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State pharmaceutical importation programmes: an analysis of the cost-effectiveness

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Abstract

Objectives This article examines the cost-effectiveness of the pharmaceutical importation programmes currently under consideration. On 18 December 2019, the Trump Administration laid out a plan to allow states, drug wholesalers and pharmacies to import some lower-cost prescription medications from Canada (https://www.washingtonpost.com/health/2019/12/18/trump-administration-unveils-plan-allow-states-buy-cheaper-drugs-canada/). This comes on the heels of recently proposed state legislation in Colorado, Connecticut, Florida, Maine, Missouri, Oklahoma, Oregon, Utah, Vermont and West Virginia aimed at reducing spending on pharmaceuticals by importing them from Canada.

Methods This study analyses 24 drugs from an online Canadian supplier, accounting for the cost savings, the cost of testing for safety and efficacy, the medical consequences of treatment failure and the cost of treating an adverse medical event. The analysis compares the presumed cost savings against the costs of 'testing into safety'. The analysis also compares the presumed cost savings against the costs of treating an adverse medical event, both at the level of the individual patient and for a 'Representative State'.

Key findings For a 'Representative State', given an adverse medical event, the presumed savings from an online Canadian supplier are exhausted in the treatment of the associated adverse event: ranging from only one patient in the case of Nexium to 24 318 adverse events for patients in the case of Advair. The analysis also shows the cost of testing for safety and efficacy (with 99.999% confidence level with 99.999% reliability) exceeds the presumed cost savings for all of the drugs considered.

Conclusions While pharmaceutical importation plans are politically attractive, the numbers demonstrate that they fail to deliver cost savings when implemented safely. These schemes can be cheap, or they can be safe, but not both.

Keywords Canadian pharmacy; cost-effectiveness; drug prices; pharmaceutical importation

Introduction

Drug importation schemes are again being presented as a remedy to high US drug prices. Recently proposed legislation in Colorado, Connecticut, Florida, Maine, Missouri, Oklahoma, Oregon, Utah, Vermont and West Virginia aims to reduce spending on pharmaceuticals by importing some drugs from Canada.[1] Advocates reason that American patients can lower their drug costs by importing cheaper drugs from countries with lower pharmaceutical prices. What escapes their attention is the need for, and cost of, testing to ensure that those imports are safe and effective. Fundamentally, it has not been established whether or not it is cost-effective to import medicine from a source from which regulatory compliance cannot be assured, and then test it into safety.

In reality, it is very expensive to test imported medication to the same level of expected safety as FDA-approved medicines made in FDA-monitored factories. Given this, the tremendous cost of testing must be taken into account when calculating the cost savings or dissavings associated with buying medicines from a source outside the highly regulated US supply chain. Beyond the costs of testing drugs into safety, it is essential to recognize that purchasing pharmaceuticals outside of the US supply chain may expose patients to the risks of counterfeit, fraudulent and substandard drugs which may be dangerous or toxic, resulting in serious patient harm. Accordingly, the cost of treating the resulting adverse medical events must also be addressed.

In order to examine the cost-effectiveness of pharmaceutical importation, this study analyses the cost savings, the cost of testing and the cost of treating an adverse medical

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event. This entailed initially examining 40 drugs, documenting the prices, the cost savings that would presumably be generated by purchasing from an unregulated supplier (either a Canadian online supplier as presented in the text of this article or a brick-and-mortar Canadian pharmacy as presented in the Data S1), the potential medical consequences of treatment failure, and the expense of treating such adverse events. The results indicate that the true costs of pharmaceutical importation outweigh the anticipated cost savings. When all potential risks and costs are accounted for, moving outside of the secure US pharmaceutical supply chain fails to deliver any savings and is, in fact, indefensible.

Methods

This study began with a list of 40 drugs and, due to lack of information and availability, ultimately examines approximately two dozen drugs. The initial set of 40 drugs identified for inclusion were selected based on several criteria:

- The selection included drugs from a wide variety of therapeutic classes and treatments for a variety of diseases and medical conditions.
- The selection included drugs that are known to be widely counterfeited.
- The selection included drugs that consumers readily seek to purchase outside the legitimate supply chain.
- The selection included drugs mentioned in news and media reports that speak to consumers purchasing drugs abroad. Specifically, the Utah Tijuana Thirteen List,[2] the list promoted by Senator Bernie Sanders,[3] and the list promoted by the National Academy for State Health Policy.[4]
- The selection drew upon recommendations from experts.

Of the 40 drugs initially selected for inclusion, the list included the thirteen drugs from the Utah Tijuana Thirteen List, the 10 drugs cited by Senator Bernie Sanders, and the ten drugs promoted for importation by the NASHP (Note that while the drug included on the NASHP list was Tracleer, no Canadian sources were found for this drug, so Letairis is listed instead. Letairis is a more popular drug in the same class as Tracleer.). In addition, the list reflects drug classes that are known to be widely counterfeited. Drawing on data from the Pharmaceutical Security Institute (PSI),[5] the list includes drugs from each of the top five therapeutic categories vulnerable to counterfeiting. Finally, several drugs were included based on the recommendations of board members of the Partnership for Safe Medicines. The full list of drugs and the source of their inclusion are included in the Data S2. For each of these 40 drugs, an attempt was made to collect pricing data from both online Canadian suppliers and a brick-and-mortar Canadian pharmacy. The analysis of the online Canadian suppliers is presented here, while the analysis of the brick-and-mortar Canadian pharmacy is available in the Data S1. The presumed savings from an online Canadian supplier exceed those of the brick-and-mortar Canadian pharmacy, which will bias this analysis against a finding of the elimination of all cost savings.

