

Appendix 6. Interrupted time series analysis

The proportion of two-year launch at each quarter in a specific country is time series data. From the data plots, no seasonality was observed. The autocorrelation functions (ACF) and partial ACF plots, and Stoffer and Toloï test for the time series of Canada, the United States, and other countries as a whole showed no autoregressive integrated moving average (ARIMA) models were needed. We further tested the autocorrelations (Yule-Walker estimates) up to lag 4 in the regressions including time, policy uncertainty period, country (control), interactions between time and country, time and period, and time and country and period. If any of autocorrelations was significant, the autoregressive model with maximum likelihood estimation method was used for the analyses. Otherwise, ordinary least squares (OLS) models were used. We then used a bootstrapping approach with 5,000 iterations to estimate the 95% confidence interval and 90% confidence interval of the expected absolute change (predicted - counterfactual) in two-year launch proportion in Canada and the comparison countries (control), and the difference between the expected absolute changes in Canada and the comparison countries.

The Autoregressive model specification is as follows:

$$\begin{aligned} \text{Proportion}_t &= \beta_0 + \beta_1 \text{time} + \beta_2 \text{after} + \beta_3 \text{time} * \text{after} + \beta_4 \text{control} + \beta_5 \text{time} * \\ &\text{control} + \beta_6 \text{control} * \text{after} + \beta_7 \text{time} * \text{control} * \text{after} + v_t; \\ v_t &= -\varphi_1 v_{t-1} - \varphi_2 v_{t-2} - \dots - \varphi_m v_{t-m} + \varepsilon_t; \end{aligned}$$

where ε_t is normally and independently distributed with mean 0 and variance σ^2 ;

time - time in quarters

after - uncertain period indicator: = 0 before uncertain period, = 1 in uncertain period

control- control indicator: = 0 Canada, = 1 the United States or Other counties as a whole.

The model is an OLS model when $\varphi = 0$.

In this model,

β_0 : the launch proportion in Canada at time zero (Q1-2012);

β_1 : the proportion trend in Canada before uncertain period (before interruption);

β_2 : the proportion level change in Canada in uncertain period (after interruption).

β_3 : the proportion trend change in Canada in uncertain period

β_4 : the level difference between the control country and Canada at time zero

β_5 : the trend difference between the control country and Canada before uncertain period

β_6 : the difference in the level change (after – before) between the control country and Canada

β_7 : the difference in the trend change (after – before) between the control country and Canada

The significances of β_6 and β_7 imply that the impact of the proposed policy change and uncertainty in Canada is significantly different from the control countries.

The regression coefficients β and the autoregressive error model parameters φ_i were estimated simultaneously. SAS AUTOREG procedure was used for the analysis.

Table S2. Autoregressive model (†) or OLS estimates in the interrupted time series analysis of two-year launch in uncertain policy period after 2017 and before uncertain policy period in 2012-2017

Variable	Interpretation	Estimate	SE	P value
After 2017 as the uncertain policy period				
Compared to US†				
Intercept	Launch proportion of Canada at time zero	0.482	0.041	<0.001
time	Trend before uncertain period	-0.002	0.003	0.6
after	Level change in uncertain period in Canada	-0.131	0.389	0.7
time*after	Slope/trend change in uncertain period in Canada	0.001	0.014	0.9
control	Difference in launch proportion at time zero in US compared to Canada	0.302	0.057	<0.001
time*control	Slope/trend difference in US compared to Canada before uncertain period	0.005	0.004	0.3
control*after	Difference in level change between US and Canada	-0.059	0.553	0.9
time*control*after	Difference in slope/trend change between US and Canada	0.004	0.020	0.8
AR(1)	Autoregressive parameter for lag 1	0.289	0.127	0.03
Compared to Other Countries				
Intercept	Launch proportion of Canada at time zero	0.489	0.055	<0.001
time	Trend before uncertain period	-0.002	0.004	0.6
after	Level change in uncertain period in Canada	0.064	0.509	0.9
time*after	Slope/trend change in uncertain period in Canada	-0.006	0.018	0.8
control	Difference in launch proportion at time zero in other countries compared to Canada	0.419	0.078	<0.001
time*control	Slope/trend difference in other countries compared to Canada before uncertain period	-0.002	0.006	0.7
control*after	Difference in level change between other countries and Canada	1.037	0.719	0.2
time*control*after	Difference in slope/trend change between other countries and Canada	-0.036	0.026	0.2
After 2015 as the uncertain policy period				
Compared to US				
Intercept	Launch proportion of Canada at time zero	0.524	0.063	<0.001
time	Trend before uncertain period	-0.008	0.007	0.3
after	Level change in uncertain period in Canada	0.177	0.173	0.3
time*after	Slope/trend change in uncertain period in Canada	-0.005	0.010	0.6
control	Difference in launch proportion at time zero in US compared to Canada	0.303	0.090	0.001

