Patented drug prices and clinical trials in 31 OECD countries 2017: implications for Canada's PMPRB.

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OUTLINE

ABSTRACT

The federal government is implementing changes to the rules used by the Patented Medicine Prices Review Board (PMRPB) to regulate the prices of new medicines sold in Canada. The regulatory changes are intended to further depress the prices of patented drugs. In its Regulatory Impact Analysis Statement, the PMPRB stated: "It is not anticipated that these amendments would generate adverse impacts on industry employment or investment in the Canadian economy." This study examined whether there is any empirical link between price and industry investment in clinical R&D. The analysis tested for statistical correlations between the geographic distribution of industry-funded clinical trials across 31 OECD countries and variation in drug price levels, controlling for differences in GDP and market size. A multi-variable regression analysis showed that price-level (P=0.000) and market size (P=0.004) were statistically significant predictors. The coefficient results show that a 1-unit variation (+/-1.00) in the average foreign-to-Canadian price ratio for patented medicines is associated with a variation of +/-613.355 industry-funded clinical trials; and a 1-unit variation (+/-1,000) in market size (defined by the population stated in thousands) is associated with a variation of +/-0.002 industry-funded clinical trials (or 2 trials per million population variation in market size). The results suggest that a lower price ceiling resulting from the PMPRB regulatory changes will likely cause a substantial decline in the number of industry-funded clinical trials in Canada. Analysis of other data suggest clinical trial activity could already be declining over time and the trend is linked to a simultaneous decline in the Canadian price level for patented medicines relative to competing markets in the 7 reference countries currently used by the PMPRB.

INTRODUCTION

The federal government is implementing changes to the rules used by the Patented Medicine Prices Review Board (PMRPB) to regulate the prices of new medicines sold in Canada.[1] The regulatory changes are intended to further depress the prices of patented drugs.[2] In its Regulatory Impact Analysis Statement, the PMPRB stated:

> "It is not anticipated that these amendments would generate adverse impacts on industry employment or investment in the Canadian economy. Although when the current regulatory framework was first conceived 30 years ago, policy makers believed that patent protection and price were key drivers of medicine research and development (R&D) investment, there is no evidence of this link. The level of industry R&D investment relative to sales by medicine patentees in Canada has been falling since the late 1990s and is now at a historic low despite Canada having among the highest patented medicine prices in the world. These amendments would aim to align Canadian prices with those in countries that, despite having lower prices, receive higher medicine industry investment."[3]

The objective of this study is to examine whether there is any empirical link between price and industry investment in clinical R&D. The analysis tests for statistical correlations between the geographic distribution of industry-funded clinical trials across OECD countries and variation in drug price levels, controlling for differences in GDP and market size. Policy implications for Canada are briefly discussed with reference to pending changes to federal drug price regulations by the PMPRB.

[1] Health Canada. Media release August 9, 2019. Government of Canada Announces Changes to Lower Drug Prices and Lay the Foundation for National Pharmacare. https://www.newswire.ca/news-releases/government-of-canada-announces-changes-to-lower-drug-prices-and-lay-the-foundation-for-national-pharmacare-841830432.html.

[2] Health Canada. Protecting Canadians from Excessive Drug Prices: Consulting on Proposed Amendments to the Patented Medicines Regulations. 2017. https://www.canada.ca/en/health-canada/programs/consultation-regulations-patented-medicine/document.html.

[3] Canada Gazette Publications Part I: Vol. 151, No. 48 — December 2, 2017. Regulations Amending the Patented Medicines Regulations. REGULATORY IMPACT ANALYSIS STATEMENT. Government of Canada. http://gazette.gc.ca/rp-pr/p1/2017/2017-12-02/html/reg2-eng.html.

DATA

Table 1 displays the data that were collected for this study, sorted alphabetically by country. All data cover the calendar year 2017, which was the most recent year available that was common across all variables. The number of countries included for analysis was determined by the availability of comparable pricing data. Proxy data were available from the PMPRB that compared average gross prices (ex-factory list prices before rebates) in 2017 for patented (defined by single-source brands in Canada) drugs across 31 Organisation for Economic Co-operation and Development (OECD) countries in bi-lateral ratios of foreign-to-Canadian prices (Variable label "F:C IPRX$", Canada = 1.00). The PMPRB uses Canadian and international prices reported in the IQVIA MIDAS™ database at the ex-factory manufacturer level, reflecting all sales to the pharmacy and hospital sectors in all OECD countries with available MIDAS™ data. The average foreign-to-Canadian price ratios are constructed using Canadian sales-weighted arithmetic averages of the corresponding foreign-to-Canadian price ratios for individual medicines and adjusted for the Purchasing Power Parities (PPP) of international currencies.[4]