Ultimately, there were 16 drugs for which some data were not available: Aubagio, Augmentin, Avonex, Celebrex, Cialis, Copaxone, Eliquis, Forteo, Humira, Letaris, Lyrica, Stelara, Stendra, Strattera, Synthroid, and Triumeq. The remaining 24 drugs were selected for extensive analysis: identification of the drug's indication, the US cost of the drug, the cost from a Canadian pharmacy (both online and brick-and-mortar), description of potential medical adverse events, calculation of cost of treating said adverse events, estimation of the cost of testing the quality, safety and efficacy of the drug. Details on the data collection methodology and sources used may be found in the Data S2.

Determination of sample size

While the pricing calculations for the USA and Canadian sourced drugs are quite straightforward, the costs of testing the quality, safety and efficacy of the drugs depend on the number of samples needed for testing. The necessary sample size is dependent on the desired confidence level and reliability one would like to have. (Please reference the Data S2 for a full discussion.) For example, in order to provide 90% confidence in the quality of the imported drugs, with 90% reliability, 22 samples must be tested. In order to increase this confidence level to 99.99%, with a 99.99% reliability, 92 099 samples must be tested. In order to increase this confidence level to 99.999%, with a 99.999% reliability, 1 151 287 samples must be tested. Table 1, below, provides the required sample size for combinations of confidence levels (ranging from 0.9 to 0.99999) and reliability (ranging from 0.9 to 0.99999).

Accordingly, the number of samples needed multiplied by the expense of a particular test may then be used to estimate the cost of 'testing drugs into safety'. The testing cost information utilized in this study was provided by NMS Labs.[6] Four tests are needed to establish quality, depending on the type of drug, the dosage and the method of administration. These are as follows: Assay, Content Uniformity, Dissolution Rate and Sterility. For the 24 drugs included in this study, the cost of testing a single sample depends on the tests required, and ranges from $2500 to $4100. Full details on test utilization and costs are included in the Data S2. Table 1 presents the highest ($4100) and lowest ($2500) costs of testing the requisite number of samples for each of the combinations of confidence level and reliability.

Results

Calculation of presumed cost savings

The presumed cost savings that will accrue to a patient who purchases their drugs from an online Canadian pharmacy are calculated as follows: Utilizing the average US price per unit and the lowest online Canadian price per unit, the average cost savings per unit were calculated for the 24 drugs for which extensive analysis is possible. For drugs taken for a chronic condition, this number was multiplied by the number of doses prescribed per month to calculate the presumed monthly savings, which was then multiplied by 12 to calculate the presumed annual savings. For drugs taken

Table 1 Sample size as a function of confidence and reliability

Confidence level (% as decimal)	Reliability (% as decimal)	Sample size required: Ln (1−Confidence)/Ln(Reliability)	Cost of testing sample at $2500[1]	Cost of testing sample at $4100[2]
0.9	0.9	22	$55 000.00	$90 200.00
0.9	0.9	22	$55 000.00	$90 200.00
0.99	0.9	44	$110 000.00	$180 400.00
0.999	0.9	66	$165 000.00	$270 600.00
0.9999	0.9	87	$217 500.00	$356 700.00
0.99999	0.9	109	$272 500.00	$446 900.00
0.9	0.99	229	$572 500.00	$938 900.00
0.99	0.99	458	$1 145 000.00	$1 877 800.00
0.999	0.99	687	$1 717 500.00	$2 816 700.00
0.9999	0.99	916	$2 290 000.00	$3 755 600.00
0.99999	0.99	1146	$2 865 000.00	$4 698 600.00
0.9	0.999	2301	$5 752 500.00	$9 434 100.00
0.99	0.999	4603	$11 507 500.00	$18 872 300.00
0.999	0.999	6904	$17 260 000.00	$28 306 400.00
0.9999	0.999	9206	$23 015 000.00	$37 744 600.00
0.99999	0.999	11 507	$28 767 500.00	$47 178 700.00
0.9	0.9999	23 025	$57 562 500.00	$94 402 500.00
0.99	0.9999	46 049	$115 122 500.00	$188 800 900.00
0.999	0.9999	69 074	$172 685 000.00	$283 203 400.00
0.9999	0.9999	92 099	$230 247 500.00	$377 605 900.00
0.99999	0.9999	115 123	$2 878 217 500.00	$4 720 276 700.00
0.9	0.99999	230 257	$575 642 500.00	$944 053 700.00
0.99	0.99999	460 515	$1 151 287 500.00	$1 888 111 500.00
0.999	0.99999	690 772	$1 726 930 000.00	$2 832 165 200.00
0.9999	0.99999	921 029	$2 302 572 500.00	$3 776 218 900.00
0.99999	0.99999	1 151 287	$2 853 217 500.00	$4 679 276 700.00

Source: Author's calculations.
[1]This calculation represents the minimal cost of testing per sample, according to the estimates provided by NMS Labs.[[6]]
[2]This calculation represents the maximum cost of testing per sample, according to the estimates provided by NMS Labs.[[6]]

for an acute condition, the average per unit cost savings was multiplied by the number of doses needed for treatment to calculate the savings per episode per patient. These calculations are presented in Table 2, below. The costs, pricing and savings data presented here correspond to the information collected for online Canadian suppliers. The corresponding analysis for a brick-and-mortar Canadian pharmacy is presented in the Data S1.

Ratio of the expense of treating an adverse event to presumed cost savings per patient

Since cost savings is the primary motivation for pharmaceutical importation, it is essential to consider whether patients actually save money. This section compares the presumed cost savings that will accrue to a patient over time and compares it to the cost of treating an adverse medical event. Simply stated, if a patient receives a counterfeit version of the imported drug and suffers negative health consequences, will they save any money?