time*control	Slope/trend difference in US compared to Canada before uncertain period	0.006	0.010	0.6
control*after	Difference in level change between US and Canada	-0.234	0.245	0.3
time*control*after	Difference in slope/trend change between US and Canada	0.010	0.014	0.5
Compared to Other Countries[†]				
Intercept	Launch proportion of Canada at time zero	0.503	0.037	<0.001
time	Trend before uncertain period	-0.006	0.004	0.2
after	Level change in uncertain period in Canada	0.154	0.097	0.1
time*after	Slope/trend change in uncertain period in Canada	-0.005	0.005	0.4
control	Difference in launch proportion at time zero in other countries compared to Canada	0.320	0.051	<0.001
time*control	Slope/trend difference in other countries compared to Canada before uncertain period	0.013	0.006	0.03
control*after	Difference in level change between other countries and Canada	0.192	0.139	0.2
time*control*after	Difference in slope/trend change between other countries and Canada	-0.020	0.008	0.01
AR(1)	Autoregressive parameter for lag 1	0.330	0.129	0.01
AR(2)	Autoregressive parameter for lag 2	0.288	0.130	0.03
AR(3)	Autoregressive parameter for lag 3	0.332	0.130	0.01

Table S3. Expected absolute change in two-year launch proportion and the difference in the expected absolute changes between Canada and comparison countries based on the controlled interrupted time series analysis

Comparison country	Uncertain policy period	Expected absolute change in Canada (predicted - counterfactual) (95% CI)	Expected absolute change in comparison country (predicted - counterfactual) (95% CI)	Difference between expected absolute changes (Canada - comparison country) (95% CI)
US	After 2017 as the uncertain policy period	-0.097 (-0.29, 0.10)	-0.031 (-0.14, 0.10)	-0.066 (-0.30, 0.15)
OTHERS	After 2017 as the uncertain policy period	-0.097 (-0.29, 0.10)	-0.069 (-0.21, 0.06)	-0.028 (-0.25, 0.21)
US	After 2015 as the uncertain policy period	0.063 (-0.24, 0.34)	0.066 (-0.14, 0.27)	-0.003 (-0.36, 0.35)
OTHERS	After 2015 as the uncertain policy period	0.037 (-0.24, 0.34)	-0.244 (-0.36, -0.05)	0.281 (-0.07, 0.60)
<i>Predicted and counterfactual proportions capped at 1</i>				
US	After 2015 as the uncertain policy period	0.063 (-0.24, 0.34)	0.066 (-0.13, 0.27)	-0.003 (-0.36, 0.34)
OTHERS	After 2015 as the uncertain policy period	0.037 (-0.24, 0.34)	-0.228 (-0.28, -0.05)	0.265 (-0.08, 0.57)
Average estimates in the uncertain policy period; the 95% CI were estimated using bootstrapping approach with 5,000 iterations CI: confidence interval US: the United States				

Comparison country	Uncertain policy period	Expected absolute change in Canada (predicted - counterfactual) (90% CI)	Expected absolute change in comparison country (predicted - counterfactual) (90% CI)	Difference between expected absolute changes (Canada - comparison country) (90% CI)
US	After 2017 as the uncertain policy period	-0.097 (-0.26, 0.07)	-0.031 (-0.12, 0.08)	-0.066 (-0.27, 0.12)
OTHERS	After 2017 as the uncertain policy period	-0.097 (-0.26, 0.07)	-0.069 (-0.19, 0.03)	-0.028 (-0.22, 0.17)
US	After 2015 as the uncertain policy period	0.063 (-0.19, 0.30)	0.066 (-0.11, 0.23)	-0.003 (-0.30, 0.29)
OTHERS	After 2015 as the uncertain policy period	0.037 (-0.19, 0.30)	-0.244 (-0.34, -0.08)	0.281 (-0.02, 0.54)