Data on the number of industry-funded clinical trials (Variable label "IND CTs") in the 31 countries matching the PMPRB's patented drug price-level data were obtained from ClinicalTrials.gov, an online database of clinical trial activity around the world operated by the U.S. National Library of Medicine (NLM), National Institutes of Health (NIH) since 2008.[5] The database query specified all industry-funded clinical trials with a registered start date from 01/01/2017 to 12/31/2017. The query returned results on 6674 registered clinical trials across 100,691 sites in 101 countries. The data were then sorted and collapsed to include only the 5,251 registered clinical trials in the 31 OECD countries matching the PMPRB data.

Corresponding 2017 data on Gross Domestic Product (GDP) per capita [Variable label "GDP percap"] and total national population in thousands [Variable label "POP ('000s)"] in each of the 31 countries were obtained from the OECD online database.[6]

[4] PMPRB. 2017 Annual Report. Figure 21. Average Foreign-to-Canadian Price Ratios, Patented Medicines, OECD, 2017.
[5] ClinicalTrials.gov. U.S. National Library of Medicine (NLM), National Institutes of Health (NIH). Data extracted: Aug 04, 2019.
[6] OECD.Stat. Datasets: Economic References, Demographic References. Data extracted: Aug 04, 2019.

TABLE 1. Industry-funded clinical trials, average foreign-to-Canadian patented drug price ratios, GDP per capita, population in thousands, 31 OECD countries, 2017.

COUNTRY	IND CTs	F:C IPRX$	GDP percap	POP ('000s)
Australia	366	0.74	$51,996	24,601
Austria	117	0.88	$53,879	8,798
Belgium	241	0.79	$49,412	11,375
Canada	357	1.00	$46,596	36,708
Chile	6	0.89	$24,376	18,374
Czechia	50	0.70	$38,020	10,594
Estonia	4	0.67	$33,448	1,317
Finland	23	0.84	$46,344	5,508
France	232	0.76	$44,256	66,865
Germany	294	0.97	$52,574	82,657
Greece	18	0.69	$28,580	10,755
Hungary	17	0.81	$28,799	9,788
Ireland	16	0.83	$76,808	4,807
Italy	73	0.85	$40,981	60,537
Japan	206	0.92	$41,985	126,706
Luxembourg	0	0.79	$107,641	596
Mexico	16	0.94	$19,797	122,478
Netherlands	105	0.80	$54,422	17,131
NZ	14	0.94	$40,439	4,794
Norway	11	0.78	$62,183	5,277
Poland	19	0.69	$29,931	37,975
Portugal	4	0.72	$32,554	10,300
Slovakia	4	0.71	$32,371	5,439
Slovenia	4	0.67	$36,153	2,066
S.Korea	199	0.54	$38,839	51,446
Spain	77	0.80	$39,037	46,593
Sweden	44	0.86	$51,405	10,058
Switzerland	38	1.06	$66,300	8,452
Turkey	12	0.34	$28,153	80,313
UK	309	0.83	$44,896	66,059
USA	2,375	3.21	$59,823	325,719

ANALYSIS

A statistical analysis was conducted to test for correlations between variation across countries in the number of industry-funded clinical trials (IND CTs) and differences in prices (F:C IPRX$), economies (GDP percap) and market size (POP '000s). Charts 1-3 show scatter plots illustrating the positive (i.e. direct) statistical relationship between the dependent variable (IND CTs) and each of the independent variables (F:C IPRX$, GDP percap, POP '000s). However, the results suggest that only price and market size have correlations of statistical significance ($R^2 \approx 1.000$).

Table 2 displays the results of a multi-variable regression analysis to test the statistical significance of the set of independent variables (model) as a predictor of the dependent variable; and the correlations between the dependent variable and each independent variable, controlling for the other independent variables in the model. Statistically significant results (Adj.RSq.≈1.000; Sig. F<0.050; P<0.050) are highlighted, as are the regression coefficients showing the predicted variation in the dependent variable associated with a 1-unit change in each independent variable.

As a set, the independent variables in the model were a statistically significant (Sig. F=0.000) predictor of the dependent variable, explaining almost 90% (Adj.RSq.=0.897) of the variation in the number of industry-funded clinical trials between countries.