Again, utilizing the average US price per unit and the lowest online Canadian price per unit, the average cost savings per unit were calculated. These presumed cost savings were then compared with the expense of treating an adverse event. Data on the costs of treating adverse medical events were gathered from medical journals and institutional sources and are fully described in the Data S2. Again, the parallel analysis for a brick-and-mortar Canadian pharmacy is presented in the Data S1.

In the case of an online Canadian supplier, the annual presumed savings fail to cover the treatment of an adverse event for 18 of the 24 drugs (75%). All calculations are presented in Table 2. The calculations indicate that the ratio of the presumed savings to the treatment cost ranges from <0.01 for Crestor to 5.65 for Enbrel (The ratio is calculated by dividing the online savings per year per patient by the cost of treating an adverse event per patient). That is, for Crestor, the presumed annual savings cover <1% of the cost of treating an adverse medical event, such that patients would require almost 105 years of presumed cost savings to cover the treatment of an adverse medical event.[1] For Enbrel, patients would require 65 days of presumed cost savings to cover the treatment of an adverse medical event.[2] For Crestor, the cost of treating an adverse event is more than 10 500% of the presumed cost savings. Of the 14 adverse medical events considered, the presumed cost savings exceed the cost of treatment for only three conditions (21%). These are as follows: multiple sclerosis (Gilenya, Tecfidera), psoriatic arthritis (Enbrel, Orencia, Otezla) and prostate cancer (Zytiga). In addition, for ten of the 24 drugs analysed, the annual presumed savings are <5% the cost of treating an adverse medical event. On average, patients

Table 2 Presumed cost savings per patient relative to the cost of treating an adverse event from online Canadian supplier

Drugs	Average US price per unit	Lowest online Canadian price per unit	US price less online Canadian price per unit	Online savings per patient: monthly[1]	Online savings per patient: yearly[2]	Online savings per patient: per episode[3]	Cost of treating adverse event per patient[4]	Number of years of savings needed to cover adverse event[5]	Per cent of adverse event treatment covered by annual savings[6]	Time needed to accrue cost savings to cover treatment of adverse event[7]
Abilify	$30.01	$1.48	$28.53	$855.88	$10 270.54		$64 729	6.30	0.16	6 years 4 months
Actos	$20.08	$0.82	$19.25	$577.61	$6931.29		$165 822	23.92	0.04	23 years 11 months
Advair	$396.55	$65.00	$331.55	$331.55	$3978.57		$11 097	2.79	0.36	2 years 9 months
Albenza	$210.21	$1.13	$209.09			$50 450.40	$55 085	1.09	0.92	1 year 1 month
Ampyra	$44.95	$12.23	$32.72	$1963.37	$23 560.40		$48 893	2.08	0.48	2 years 10 months
Crestor	$5.82	$1.43	$4.39	$131.67	$1580.07		$165 822	104.95	0.01	105 years
Enbrel	$1217.99	$430.00	$787.99	$3151.98	$37 823.70		$6699	0.18	5.65	65 days
EpiPen	$308.53	$137.00	$171.53			$171.53	$4719	27.51	0.04	27 years 6 months
Gilenya	$261.73	$107.14	$154.58	$4637.54	$55 650.44		$48 893	0.88	1.14	10 months 17 days
Harvoni	$1124.18	$736.80	$387.38			$34 864.52	$812 500	23.30	0.04	23 years 3 months
Januvia	$14.70	$1.43	$13.27	$398.11	$4777.35		$29 023	6.08	0.16	6 years 1 month
Lipitor	$14.25	$1.17	$13.08	$392.41	$4708.92		$165 822	35.21	0.03	35 years 3 months
Nexium	$5.60	$1.00	$4.60	$137.96	$1655.49		$93 966	56.76	0.02	56 years 9 months
Orencia	$1080.41	$404.00	$676.41	$2705.63	$32 467.60		$6699	0.21	4.85	2 months 16 days
Otezla	$56.03	$21.40	$34.63	$2077.83	$24 933.99		$6699	0.27	3.72	3 months 7 days
Premarin	$5.05	$0.77	$4.28	$128.38	$1540.51		$12 409	8.06	0.12	8 years 1 month
Revatio	$23.87	$6.54	$17.32	$1558.97	$18 707.61		$41 617	2.22	0.45	2 years 3 months
Sovaldi	$997.05	$809.90	$187.15			$16 843.18	$812 500	48.24	0.02	48 years 3 months
Tecfidera	$126.10	$37.41	$88.69	$5321.48	$63 857.73		$48 893	0.77	1.31	9 months 7 days
Tresiba	$192.19	$37.80	$154.39	$154.39	$1852.70		$29 023	15.67	0.06	15 years 8 months
Truvada	$56.12	$4.17	$51.95	$1558.53	$18 702.39		$447 758	23.94	0.04	23 years 11 months
Xarelto	$14.21	$1.73	$12.49	$374.65	$4495.76		$165 822	36.88	0.03	36 years 11 months
Zetia	$11.42	$2.02	$9.39	$281.85	$3382.19		$165 822	49.03	0.02	49 years 11 days
Zytiga	$85.19	$33.33	$51.86	$6223.75	$74 685.00		$23 243	0.31	3.21	3 months 22 days

Source: Author's calculations, May 2019. Details on the source of these data may be found in the Data S2.

[1]This dollar value was calculated by multiplying the average cost savings per unit by the number of doses prescribed per month.

[2]This dollar value was calculated by multiplying the average cost savings per unit by the number of doses prescribed per month by 12.

[3]In the case of drugs that are taken for an episode, rather than on a regular basis, this dollar value was calculated by multiplying the average cost savings per unit by the number of doses taken per episode.

[4]These costs are based on estimates found in published journal articles.

[5]This number is calculated by dividing the cost of treating an adverse event by the presumed online savings per year (e.g. in the case of Crestor, $165 822/$1580.07 = 104.95).