<i>Predicted and counterfactual proportions capped at 1</i>				
OTHERS	After 2015 as the uncertain policy period	0.037 (-0.19, 0.30)	-0.228 (-0.26, -0.08)	0.265 (-0.02, 0.51)
Average estimates in the uncertain policy period; the 90% CI were estimated using bootstrapping approach with 5,000 iterations CI: confidence interval US: the United States				

Table S4. The impact of uncertain policy period on the log odds of two-year launching in specific countries compared to Canada

Parameter	US	Other Countries	Australia	Belgium	France	Germany	Italy	Japan	Netherlands	Norway	Spain	Sweden	Switzerland	UK
Intercept	-0.79 (0.37)**	-0.41 (0.32)	-0.74 (0.40)*	-0.90 (0.36)**	-0.49 (0.34)	-0.61 (0.33)*	-1.07 (0.34)***	-0.43 (0.27)	-1.07 (0.33)***	-0.74 (0.35)**	-0.81 (0.34)**	-0.51 (0.34)	-0.50 (0.37)	-0.50 (0.33)
Period														
after 2017	-0.59 (0.30)*	-0.48 (0.26)*	-0.54 (0.31)*	-0.50 (0.28)*	-0.58 (0.27)**	-0.52 (0.27)*	-0.48 (0.27)*	-0.52 (0.25)**	-0.46 (0.28)	-0.58 (0.27)**	-0.52 (0.27)*	-0.59 (0.28)**	-0.59 (0.29)**	-0.55 (0.27)**
2012-2017	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Country														
The specific country	2.29 (0.22)***	2.21 (0.23)***	-0.74 (0.17)***	-0.49 (0.16)***	-0.41 (0.16)**	0.96 (0.17)***	-0.02 (0.16)	-0.06 (0.19)	-0.85 (0.19)***	0.31 (0.14)**	-0.37 (0.16)**	0.63 (0.15)***	-0.02 (0.15)	0.80 (0.16)***
Canada	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Country*Period														
Country*after 2017	0.75 (0.42)*	-0.28 (0.36)	-0.16 (0.37)	-0.52 (0.36)	0.56 (0.33)*	0.16 (0.30)	0.02 (0.32)	0.42 (0.34)	-0.68 (0.40)*	-0.69 (0.31)**	-0.38 (0.35)	-0.63 (0.29)**	-0.32 (0.31)	0.02 (0.31)
Country*2012-2017	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
ATC classification														
B: Blood and blood forming organs	-0.86 (0.40)**	-1.24 (0.43)***	-2.18 (0.63)***	-1.15 (0.60)*	-1.32 (0.45)***	-1.17 (0.44)***	-1.09 (0.45)**	-0.40 (0.37)	-0.22 (0.51)	-1.09 (0.54)**	-0.98 (0.52)*	-0.93 (0.48)*	-1.59 (0.47)***	-1.70 (0.46)***
J: Antiinfectives for systemic use	-0.20 (0.35)	0.08 (0.31)	0.40 (0.33)	0.40 (0.33)	0.05 (0.31)	-0.09 (0.31)	0.48 (0.30)	0.14 (0.27)	1.01 (0.33)***	0.20 (0.32)	0.41 (0.30)	-0.03 (0.33)	-0.23 (0.34)	-0.04 (0.31)
N: Nervous system	-1.09 (0.40)***	-1.45 (0.45)***	-1.05 (0.49)**	-1.41 (0.44)***	-1.44 (0.43)***	-1.13 (0.44)**	-0.94 (0.43)**	-1.39 (0.36)***	-0.55 (0.49)	-0.92 (0.47)**	-0.61 (0.47)	-1.42 (0.50)***	-1.38 (0.49)***	-1.21 (0.44)***
Other ATC	-0.90 (0.28)***	-0.50 (0.26)*	-0.54 (0.27)*	-0.45 (0.27)*	-0.98 (0.25)***	-0.69 (0.25)***	-0.44 (0.25)*	-0.33 (0.21)	0.27 (0.24)	-0.57 (0.26)**	-0.39 (0.25)	-0.81 (0.26)***	-0.81 (0.27)***	-0.85 (0.26)***
L: Antineoplastic and immunomodulating agents	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Number of comparators in Canada														
0	-0.35 (0.34)	0.09 (0.35)	0.02 (0.37)	-0.20 (0.39)	0.04 (0.35)	0.17 (0.33)	0.11 (0.35)	-0.18 (0.29)	-0.43 (0.32)	-0.01 (0.34)	-0.12 (0.37)	-0.18 (0.35)	-0.17 (0.38)	-0.04 (0.34)
1-4	-0.37 (0.26)	-0.46 (0.24)*	-0.66 (0.27)**	-0.32 (0.25)	-0.16 (0.24)	-0.36 (0.25)	-0.01 (0.24)	-0.23 (0.20)	-0.53 (0.24)**	-0.19 (0.25)	-0.37 (0.24)	-0.37 (0.25)	-0.32 (0.26)	-0.30 (0.25)
>4	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
High price (top 10%)	0.06 (0.23)	-0.01 (0.24)	-0.09 (0.26)	0.11 (0.25)	-0.04 (0.26)	0.35 (0.24)	0.33 (0.24)	-0.14 (0.21)	-0.20 (0.22)	-0.17 (0.24)	0.22 (0.24)	-0.04 (0.25)	-0.19 (0.25)	0.09 (0.25)
First year sales in US														
> 20M	2.19 (0.24)***	1.42 (0.22)***	2.09 (0.25)***	1.88 (0.25)***	1.55 (0.22)***	1.57 (0.21)***	1.63 (0.22)***	1.09 (0.18)***	1.79 (0.25)***	1.71 (0.23)***	1.60 (0.23)***	1.73 (0.22)***	1.82 (0.23)***	1.62 (0.21)***