The analysis of the correlations between the dependent variable and each independent variable, showed that only price (P=0.000) and market size (P=0.004) remained statistically significant predictors of the dependent variable after controlling for the other independent variables in the model. The coefficient results show that a 1-unit variation (+/-1.00) in the average foreign-to-Canadian price ratio for patented medicines is associated with a variation of +/-613.355 industry-funded clinical trials. Similarly, the coefficient results show that a 1-unit variation (+/-1,000) in market size (defined by the population stated in thousands) is associated with a variation of +/-0.002 industry-funded clinical trials (or 2 trials per million population variation in market size).

CHART 1. Prices and industry-funded clinical trials, 31 OECD countries, 2017.

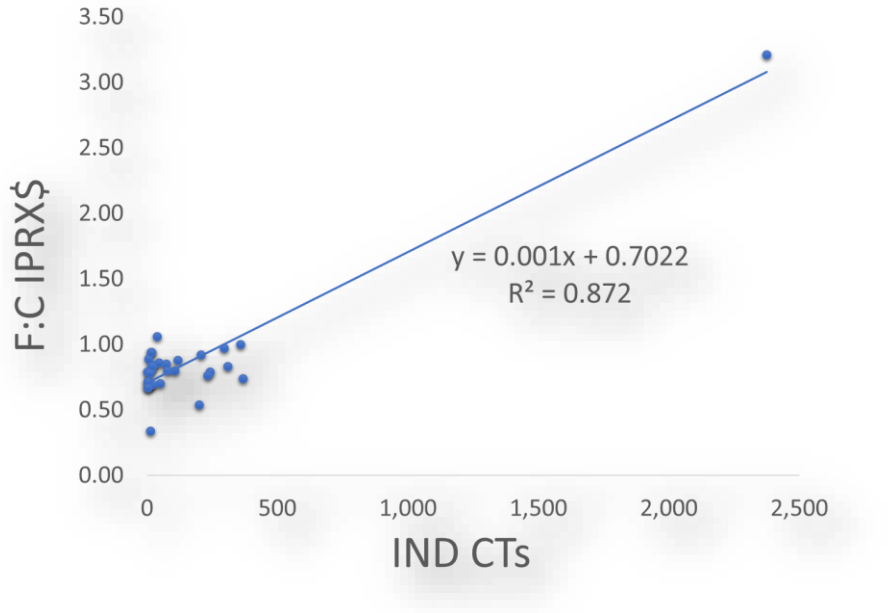


CHART 2. GDP and industry-funded clinical trials, 31 OECD countries, 2017.

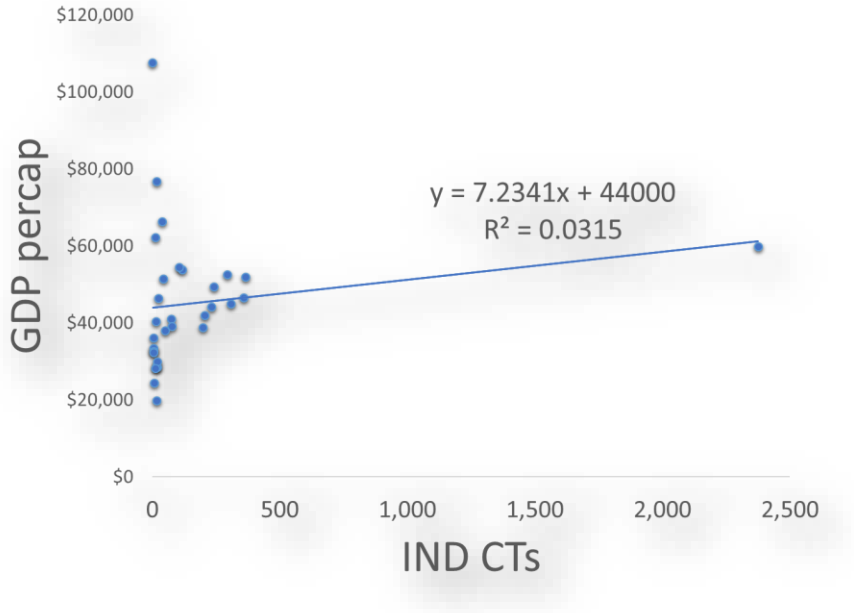


CHART 3. Market size and industry-funded clinical trials, 31 OECD countries, 2017.