[6]This number is calculated by dividing the online savings per year per patient by the cost of treating an adverse event per patient.

[7]This number of months needed is calculated by multiplying the decimal (e.g. 0.31 in the case of Zytiga) by 12 (0.31*12 = 3.72). The number of days needed is then calculated by multiplying the decimal (e.g. 0.72 in this case) by 30 (0.72*30 = 21.6).

would need to accumulate 24 years of the presumed cost savings to cover the cost of treatment for an adverse medical event. Admittedly, it is unknown and unknowable how often these adverse events happen, and therefore whether 24 years of cost savings are worth the risk.

It is essential to recognize the true danger posed to US patients from drugs that are obtained outside of the highly regulated US supply chain. That is, when an attempt to save money ends up leading to even greater expenses. In a relatable situation, at least a dozen US patients have travelled to Mexico for surgical procedures that were less expensive in Tijuana. These patients contracted a rare and potentially deadly strain of bacteria resistant to virtually all antibiotics. Treatment of the deadly superbug has resulted in medical expenses that far outstrip the initial savings.[7] Also, consider two instances in which Canada Drugs, through its subsidiary River East Supplies, distributed counterfeit cancer drugs Avastin and Altuzan (the Turkish version of the drug) in the United States. According to the US FDA, testing of vials of the drugs recovered from these shipments revealed that neither contained any active ingredient. In April 2018, the Canadian firm admitted to widespread illegal sales of misbranded and counterfeit prescription drugs in the United States.[8] Again, the cost savings are eliminated in the face of complete treatment failure.

Per patient takeaway

In the case of 75% of the drugs analysed, the annual presumed savings fail to cover the costs of an adverse medical event. For these drugs, patients would need to acquire the presumed cost savings over a period of up to 105 years (Crestor) to cover the costs of one adverse event. Not surprisingly, for the six drugs for which the savings exceed the cost of treating an adverse medical event, the expense of an adverse medical event is modest (<$50 000), compared with the average cost of treating an adverse medical event for the other 18 drugs (approximately $183 000). For the majority of drugs, the cost of treating an adverse event will significantly exceed $50 000 and may reach more than $800 000 in the case of Sovaldi.

Presumed cost savings for a 'representative state' relative to the cost of a potential adverse medical event

This study places the cost savings from Canadian importation into context with comparisons to two critical dimensions: the costs of potential adverse medical events and the costs of 'testing into safety'. Given that the majority of importation proposals are presented at the state level, it is worthwhile to consider the financial implications for a 'Representative State'. This study derives the results for a 'Representative State' by calculating the impact for 1/50th of the population of the United States. While recognizing that some states will be larger and others smaller, it is still illustrative to consider the implications. Each of the cost-versus-savings calculations for a 'Representative State' described in here is presented in Table 3 and explained below.

Number of patients

The population of a 'Representative State' is assumed to be 1/50th of the population of the United States, approximately 6 540 000 people. The number of patients for each condition considered here is assumed to be the representative share (1/50th) of the US patient population suffering from the named condition. For example, according to the National Multiple Sclerosis Society, approximately 1 million people in the United States suffer from MS. Dividing this number by 50, the 'Representative State' will have approximately 20 000 patients with MS (Column 4 in Table 3).

Covered patients

In order to estimate the number of 'covered patients' in a 'Representative State', it is assumed that 20% of the impacted patient population will enrol in the state programme. This fraction was utilized because approximately one in five individuals in the United States is currently covered by Medicaid (Column 5 in Table 3).

Total presumed cost savings

The total amount of presumed cost savings from purchases made from an online Canadian pharmacy is calculated by multiplying the number of covered patients by the presumed cost savings (either per patient/year or per patient/episode). Again, this number may be an overestimation which again biases the analysis against a finding of the elimination of all cost savings (Column 6 in Table 3).

Cost of treating an adverse medical event

Estimates of the cost of treating an adverse medical event were gleaned from medical journals and government sources. These are presented and detailed in the Data S2 (Column 7 in Table 3).

Number of adverse events covered by presumed savings

This number corresponds to the maximum number of adverse events that could be covered through the expenditure of the Representative State's cost savings. It is calculated by dividing the total presumed savings from an online Canadian pharmacy by the cost of treating an adverse event. These numbers range from a low of 0.59 adverse events in the case of Nexium to 24 318 adverse events in the case of Advair. That is, the Representative State's cost savings would be exhausted before treating one adverse medical event in the case of Nexium, and after more than 24 300 patients in the case of Advair (Column 8 in Table 3).

Adverse events would exhaust presumed savings

If the presumed cost savings were exhausted covering adverse events, it is important to also know the share of

Table 3 Presumed online cost savings for a 'representative state' relative to cost of an adverse medical event