≤ 20M	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Coefficients and standard errors estimated from the generalized estimating equation logistic regression corresponding to each specific country compared to Canada; *:0.05 ≤ p-value < 0.1, **:0.01 ≤ p-value < 0.05, ***: p-value < 0.01 ATC: Anatomical Therapeutic Chemical; UK: the United Kingdom; US: the United States; Ref: the reference group														

Table S5. The impact of uncertain policy period on log odds of two-year launching in the United States and other countries compared to Canada in ATC sub-groups

Parameter	Main Analysis: After 2017 as the uncertain policy period				Sensitivity Analysis: After 2015 as the uncertain policy period			
	US		Other Countries		US		Other Countries	
	Coefficient (SE)	P value	Coefficient (SE)	P value	Coefficient (SE)	P value	Coefficient (SE)	P value
ATC: Blood and blood forming organs								
Period: Uncertain policy period	N/A		2.14 (1.37)	0.1	N/A		N/A	
Country	N/A		5.51 (1.56)***	<0.001	N/A		N/A	
Country*Uncertain policy period	N/A		-1.87 (1.84)	0.3	N/A		N/A	
ATC: Anti-infectives for systemic use								
Period: Uncertain policy period	-0.18 (1.07)	0.9	0.11 (0.87)	0.9	0.21 (0.87)	0.8	0.09 (0.79)	0.9
Country	2.09 (0.52)***	<0.001	4.13 (0.86)***	<0.001	2.56 (0.79)***	0.001	4.42 (1.16)***	<0.001
Country*Uncertain policy period	1.75 (1.27)	0.2	-1.70 (1.18)	0.1	0.06 (1.05)	1.0	-1.63 (1.35)	0.2
ATC: Antineoplastic and immunomodulating agents								
Period: Uncertain policy period	-0.52 (0.43)	0.2	-0.54 (0.44)	0.2	-0.35 (0.44)	0.4	-0.33 (0.45)	0.5
Country	2.09 (0.46)***	<0.001	1.64 (0.37)***	<0.001	2.01 (0.55)***	<0.001	2.03 (0.55)***	<0.001
Country*Uncertain policy period	-0.03 (0.71)	1.0	-0.51 (0.55)	0.4	0.10 (0.70)	0.9	-0.92 (0.63)	0.1
ATC: nervous system								
Period: Uncertain policy period	-0.96 (1.14)	0.4	-0.94 (1.02)	0.4	-1.64 (1.26)	0.2	-1.23 (1.01)	0.2
Country	3.06 (1.24)**	0.01	1.21 (0.70)*	0.09	2.41 (1.37)*	0.08	1.07 (1.05)	0.3
Country*Uncertain policy period	2.16 (1.64)	0.2	0.89 (1.06)	0.4	2.38 (1.41)*	0.09	0.82 (1.22)	0.5
Other ATC								
Period: Uncertain policy period	-0.93 (0.58)	0.1	-0.76 (0.47)	0.1	-0.43 (0.46)	0.4	-0.23 (0.36)	0.5
Country	2.54 (0.42)***	<0.001	2.38 (0.36)***	<0.001	2.42 (0.48)***	<0.001	2.58 (0.39)***	<0.001
Country*Uncertain policy period	0.69 (0.73)	0.3	0.62 (0.79)	0.4	0.56 (0.58)	0.3	-0.17 (0.60)	0.8