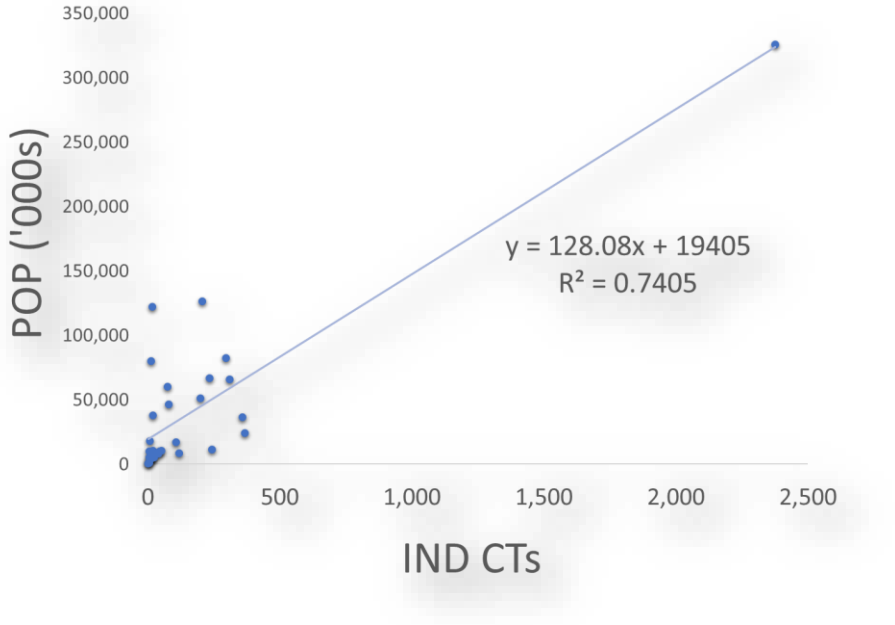


TABLE 2. Correlations statistics.

Dependent Variable: IND CTs

Model

Regression Statistics	
Multiple R	0.953
R Square	0.907
Adjusted R Square	0.897
Standard Error	136.551
Observations	31

ANOVA

	df	*SS*	*MS*	*F*	*Significance F*
Regression	3	4929415.634	1643138.545	88.121	0.000
Residual	27	503449.720	18646.286		
Total	30	5432865.355			

Independent Variables

	Coefficients	*Standard Error*	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*	*Lower 95.0%*	*Upper 95.0%*
Intercept	-498.919	79.124	-6.306	0.000	-661.267	-336.570	-661.267	-336.570
F:C IPRX$	613.355	101.934	6.017	0.000	404.204	822.506	404.204	822.506
GDP percap	0.001	0.002	0.576	0.570	-0.002	0.004	-0.002	0.004
POP ('000s)	0.002	0.001	3.141	0.004	0.001	0.004	0.001	0.004

POLICY IMPLICATIONS

Industry decisions about where to invest in pharmaceutical R&D are driven by a complex set of variables. This study provides empirical evidence of a link between the price level for patented medicines and the number of industry-funded clinical trials across economically comparable countries. The results suggest that a lower price ceiling resulting from the PMPRB regulatory changes will likely cause a substantial decline in the number of industry-funded clinical trials in Canada. Other data from the PMPRB suggest clinical trial activity could already be declining over time and that this is linked to a simultaneous decline in the Canadian price level for patented medicines relative to competing markets.[7]

An analysis of data published in the PMPRB's annual reports confirmed that Canadian gross (i.e. list) prices for patented medicines have been declining relative to international prices in the PMPRB7 countries for the last 11 years.[8] Table 2 shows PMPRB data comparing Canadian prices for patented medicines to international prices averaged across the PMPRB7 countries and stated as foreign-to-Canadian (F:C) ratios. The PMPRB publishes median and mean figures for international prices adjusted for market exchange rates (MER) and purchasing power parities (PPP) of currencies. Table 2 also shows the inverse equivalent Canadian-to-foreign (C:F) ratios (C:F = 1/F:C).[9] Measured at median prices adjusted for MER, the C:F price ratio fell from .97:1 in 2007 to .79:1 in 2017. Measured at mean prices adjusted for PPP, the C:F price ratio fell from .96:1 in 2007 to .65:1 in 2017. [CHART 4]

PMPRB data also show [CHART 5] that from 2007 to 2017 spending on qualifying pharmaceutical R&D in Canada fell from over $1.325 billion to $791.1 million.[10,11] The decline of spending on R&D coincides with a deteriorating Canadian price level relative to competing markets in the PMPRB7 countries. To illustrate this, Chart 6 plots R&D spending and C:F price ratios on the same graph using two vertical axes.

