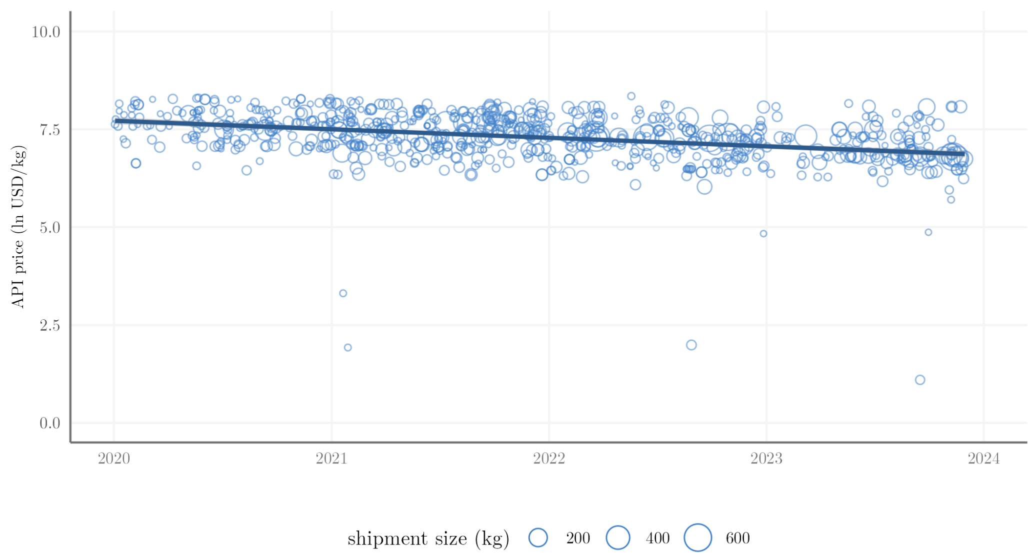
2.1 API cost

The price of active pharmaceutical ingredient (API) is the most important determinant in the cost of a production of a medicine. In order to identify shipments of API, a proprietary export/import database was searched for dates between Jan 2020 and Dec 2023, including import-export shipments from India, the United States, Mexico, Costa Rica, Panama, Bolivia, Brazil, Chile, Colombia, Ecuador, India, Paraguay, Peru, Uruguay, Venezuela, China, India, Indonesia, Pakistan, Sri Lanka, and the Philippines.[a] Data were not available for etanercept.

Data on shipments were manually cleaned to exclude shipments that did not represent genuine API, using criteria developed in peer-reviewed publications (e.g., shipments of working or reference standard, API with impurities, finished product, etc).[b] Outliers were defined as those with values higher than the third quartile plus 1.5 times the interquartile range, or lower than the first quartile minus 1.5 times the interquartile range, and were excluded. Weighted least-squares regression was used to fit linear models, with weights corresponding to shipment volume in kilograms. The outcome (unit cost) was log-transformed to reduce skew in the residuals. The predicted value on 1 December 2023 was used as the assumed average market price for API; we did not extrapolate beyond observed data.

Statistical analyses were performed and visualizations generated in *R* version 4.2.

Figure A1. Example of API cost data: rivaroxaban



2.2 Excipients

Excipients are ingredients other than the API that comprise a given formulation.

In general, specific weights of excipients for solid oral dosage formulations are not publicly available. The total proportion of finished product weight made up by excipient

[a] Not all import data sources available for all dates.

[b] See Appendix for details on approach to data cleaning, available here: https://gh.bmj.com/content/bmjgh/3/1/e000571/DC1/embed/inline-supplementary-material-1.pdf?download=true

is typically between 20% and 60%.[12] Table A2, below, shows typical costs of excipients used in solid oral formulations, and typical proportion of total finished pharmaceutical product (FPP) weight made up by each excipient.

Table A2. Costs of excipients used in solid oral formulations, and typical proportion of total FPP weight made up by each excipient.