Drugs	Savings per patient/ year	Savings per patient/ episode	Number of patients[1]	Covered patients[2]	Total presumed savings from online pharmacy[3]	Cost of treating an adverse event per patient[4]	Number of adverse events covered by presumed savings[5]	Adverse events would exhaust presumed savings after covering this share of covered patients[6]	Cost of treating an adverse event in 100% of covered patients[7]	Gains or losses from treating adverse events in 100% of covered patients beyond presumed cost saving[8]	Gains or Losses from treating adverse events in 10% of covered patients beyond presumed cost savings[9]
Abilify	$10 270.54		29 192	5838	$59 963 520.74	$64 729	926.38	15.87%	$377 913 793.60	($317 950 272.86)	$22 172 141.38
Actos	$6931.29		606 000	121 200	$840 072 348.00	$165 822	5066.11	4.18%	$20 097 626 400.00	($19 257 554 052.00)	($1 169 690 292.00)
Advair	$3978.57		392 400	78 480	$312 238 173.60	$11 097	28 137.17	35.85%	$870 892 560.00	($558 654 386.40)	$225 148 917.60
Albenza		$50 450.40	41	8	$413 693.28	$55 085	7.51	91.59%	$451 697.00	($38 003.72)	$368 523.58
Ampyra	$23 560.40		20 000	4000	$94 241 600.00	$48 893	1927.51	48.19%	$195 572 000.00	($101 330 400.00)	$74 684 400.00
Crestor	$1580.07		860 000	172 000	$271 772 040.00	$165 822	1638.94	0.95%	$28 521 384 000.00	($28 249 611 960.00)	($2 580 366 360.00)
Enbrel	$37 823.70		3490	698	$26 400 942.60	$6699	3941.03	564.62%	$4 675 902.00	$21 725 040.60	$25 933 352.40
EpiPen		$171.53	131 200	26 240	$4 500 947.20	$4719	953.79	3.63%	$123 826 560.00	($119 325 612.80)	($7 881 708.80)
Gilenya	$55 650.44		20 000	4000	$222 601 760.00	$48 893	4552.83	113.82%	$195 572 000.00	$27 029 760.00	$203 044 560.00
Harvoni		$34 864.52	48 000	9600	$334 699 392.00	$812 500	411.94	4.29%	$7 800 000 000.00	($7 465 300 608.00)	($445 300 608.00)
Januvia	$4777.35		606 000	121 200	$579 014 820.00	$29 023	19 950.21	16.46%	$3 517 587 600.00	($2 938 572 780.00)	$227 256 060.00
Lipitor	$4708.92		860 000	172 000	$809 934 240.00	$165 822	4884.36	2.84%	$28 521 384 000.00	($27 711 449 760.00)	($2 042 204 160.00)
Nexium	$1655.49		300	60	$99 329.40	$93 966	1.06	1.76%	$5 637 960.00	($5 538 630.60)	($464 466.60)
Orencia	$32 467.60		3490	698	$22 662 384.80	$6699	3382.95	484.66%	$4 675 902.00	$17 986 482.80	$22 194 794.60
Otezla	$24 933.99		3490	698	$17 403 925.02	$6699	2597.99	372.20%	$4 675 902.00	$12 728 023.02	$16 936 334.82
Premarin	$1540.51		204 000	40 800	$62 852 808.00	$12 409	5065.10	12.41%	$506 287 200.00	($443 434 392.00)	$12 224 088.00
Revatio	$18 707.61		4000	800	$14 966 088.00	$41 617	359.61	44.95%	$33 293 600.00	($18 327 512.00)	$11 636 728.00
Sovaldi		$16 843.18	48 000	9600	$161 694 528.00	$812 500	199.01	2.07%	$7 800 000 000.00	($7 638 305 472.00)	($618 305 472.00)
Tecfidera	$63 857.73		20 000	4000	$255 430 920.00	$48 893	5224.28	130.61%	$195 572 000.00	$59 858 920.00	$235 873 720.00
Tresiba	$1852.70		606 000	121 200	$224 547 240.00	$29 023	7736.87	6.38%	$3 517 587 600.00	($3 293 040 360.00)	($127 211 520.00)
Truvada	$18 702.39		22 000	4400	$82 290 516.00	$447 758	183.78	4.18%	$1 970 135 200.00	($1 887 844 684.00)	($114 723 004.00)
Xarelto	$4495.76		860 000	172 000	$773 270 720.00	$165 822	4663.26	2.71%	$28 521 384 000.00	($27 748 113 280.00)	($2 078 867 680.00)
Zetia	$3382.19		860 000	172 000	$581 736 680.00	$165 822	3508.20	2.04%	$28 521 384 000.00	($27 939 647 320.00)	($2 270 401 720.00)
Zytiga	$74 685.00		3671	734	$54 833 727.00	$23 243	2359.15	321.32%	$17 065 010.60	$37 768 716.40	$53 127 225.94

Source: Author's calculations.

[1]The population of a 'Representative State' is assumed to be 1/50th of the population of the United States, approximately 6 540 000 people. The number of patients for each condition considered here is assumed to be 1/50th of the US patient population. For example, approximately 1 million people in the US have MS, so the number of MS patients in a 'Representative State' would be 20 000.

[2]The number of 'covered patients' is assumed to be 20% of the patient population in a 'Representative State'. This fraction was utilized to mirror Medicaid coverage which is approximately one in five individuals in the United States.

[3]This number comes from multiplying the number of covered patients by the savings (either per patient/year or per patient/episode).

[4]These figures were gathered from medical journals and government sources. The specifics of the adverse medical event and the details of cost estimates are presented in the Data S2.

[5]This number comes from dividing the total presumed savings by the cost of treating an adverse event. For example, in the case of Actos, the potential adverse medical event is diabetic ketoacidosis with a treatment cost of $165 822. Dividing the total presumed savings from an online pharmacy ($840 072 348.00) by this cost provides 5066.11. That is, in a 'Representative State', the total presumed savings from an online pharmacy would be exhausted by the treatment of 5066 adverse events.

[6]This number comes from dividing the number of adverse events covered by total presumed savings by the number of covered patients. For example, in the case of Actos in a 'Representative State', the total presumed cost savings ($840 072 348) would be exhausted after treating 4.18% of all covered patients (5066 patients) [5066/840 072 348 = 0.0418].

[7]This number comes from multiplying the cost of treating a potential adverse event by the total number of covered patients. For example, in the case of Actos in a 'Representative State', 121 200 covered patients * $165 822 = more than $20 billion dollars.

[8]This is the worst-case scenario in which all covered patients suffer an adverse medical event that requires treatment. This number comes from subtracting the cost of treating an adverse event in 100% of covered patients from the total presumed cost savings. That is, column 6 minus column 10. In the case of Actos in a 'Representative State': $840 072 348.00 − $20 097 626 400.00 = −$19 257 554 052.00. (A loss of more than $19 billion dollars.)