It is important to note that there is a statistical lag effect linking industry-funded R&D to the number of clinical trials. Canada accounted for less than 2% (US$22.2 billion sales) of the global pharmaceuticals (patented and non-patented) market (US$1,204.8 billion sales) by 2018, yet since 2008 almost 10% (10,080) of the cumulative global total number of industry-funded clinical trials (103,352) have been located in Canada.[12,13] The country's

[7] Year-to-year trends in the number of clinical trials could not be calculated due to database record download limits.
[8] PMPRB7 countries used for regulatory price reference: United States, United Kingdom, France, Germany, Switzerland, Italy and Sweden.
[9] Authors calculation.
[10] R&D spending reported by PMPRB only include expenditures that qualify for SRED tax credits.
[11] PMPRB. 2008 and 2017 Annual Reports. Tables 21 (2008) and 18 (2017).
[12] IQVIA. The Global Use of Medicines in 2019 and Outlook to 2023. IQVIA Institute for Human Data Science. January 2019.
[13] ClinicalTrials.gov. U.S. National Library of Medicine (NLM), National Institutes of Health (NIH). Data extracted: Aug 07, 2019.

relative success attracting industry-funded clinical trials is a legacy from earlier investment decisions when Canada's price level was higher relative to the PMPRB7 comparator countries. A statistical lag between data for R&D spending and the number of clinical trials occurs because clinical trials can take more than 6 years to complete.[14] Declining recent (2008 to 2017) trends in industry investment in pharmaceutical R&D will be reflected in future statistics which should be expected to show a subsequent parallel decline in the number of industry-funded clinical trials located in Canada. The federal government's pending PMPRB regulatory changes will probably exacerbate this trend.

TABLE 2. Foreign-to-Canadian, Canadian-to-Foreign (PMPRB7) price ratios, patented medicines: Market Exchange Rates *v* Purchasing Power Parities, factory list prices 2007 to 2017.[15]

	F:C Median at MER	F:C Mean at PPP	C:F Median at MER	C:F Mean at PPP
2007	1.03	1.04	0.97	0.96
2008	1.03	1.07	0.97	0.93
2009	1.04	1.07	0.96	0.93
2010	1.06	1.22	0.94	0.82
2011	1.05	1.22	0.95	0.82
2012	1.07	1.29	0.93	0.78
2013	1.06	1.34	0.94	0.75
2014	1.13	1.45	0.88	0.69
2015	1.18	1.43	0.85	0.70
2016	1.25	1.51	0.80	0.66
2017	1.26	1.53	0.79	0.65

[14] US FDA. https://www.fda.gov/patients/drug-development-process/step-3-clinical-research.
[15] PMPRB. 2017 Annual Report, Table 10 and corresponding tables in 2008 to 2016 annual reports.

CHART 4. Canadian-to-Foreign (PMPRB7) price ratios, patented medicines: Market Exchange Rates *v* Purchasing Power Parities, factory list prices 2007 to 2017.