Coefficients (standard error) estimated from generalized estimating equation logistic regression adjusted for number of comparators in Canada, high price, and first year sales in the US; N/A: regressions could not be estimated due to small samples and sparseness; US: the United States; ATC: WHO Anatomic Therapeutic Chemical; *:0.05 ≤ p-value < 0.1, **:0.01 ≤ p-value < 0.05, ***: p-value < 0.01.

Table S6. The impact of uncertain policy period on log odds of two-year launching in the United States and other countries compared to Canada in sub-groups of number of comparators in Canada

Parameter	Main Analysis: After 2017 as the uncertain policy period				Sensitivity Analysis: After 2015 as the uncertain policy period			
	US		Other Countries		US		Other Countries	
	Coefficient (SE)	P value	Coefficient (SE)	P value	Coefficient (SE)	P value	Coefficient (SE)	P value
Number of comparators: 0								
Period: Uncertain policy period	0.24 (0.82)	0.8	-0.24 (0.73)	0.7	-0.23 (0.73)	0.8	-0.79 (0.68)	0.2
Country	3.75 (0.75)***	<0.001	3.72 (0.82)***	<0.001	3.63 (0.83)***	<0.001	3.27 (0.83)***	<0.001
Country*Uncertain policy period	-1.57 (1.29)	0.2	-0.77 (1.30)	0.6	-1.05 (1.21)	0.4	0.30 (1.25)	0.8
Number of comparators: 1-4								
Period: Uncertain policy period	-0.44 (0.39)	0.3	-0.29 (0.33)	0.4	-0.31 (0.35)	0.4	-0.19 (0.29)	0.5
Country	2.33 (0.30)***	<0.001	1.98 (0.27)***	<0.001	2.16 (0.35)***	<0.001	2.34 (0.34)***	<0.001
Country*Uncertain policy period	0.81 (0.51)	0.1	0.08 (0.47)	0.9	0.83 (0.46)*	0.07	-0.59 (0.44)	0.2
Number of comparators: >4								
Period: Uncertain policy period	-0.85 (0.56)	0.1	-0.95 (0.48)**	0.047	-0.11 (0.53)	0.8	-0.02 (0.48)	1.0
Country	1.88 (0.39)***	<0.001	2.99 (0.68)***	<0.001	2.10 (0.55)***	<0.001	2.64 (0.63)***	<0.001
Country*Uncertain policy period	1.64 (0.88)*	0.06	-1.33 (0.81)	0.1	0.52 (0.73)	0.5	-0.68 (0.75)	0.4
Coefficients (standard error) estimated from generalized estimating equation logistic regression adjusted for the 1 st level of Anatomical Therapeutic Chemical, high price, and first year sales in the US; US: the United States; *:0.05 ≤ p-value < 0.1, **:0.01 ≤ p-value < 0.05, ***: p-value < 0.01.								