[9]This represents the outcome under a more modest scenario in which only 10% of covered patients suffer an adverse medical event. This number comes from subtracting 10% the cost of treating an adverse event in 100% of covered patients from the total presumed cost savings. That is, column 6 – 10% of column10. In the case of Actos in a 'Representative State': $840 072 348 − [(0.10)* ($20 097 626 400.00)] = −$1 169 690 292.00. (A loss of more than $1.16 billion dollars.)

Table 4 Presumed online cost savings for a 'representative state' relative to the cost of testing

Drugs	Savings per patient/ year[1]	Savings per patient/ episode[1]	Number of patients[1]	Covered patients[1]	Total presumed savings from online pharmacy[1]	Cost of quality testing (per sample)[2]	Number of samples that could be tested, exhausting the presumed savings[3]	Gain or loss from online presumed savings less cost of testing with 90% confidence and 90% reliability (22 samples)[4]	Gain or loss from online presumed savings less cost of testing with 99.99% confidence and 99.99% reliability (92 099 samples)[5]	Gain or loss from online presumed savings less cost of testing with 99.999% confidence and 99.999% reliability (1 151 287 samples)
Abilify	$9004.23		29 192	5838	$59 963 520.74	$4000	14 991	$59 875 520.74	($308 432 479.26)	($4 545 184 479.26)
Actos	$5722.84		606 000	121 200	$840 072 348.00	$2500	336 029	$840 017 348.00	$609 824 848.00	($2 038 145 152.00)
Advair	$3438.61		392 400	78 480	$312 238 173.60	$4100	76 156	$312 147 973.60	($65 367 726.40)	($4 408 038 526.40)
Albenza		$50 021.87	41	8	$413 693.28	$2500	165	$358 693.28	($229 833 806.72)	($2 877 803 806.72)
Ampyra	$23 367.67		20 000	4000	$94 241 600.00	$2500	37 697	$94 186 600.00	($136 005 900.00)	($2 783 975 900.00)
Crestor	$1494.40		860 000	172 000	$271 772 040.00	$2500	108 709	$271 717 040.00	$41 524 540.00	($2 606 445 460.00)
Enbrel	$34 379.70		3490	698	$26 400 942.60	$2800	9429	$26 339 342.60	($231 476 257.40)	($3 197 202 657.40)
EpiPen		$168.54	131 200	26 240	$4 500 947.20	$2800	1607	$4 439 347.20	($253 376 252.80)	($3 219 102 652.80)
Gilenya	$58 222.00		20 000	4000	$222 601 760.00	$2500	89 041	$222 546 760.00	($7 645 740.00)	($2 655 615 740.00)
Harvoni		$17 604.88	48 000	9600	$334 699 392.00	$2500	133 880	$334 644 392.00	$104 451 892.00	($2 543 518 108.00)
Januvia	$3731.76		606 000	12 1200	$579 014 820.00	$2500	23 1606	$578 959 820.00	$348 767 320.00	($2 299 202 680.00)
Lipitor	$4808.96		860 000	17 2000	$809 934 240.00	$2500	32 3974	$809 879 240.00	$579 686 740.00	($2 068 283 260.00)
Nexium	$922.76		300	60	$99 329.40	$3000	33	$33 329.40	($276 197 670.60)	($3 453 761 670.60)
Orencia	$18 260.08		3490	698	$22 662 384.80	$2800	8094	$22 600 784.80	($235 214 815.20)	($3 200 941 215.20)
Otezla	$22 343.41		3490	698	$17 403 925.02	$2500	6962	$17 348 925.02	($212 843 574.98)	($2 860 813 574.98)
Premarin	$1540.55		204 000	40 800	$62 852 808.00	$2600	24 174	$62 795 608.00	($176 604 592.00)	($2 930 493 392.00)
Revatio	$16 055.72		4000	800	$14 966 088.00	$3600	4157	$14 886 888.00	($316 590 312.00)	($4 129 667 112.00)
Sovaldi		$28 662.91	48 000	9600	$161 694 528.00	$2500	64 678	$161 639 528.00	($68 552 972.00)	($2 716 522 972.00)
Tecfidera	$65 233.44		20 000	4000	$255 430 920.00	$2500	102 172	$255 375 920.00	$25 183 420.00	($2 622 786 580.00)
Tresiba	$1826.32		606 000	121 200	$224 547 240.00	$2800	80 195	$224 485 640.00	($33 329 960.00)	($2 999 056 360.00)
Truvada	$7854.39		22 000	4400	$82 290 516.00	$2500	32 916	$82 235 516.00	($147 956 984.00)	($2 795 926 984.00)
Xarelto	$3797.23		860 000	172 000	$773 270 720.00	$2500	309 308	$773 215 720.00	$543 023 220.00	($2 104 946 780.00)
Zetia	$3230.80		860 000	172 000	$581 736 680.00	$2500	232 695	$581 681 680.00	$351 489 180.00	($2 296 480 820.00)
Zytiga	$72 093.12		3671	734	$54 833 727.00	$2500	21 933	$54 778 727.00	($175 413 773.00)	($2 823 383 773.00)

Source: Author's calculations.

[1]These numbers are identical to those presented in Exhibit 3.

[2]These numbers correlate to the estimates provided by NMS Labs. Details may be found in the Data S2.

[3]This number is calculated by dividing the total presumed savings by the cost of testing. That is, column 6 divided by column 7.

[4]This number is calculated by subtracting the cost of testing 22 samples from the total presumed savings from an online pharmacy. That is, column 6 minus (22 times column 7).

[5]This number is calculated by subtracting the cost of testing 92 099 samples from the total presumed savings from an online pharmacy. That is, column 6 minus (92 099 times column 7).