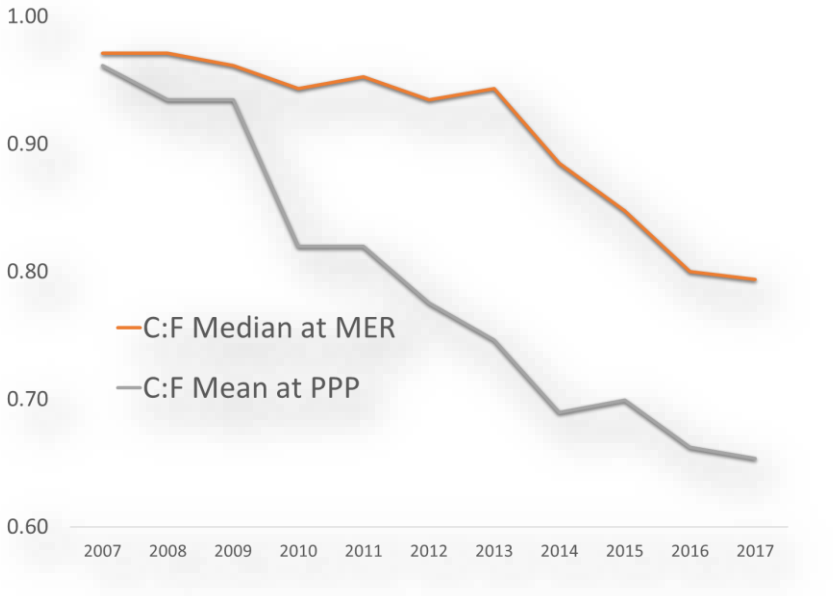
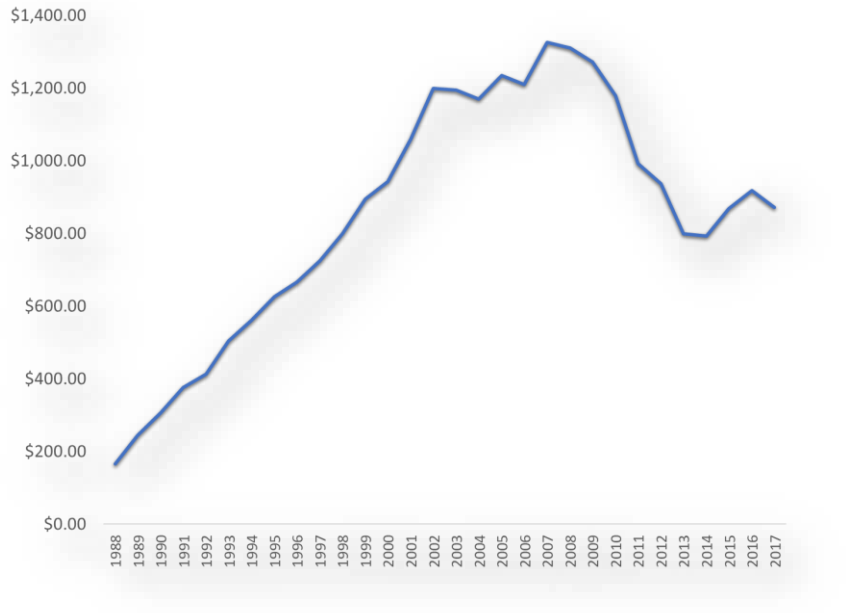
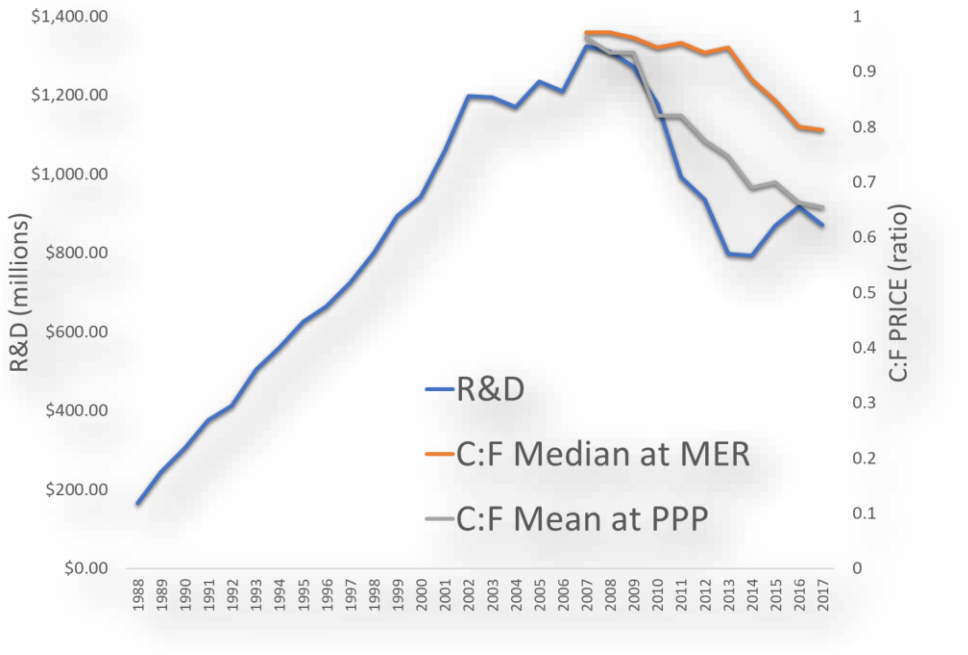


CHART 5. Total R&D spending (millions current C$) by patented pharmaceutical companies, Canada 1988 to 2017.[16]



[16] PMPRB 2017 Annual Report. Table 14.

CHART 6. R&D and C:F Price Ratios.



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