Table S7. The impact of uncertain policy period on log odds of two-year launching in the United States and other countries compared to Canada in sub-groups of high price and subgroups of first-year sales in the United States

Parameter	Main Analysis: After 2017 as the uncertain policy period				Sensitivity Analysis: After 2015 as the uncertain policy period			
	US		Other Countries		US		Other Countries	
	Coefficient (SE)	P value	Coefficient (SE)	P value	Coefficient (SE)	P value	Coefficient (SE)	P value
High price in the top 10%								
Period: Uncertain policy period	-0.55 (0.80)	0.5	-0.03 (0.56)	0.9	-0.08 (0.53)	0.9	0.15 (0.48)	0.8
Country	3.05 (0.56)***	<0.001	2.66 (0.47)***	<0.001	2.98 (0.69)***	<0.001	2.61 (0.60)***	<0.001
Country*Uncertain policy period	1.56 (1.62)	0.3	-0.00 (0.94)	1.0	0.78 (0.98)	0.4	0.10 (0.80)	0.9
Price not in the top 10%								
Period: Uncertain policy period	-0.62 (0.34)*	0.07	-0.56 (0.29)*	0.05	-0.40 (0.33)	0.2	-0.33 (0.27)	0.2
Country	2.08 (0.24)***	<0.001	2.11 (0.26)***	<0.001	2.10 (0.30)***	<0.001	2.47 (0.33)***	<0.001
Country*Uncertain policy period	0.84 (0.44)*	0.05	-0.32 (0.41)	0.4	0.47 (0.40)	0.2	-0.81 (0.40)**	0.045
First-year sales in US >\$20M								
Period: Uncertain policy period	-0.68 (0.36)*	0.06	-0.62 (0.37)*	0.09	0.03 (0.33)	0.9	0.07 (0.33)	0.8
Country	2.97 (0.55)***	<0.001	1.44 (0.27)***	<0.001	3.05 (0.62)***	<0.001	1.97 (0.37)***	<0.001
Country*Uncertain policy period	0.46 (0.93)	0.6	-0.22 (0.46)	0.6	0.13 (0.88)	0.9	-1.07 (0.45)**	0.02
First-year sales in US ≤\$20M								
Period: Uncertain policy period	-0.37 (0.47)	0.4	-0.17 (0.45)	0.7	-0.91 (0.45)**	0.045	-0.77 (0.43)*	0.08
Country	2.19 (0.32)***	<0.001	3.03 (0.34)***	<0.001	1.86 (0.36)***	<0.001	2.86 (0.40)***	<0.001
Country*Uncertain policy period	0.56 (0.57)	0.3	-0.47 (0.55)	0.4	1.00 (0.52)*	0.05	0.09 (0.54)	0.9

Coefficients (standard error) estimated from generalized estimating equation logistic regression adjusted for the 1st level of Anatomical Therapeutic Chemical, number of comparators in Canada, and high price or first year sales in the US; US: the United States; *:0.05 ≤ p-value < 0.1, **:0.01 ≤ p-value < 0.05, ***: p-value < 0.01.

Table S8. The impact of uncertain policy period on log odds of two-year launching in the United States and other countries compared to Canada in sub-groups of therapeutic benefit

Parameter	Main Analysis: After 2017 as the uncertain policy period				Sensitivity Analysis: After 2015 as the uncertain policy period			
	US		Other Countries		US		Other Countries	
	Coefficient (SE)	P value	Coefficient (SE)	P value	Coefficient (SE)	P value	Coefficient (SE)	P value
Major								
Period: Uncertain policy period	N/A		0.32 (0.70)	0.6	-0.41 (1.20)	0.7	N/A	
Country	N/A		3.04 (0.96)**	0.002	2.71 (1.52)*	0.07	N/A	
Country*Uncertain policy period	N/A		-0.88 (1.24)	0.5	3.79 (1.66)**	0.02	N/A	
Moderate								
Period: Uncertain policy period	N/A		N/A		N/A		N/A	
Country	N/A		N/A		N/A		N/A	
Country*Uncertain policy period	N/A		N/A		N/A		N/A	
Little to No								
Period: Uncertain policy period	N/A		-0.22 (0.41)	0.6	-0.13 (0.38)	0.7	-0.12 (0.37)	0.7
Country	N/A		2.30 (0.40)***	<0.001	2.20 (0.46)***	<0.001	2.18 (0.45)***	<0.001
Country*Uncertain policy period	N/A		-0.48 (0.70)	0.5	1.17 (0.73)	0.1	-0.09 (0.65)	0.9
Missing rating								
Period: Uncertain policy period	N/A		N/A		0.75 (1.15)	0.5	-0.45 (1.13)	0.7
Country	N/A		N/A		5.38 (1.11)***	<0.001	4.13 (0.87)***	<0.001
Country*Uncertain policy period	N/A		N/A		-0.42 (1.19)	0.7	-0.51 (1.17)	0.7
Sensitivity Analysis: Imputed therapeutic ratings								
Major								
Period: Uncertain policy period	0.46 (0.81)	0.6	0.80 (0.64)	0.2	0.67 (0.95)	0.5	1.38 (0.89)	0.1
Country	4.58 (1.31)***	<0.001	2.70 (0.65)***	<0.001	4.38 (1.91)**	0.02	3.27 (0.98)***	<0.001
Country*Uncertain policy period	1.50 (1.58)	0.3	-0.39 (0.89)	0.7	0.84 (1.76)	0.6	-1.03 (1.03)	0.3
Moderate								