[6]This number is calculated by subtracting the cost of testing 1 151 287 samples from the total presumed savings from an online pharmacy. That is, column 6 minus (1 151 287 times column 7).

patients enrolled in the plan taking a particular drug. This share is calculated by dividing the number of adverse events covered by presumed savings by the number of covered patients. In the case of an online Canadian supplier, this number ranges from 0.95% (Crestor) to 564% (Enbrel). Accordingly, if an adverse medical event affected <1% (only 0.95%) of all patients taking Crestor, the entire presumed cost savings would be wiped out. Alternatively, one can think of this as the share of counterfeit drugs that would wipe out all cost savings from an importation programme (Column 9 in Table 3).

Cost of treating an adverse event in 100% of covered patients

The cost of treating an adverse medical event in 100% of covered patients taking a particular drug is calculated by multiplying the cost of treating an adverse event by the total number of covered patients. (That is, the enrolled population, 20% of the patients suffering from this condition in the Representative State.)[3] This number ranges from approximately $452 000 (Albenza) to more than $28.5 billion dollars (Lipitor; Column 10 in Table 3). Alternatively, one can think of this as the cost of treating all covered patients in the case of counterfeits that adversely affect all covered patients taking the drug.

Gains or losses from treating adverse events in 100% of covered patients less presumed cost savings

The extent to which the expense of treating an adverse event in 100% of covered patients exceeds the presumed cost savings – the overage – is calculated. For 19 of the 24 drugs (all but five cases, for three conditions), the expense of treatment far exceeds the presumed cost savings. The presumed savings are dwarfed by the potential cost of treating adverse medical events. These estimates range from savings of approximately $60 million (Tecfidera) to losses of $28 billion (Lipitor; Column 10 in Table 3).

Gains or losses from treating adverse events in 10% of covered patients beyond presumed cost savings

It is highly unlikely that 100% of covered patients will experience an adverse medical event, the worst-case scenario. Assuming more modest circumstances that only 10% of drugs result in an adverse event, eleven (46%) of the 24 drugs will result in a situation in which the presumed savings are eliminated by the cost of treating an adverse event (These are the eleven drugs for which a loss is calculated in column 12 in Table 3.). Alternatively, one can think of this as the cost of treating patients in the case of counterfeits that adversely affect only 10% covered patients taking the drug.

Online suppliers

In the case of online Canadian suppliers, for this selection of 24 drugs, the cost savings will be completely eliminated if a mere 9.5% of imported drugs are counterfeit, and result in an adverse medical event (the average of Column 9 in Table 3). The parallel analysis for a brick-and-mortar pharmacy (found in the Data S1) indicates that counterfeiting at the rate of a mere 8.1% of imported drugs would completely eliminate the total presumed cost savings.

Presumed cost savings for a 'representative state' relative to the cost of 'testing into safety'

This study places the cost savings from Canadian importation into context with comparisons to two critical dimensions: first, the costs of potential adverse medical events examined above, and second, the costs of 'testing into safety'. For the second, the cost of testing the authenticity and quality of the imported medicine is based on the estimated cost provided by NMS Labs. Table 4 includes the total cost of testing a single sample to ensure the quality of each drug based on the different tests necessary for each drug. Additional details on testing costs may be found in the Data S2. Table 4 utilizes the calculations for several levels of authenticity and the testing cost information to determine the savings or dissavings available to a 'Representative State' for the 24 drugs included in the analysis, presenting calculations for several levels of confidence and reliability, (ranging from 90%/90% to 99.999%/99.999%), based on the number of samples required, as presented in Table 1.

It is important to recognize that the testing estimates provided here only include the cost of the tests. The cost of purchasing the requisite number of samples needed for testing is not included in these cost estimates. Again, this assumption biases the results against a finding of the elimination of the presumed cost savings.

Number of samples that could be tested, exhausting the presumed savings

The maximum number of doses that could be tested for safety, by exhausting the presumed cost savings, is calculated by dividing the total presumed savings by the cost of testing a specific drug (Column 8 in Table 4).

Presumed savings less the cost of testing

In order to ensure the quality of a particular drug at a particular confidence level with a particular level of reliability, different numbers of samples must be tested.

- To establish a 90% confidence level and 90% reliability, 22 samples must be tested. The calculations for this level of accuracy are presented in Column 9 in Table 4: the presumed cost savings less the cost of testing to 90%/90%.
- To establish a 99.99% confidence level and 99.99% reliability, 92 099 samples must be tested. The difference in the cost of testing 92 099 samples of the imported drugs and the presumed cost savings available from importation is presented in Column 10 in Table 4.
- To establish a 99.999% confidence level and 99.999% reliability, 1 151 287 samples must be tested. The

calculation of this level of accuracy is presented in Column 11 in Table 4.

Bottom line

In the case of online Canadian suppliers, to ensure the safety and quality of a particular drug with a 90% confidence level and 90% reliability, 22 samples must be tested, and the presumed savings exceed the cost of testing for all 24 drugs. For a 99.99% confidence level and 99.99% reliability, 92 099 samples must be tested, the drugs for which the presumed savings exceed the cost of testing falls to only eight. And for a 99.999% confidence level and 99.999% reliability, 1 151 287 samples must be tested. In every case, the presumed savings are dwarfed by the cost of testing. The cost of testing ranges from 243 times the presumed savings for Advair to 34 770 times the presumed savings for Orencia. That is, the cost of testing ranges from 243% the presumed savings for Advair to 3 477 079% the presumed savings for Orencia. Notably, all assumptions made in this analysis bias the results against a finding of the elimination of the presumed cost savings, yet the results indicate that the presumed cost savings will almost certainly be dwarfed by both (1) the costs of treating adverse medical events and (2) the costs of 'testing into safety'.