	Typical weight as % of FPP weight		Cost per Kg (USD)	
Excipient	**Min**	**Max**	**Min**	**Max**
Sodium benzoate	1%	3%	$1.62	$2.19
Cellulose or microcrystalline cellulose	10%	60%	$2.00	$3.22
Talc	0.2%	2%	$2.00	$3.57
Sodium starch glycolate	1%	5%	$0.96	$4.93
Crospovidone	2%	5%	$3.03	$3.03
Lactose	5%	40%	$3.03	$3.77
Xylitol	5%	10%	$2.20	$5.75
Calcium phosphate, dibasic	5%	50%	$2.46	$5.70
Carboxymethylcellulose sodium	5%	25%	$3.25	$5.99
Starch, pregelatinised	5%	35%	$2.00	$9.00
Xanthan gum	5%	15%	$5.02	$7.44
Croscarmellose sodium	1%	5%	$6.56	$9.51
Methyl paraben	1%	2%	$11.50	$11.50
Povidone	5%	20%	$8.59	$17.11
Magnesium stearate	0.25%	4%	$4.30	$23.50
Potassium sorbate	0%	2%	$18.00	$37.00
Sodium lauryl sulfate	1%	2%	$36.00	$51.00
Aluminium oxide	0%	5%	N/A	N/A

Excipients composing the major part of FPP weight are in general very cheap – for example, cellulose, lactose, calcium phosphate, carboxymethylcellulose, pregelatinised starch. More expensive excipients, for example potassium sorbate, methyl paraben, and sodium lauryl sulfate, typically account for only a small proportion of the pill weight (<5%).

Using the data in the table above, and the assumption that excipients make up 50% of the FPP weight for tablets, we have calculated an average excipient cost of $2.63 per kilogram of FPP.

Excipients for injectable formulations were sourced from Niazi (2020) and/or regulatory submissions to FDA or EMA.[13][14]

1.3 Formulation costs

These are operating expenditures, minus API and excipients, needed to convert raw API into a FPP. Similar algorithms have been used and validated in previous studies.[15]

Multiple sources were consulted in order to inform a choice of assumed conversion cost per tablet/capsule. These are described individually below, summarized, and the final choice of assumed conversion cost is explained.

It is our view that, based on the values suggested by the available analyses, outlined above, the most plausible average conversion cost is between $0.005 and $0.01 for a solid oral dosage formulation. Of all the cost of production analyses identified (Table A3), it is only the Pinheiro et al study from Brazil in 2001 that has a per-unit estimate significantly greater than $0.01. We have set the assumed conversion cost in our generic price estimation algorithm at $0.01/tablet.

Table A3. Per-unit cost component values available from various analyses.

Report	Cost components included in estimate	Conversion cost per tablet
LOCOST/JSS (2004)[16]	Conversion cost not including depreciation of capital, distribution, but including quality control (testing) and packaging	$0.0016
Lowest-priced product in UK, South Africa, India (2016)	Cost per unit of lowest-priced solid oral formulation FPP	$0.0011–$0.0043
Chaudhuri et al (2015)[17]	Conversion cost including depreciation of capital and packaging, but not including sales and distribution	$0.0056
	Conversion cost including depreciation of capital and packaging, and including sales and distribution	$0.0105
Discussion by authors with large generic companies (2016)	Conversion cost including packaging, but not sales and distribution	$0.006
McKinsey & Company (2014)[18]	Total production costs, lowest-cost plants (not further specified)	$0.013
Pinheiro et al (2006, data from 2001)[19]	Conversion cost (direct and indirect costs)	$0.057
	Conversion cost (direct and indirect costs) plus operating margin	$0.101

Formulation costs for injectable products are described in *Estimation of cost-based prices for injectable medicines in the WHO Essential Medicines List, Production costs and potential prices for biosimilars of human insulin and insulin analogues,* and a publication in press.[3,4]

[1] WHO. At WHO Forum on Medicines, countries and civil society push for greater transparency and fairer prices. WHO. 2019; published online April 13. https://www.who.int/news/item/13-04-2019-at-who-forum-on-medicines-countries-and-civil-society-push-for-greater-transparency-and-fairer-prices

[2] Hill A, Barber MJ, Gotham D. Estimated costs of production and potential prices for the WHO Essential Medicines List. *BMJ Global Health* 2018; 0: e000571. https://gh.bmj.com/content/bmjgh/3/1/e000571.full.pdf

[3] Gotham D, Barber MJ, Hill AM. Estimation of cost-based prices for injectable medicines in the WHO Essential Medicines List. *BMJ Open* 2019; 9: e027780. https://bmjopen.bmj.com/content/bmjopen/9/9/e027780.full.pdf

[4] Gotham D, Barber MJ, Hill A. Production costs and potential prices for biosimilars of human insulin and insulin analogues. *BMJ Global Health* 2018; 3: e000850. https://gh.bmj.com/content/bmjgh/3/5/e000850.full.pdf

[5] Barber M, Gotham D, Hill A. Cost-based estimated prices for key HIV, HCV, and MDR-TB medicines. Poster presentation at 23rd International AIDS Conference (AIDS 2020: Virtual), 6-10 July 2020.