Period: Uncertain policy period	-0.64 (0.58)	0.3	N/A		0.10 (0.58)	0.9	N/A	
Country	3.31 (0.76)***	<0.001	N/A		3.96 (1.08)***	<0.001	N/A	
Country*Uncertain policy period	0.62 (1.37)	0.6	N/A		-0.72 (1.36)	0.6	N/A	
Little to No								
Period: Uncertain policy period	N/A		-0.35 (0.39)	0.4	-0.28 (0.36)	0.4	-0.21 (0.34)	0.5
Country	N/A		1.81 (0.32)***	<0.001	2.37 (0.45)***	<0.001	1.90 (0.38)***	<0.001
Country*Uncertain policy period	N/A		-0.33 (0.57)	0.6	1.27 (0.71)*	0.08	-0.35 (0.52)	0.5
Missing rating								
Period: Uncertain policy period	N/A		N/A		N/A		N/A	
Country	N/A		N/A		N/A		N/A	
Country*Uncertain policy period	N/A		N/A		N/A		N/A	
Coefficients (standard error) estimated from generalized estimating equation logistic regression adjusted for the 1 st level of Anatomical Therapeutic Chemical, number of comparators in Canada, high price and first year sales in the US; US: the United States; N/A: regressions could not be estimated due to small samples and sparseness; *:0.05 ≤ p-value < 0.1, **:0.01 ≤ p-value < 0.05, ***: p-value < 0.01.								

Table S9. Sensitivity analysis: number and proportion of new molecules launched within two years of their global first launch by country, policy period and therapeutic benefit

Therapeutic Benefit Rating ^a	Before uncertain period in 2012-2017 (N=242)				Uncertain period after 2017 (N=107)				P value: US vs. Canada ^b	P value: Other countries vs. Canada ^b
	Total	Canada	US	Other countries	Total	Canada	US	Other countries		
Overall	242	109 (45.0%)	197 (81.4%)	203 (83.9%)	107	33 (30.8%)	88 (82.2%)	75 (70.1%)	0.08	0.4
Major	34	12 (35.3%)	31 (91.2%)	27 (79.4%)	20	5 (25%)	19 (95%)	12 (60%)	0.3	0.7
Moderate	57	34 (59.6%)	54 (94.7%)	46 (80.7%)	24	8 (33.3%)	22 (91.7%)	14 (58.3%)	0.6	N/A
Little to No	117	63 (53.8%)	105 (89.7%)	99 (84.6%)	44	20 (45.5%)	44 (100%)	33 (75%)	N/A	0.6
Missing rating	34	0 (0%)	7 (20.6%)	31 (91.2%)	19	0 (0%)	3 (15.8%)	16 (84.2%)	N/A	N/A
	Before uncertain period in 2012-2015 (N=162)				Uncertain period after 2015 (N=187)					
Overall	162	72 (44.4%)	131 (80.9%)	140 (86.4%)	187	70 (37.4%)	154 (82.4%)	138 (73.8%)	0.2	0.09
Major	18	7 (38.9%)	17 (94.4%)	16 (88.9%)	36	10 (27.8%)	33 (91.7%)	23 (63.9%)	0.6	0.3
Moderate	44	24 (54.5%)	42 (95.5%)	35 (79.5%)	37	18 (48.6%)	34 (91.9%)	25 (67.6%)	0.6	N/A
Little to No	77	41 (53.2%)	69 (89.6%)	66 (85.7%)	84	42 (50%)	80 (95.2%)	66 (78.6%)	0.08	0.5
Missing rating	23	0 (0%)	3 (13%)	23 (100%)	30	0 (0%)	7 (23.3%)	24 (80%)	N/A	N/A