Limitations: issues affecting cost not studied

There are several issues that will certainly impact the cost of an importation programme that are not included in this study. These issues are beyond the scope of this work but will undoubtedly reduce the estimated cost savings. These include the following: shortages, quality controls, legal liability, post-sale pharmacovigilance and the implementation cost. Each is briefly addressed in the Data S2.

Discussion

Numerous states, as well as the Trump Administration, are currently exploring proposals to import lower-cost drugs from Canada, a seemingly simple way to address the demand for costly therapies with quick and substantial price relief for patients. However, policymakers and patients must recognize that the presumed cost savings may be elusive. This study evaluates the presumed cost savings from the purchase of drugs from an online Canadian supplier with a focus on two critical considerations: the cost of treating a potential adverse medical event and the cost of 'testing drugs into safety'. Accounting for these essential, but less visible, costs, these data establish that pharmaceutical importation does not ultimately result in cost savings when the expenses associated with treatment failure and quality testing are included in the calculus.

The consequences of pharmaceutical importation are worrying for Canadians, potentially exacerbating drug shortages for the country's 37 million residents, and at the same time, the impact on US pharmaceutical spending may not live up to expectations. For a 'Representative State', in the presence of an adverse medical event, the presumed savings from an online Canadian supplier are exhausted in the treatment of only one patient in the case of Nexium, to 24 318 adverse events for patients in the case of Advair. Further, the analysis shows that in every case, the cost of testing (99.999% confidence level with 99.999% reliability) exceeds the presumed cost savings, from more than two times the presumed costs savings to more than 34 000 times. Importantly, the assumptions underlying this analysis were biased against this finding, resulting in a likely underestimation of the true cost of pharmaceutical importation programmes.

Conclusions

Pharmaceutical importation plans are politically attractive, but realistically dangerous and expensive if implemented safely and responsibly. The risks seem too great to justify the presumed cost savings that would quickly evaporate in the face of adverse medical events or a serious attempt to systematically test the quality of the imported drugs. While purchasing price-controlled medicines from a Canadian supplier has the potential to deliver some cost savings, it also involves significant risk. Accounting for treatment and testing, the numbers ultimately demonstrate that pharmaceutical importation fails to deliver cost savings. This analysis demonstrates that these schemes can be cheap, or they can be safe, but not both.

Declarations

Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose.

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Authors' contributions

The author is responsible for the research, design and content of the entirity of this article.

Notes

[1]For Crestor: Annual savings = \$1580; Cost of treating Adverse Event = \$165 822. Ratio of treatment relative to annual savings is the number of years of savings needed to cover the treatment cost. Specifically, \$165 822/\$1580 $\approx$ 105 years.

[2]For Enbrel: Annual savings = $37 824; Cost of treating Adverse Event = $6699. Ratio of treatment relative to annual savings is the number of years of savings needed to cover the treatment cost. Specifically, $6699/$37 824 = 0.177 years. Multiplying by 365 provides the number of days of savings needed to cover the treatment cost. Specifically, 0.177 years * 365 days/year ≈ 65 days.
[3]For example, in the case of Actos, the Representative State has a population of 6.54 million, of whom, there are 606 000 patients who take this drug. 20% of those patients are assumed to be enrolled in the State program, such that 121 200 patients are covered by the State program. Multiplying the number of covered patients (121 200) by the cost of treating an adverse event ($165 822) provides the cost of treating an adverse event in 100% of covered patients ($20 097 626 400.00).

References

1. Abutaleb Y, McGinley L. "Trump Administration Unveils Plan to Allow States to Buy Cheaper Drugs from Canada," *Washington Post*. 2019. https://www.washingtonpost.com/health/2019/12/18/trump-administration-unveils-plan-allow-states-buy-cheaper-drugs-canada/ (accessed 18 December 2019).
2. Roe G. "Utah Insurer Plans to Send Patients to Mexico for Cheaper Medicine," *KUTV.com*. 2019. https://kutv.com/news/local/utah-insurer-plans-to-send-patients-to-mexico-for-cheaper-medicine (accessed 29 October 2019).
3. IsraelPharm. "USA vs Canada vs Israel Drug Prices," *webpost*. 2017. http://www.israelpharm.com/blog/canada-vs-israel-drug-price-comparison/ (accessed 11 March 2020).
4. National Academy for State Health Policy (NASHP). "Will States Save by Importing Drugs from Canada? Yes, Here's How," *webpost*. https://nashp.org/wp-content/uploads/2017/11/drug-infographic-2.pdf (accessed 11 March 2020)
5. Pharmaceutical Security Institute (PSI). "Counterfeiting Situation: Therapeutic Categories," *webpost*, 2019. http://www.psi-inc.org/therapeuticcategories.cfm
6. NMS Labs. *Correspondence with Author, February 2019*. https://www.nmslabs.com/ (accessed 11 February 2019)
7. Sun LH. "They Went to Mexico for Surgery. They Came Back with a Deadly Superbug," *The Seattle Times*. 2019. https://www.seattletimes.com/nation-world/they-went-to-mexico-for-surgery-they-came-back-with-a-deadly-superbug/ (accessed 23 January 2019).
8. U.S. Food and Drug Administration Office of Criminal Investigations. "April 13, 2018: Canadian Drug Firm Admits Selling Counterfeit and Misbranded Prescription Drugs Throughout the United States," *webpost*. 2018. https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/criminal-investigations/april-13-2018-canadian-drug-firm-admits-selling-counterfeit-and-misbranded-prescription-drugs (accessed 13 April 2018).

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Data S1. This supplemental appendix contains the calculations for a brick-and-mortar Canadian pharmacy.
Data S2. This supplemental appendix describes how the drugs were selected and the methodology behind the collection of each piece of data utilized.