[6] Barber M, Gotham D, Hill A. Estimated cost-based generic prices for treatments of opportunistic infections. AIDS 2018, Amsterdam. https://www.researchgate.net/publication/326914620_Estimated_cost-based_generic_prices_for_treatments_of_opportunistic_infections

[7] Barber MJ, Gotham D, Khwairakpam G, Hill A. Price of a hepatitis C cure: Cost of production and current prices for direct-acting antivirals in 50 countries. *Journal of Virus Eradication* 2020; 6: 100001. https://pubmed.ncbi.nlm.nih.gov/33251019/

[8] Hoen E, Meyer S, Durisch P, et al. Improving affordability of new essential cancer medicines. *The Lancet Oncology* 2019; 20: 1052–4. https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(19)30459-0/fulltext

[9] MSF, Resolve to Save Lives. Under Pressure: Strategies to improve access to medicines to treat high blood pressure in low- and middle-income countries report. 2022 https://msfaccess.org/under-pressure-strategies-improve-access-antihypertensive-medicines-low-and-middle-income-0.

[10] Siirola E, Debon A, Eggimann F, Snajdrova R. Computer-guided substrate scope exploration of engineered peptide-modifying biocatalysts. (Preprint). Available from: https://www.researchsquare.com/article/rs-3639162/v1

[11] U.S. Department of Health and Human Services. HHS Selects the First Drugs for Medicare Drug Price Negotiation. 2023; published online August 29**.** https://www.hhs.gov/about/news/2023/08/29/hhs-selects-the-first-drugs-for-medicare-drug-price-negotiation.html

[12] Joseph Fortunak, Ngozwana S, Tsige Gebre-Mariam, Tiffany Ellison, Paul Watts, Martins Emeje, et al. Raising the Technological Level: The Scope for API, Excipients, and Biologicals Manufacture in Africa. In: *Making Medicines in Africa: the Political Economy of Industrializing for Local Health*. 2016.

[14] Niazi S. *Handbook of Pharmaceutical Manufacturing Formulations: Sterile Products*. Boca Raton, FL: CRC Press, Taylor Francis Group; 2020.

[15] Van de Ven N, Fortunak J, Simmons B, Ford N, Cooke GS, Khoo S, et al. Minimum target prices for production of direct-acting antivirals and associated diagnostics to combat hepatitis C virus. *Hepatol Baltim Md*. 2015 Apr;61(4):1174–82; Hill A, Gotham D, Cooke G, Bhagani S, Andrieux-Meyer I, Cohn J, et al. Analysis of minimum target prices for production of entecavir to treat hepatitis B in high- and low-income countries. *J Virus Erad*. 2015 Apr 1;1(2):103–10; Hill A, Gotham D, Fortunak J, Meldrum J, Erbacher I, Martin M, et al. Target prices for mass production of tyrosine kinase inhibitors for global cancer treatment. *BMJ Open*. 2016 Jan 27;6(1):e009586; Hill A, Simmons B, Gotham D, Fortunak J. Rapid reductions in prices for generic sofosbuvir and daclatasvir to treat hepatitis C. *J Virus Erad*. 2016 Jan 1;2(1):28–31; Gotham D, Fortunak J, Pozniak A, Khoo S, Cooke G, Nytko FE, et al. Estimated generic prices for novel treatments for drug-resistant tuberculosis. *J Antimicrob Chemother*. 2017 Jan 10;dkw522.

[16] LOCOST/JSS. *Impoverishing the Poor: Pharmaceuticals and Drug Pricing in India* [Internet]. 2004 [cited 2017 Jan 2]. Available from: http://www.jssbilaspur.org/wordpress/wp-content/uploads/2015/10/Impoverishing-the-poor-Pharmaceuticals-and-drug-pricing-in-India.pdf

[17] Chaudhuri S, West A. Can local producers compete with low-cost imports? A simulation study of pharmaceutical industry in low-income Africa. *Innov Dev.* 2015 Jan 2;5(1):23–38.

[18] Keeling D, Lösch M, Schrader U. *Outlook on pharma operation*s. McKinsey & Company; 2014.

[19] Pinheiro E, Vasan A, Kim JY, Lee E, Guimier JM, Perriens J. Examining the production costs of antiretroviral drugs: *AIDS*. 2006 Aug;20(13):1745–52.