^afirst based on the highest rating from the Patented Medicine Prices Review Board, the Institute for Quality and Efficiency in Health Care in Germany, and the independent French medicine bulletin Prescrire International, then the breakthrough therapy designation by the Center for Drug Evaluation and Research (CDER) of US Food and Drug Administration (FDA), and then the first-in-class and priority review designation by FDA CDER.

^bp value for the coefficient of the interaction term in the generalized estimating equation logistic regression, including uncertain period, comparison country, and interaction between uncertain period and comparison country, adjusted for the 1st level of Anatomical Therapeutic Chemical, number of comparators in Canada, high price, and first year sales in the US.

N/A: regressions could not be estimated due to small samples and sparseness.

US: the United States

Table S10. Result summary by uncertain period, comparison country, and analysis method at a significance level of 0.1

Analysis	After 2017 as the uncertain period			After 2015 as the uncertain period	
	US	Other Countries	Individual Country	US	Other Countries
Interrupted Time Series: two-year launch^a	No	No	-	No	No
GEE Logistic Regression: two-year launch^b	Fewer launches in Canada	No	<ul style="list-style-type: none"> • Fewer launches than France • More launches than the Netherlands, Norway and Sweden • No detectable difference from Australia, Belgium, Germany, Italy, Japan, Spain, Switzerland, UK 	No	More launches in Canada
Sub-groups: two-year Launch^b					
ATC: Blood and blood forming organs	N/A	No	-	N/A	N/A
ATC: Anti-infectives for systemic use	No	No	-	No	No
ATC: Antineoplastic and immunomodulating agents	No	No	-	No	No
ATC: nervous system	No	No	-	Fewer launches in Canada	No
Other ATC	No	No	-	No	No
Number of comparators: 0	No	No	-	No	No
Number of comparators: 1-4	No	No	-	Fewer launches in Canada	No
Number of comparators: >4	Fewer launches in Canada	No	-	No	No
High price in the top 10%	No	No	-	No	No
Price not in the top 10%	Fewer launches in Canada	No	-	No	More launches in Canada
First-year sales in US >\$20M	No	No	-	No	More launches in Canada
First-year sales in US ≤\$20M	No	No	-	Fewer launches in Canada	No

Major therapeutic benefit	N/A	No	-	Fewer launches in Canada	N/A
Moderate therapeutic benefit	N/A	N/A	-	N/A	N/A
Little to no therapeutic benefit	N/A	No	-	No	No
Imputed Therapeutic Benefit Rating^c			-		
Major therapeutic benefit	No	No	-	No	No
Moderate therapeutic benefit	No	N/A	-	No	N/A
Little to no therapeutic benefit	N/A	No	-	Fewer launches in Canada	No
GEE Logistic Regression: one-year launch^b	No	No	-	No	No
<p>US: the United States; UK: the United Kingdom; GEE logistic regression: generalized estimating equation logistic regression adjusted for the 1st level of Anatomical Therapeutic Chemical, number of comparators in Canada, high price, and first year sales in the US; ATC: Anatomical Therapeutic Chemical</p> <p>No: no detectable difference</p> <p>^abased on the 90% confidence interval of the difference between expected absolute changes over policy periods in Canada and the comparison country;</p> <p>^bbased on p value <0.1 for the coefficient of the interaction term of comparison country and uncertain period in the GEE logistic regression; fewer launches: the decrease of the log odds of launching in Canada was larger; more launches: the decrease of the log odds of launching in Canada was smaller;</p> <p>^cfurther imputed by the designation of first-in-class and priority review by US Food and Drug Administration</p> <p>-: the analysis was not conducted</p> <p>N/A: regressions could not be estimated due to small samples and sparseness</p>					