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Impact of free trade agreements (FTAs) on generic & biosimilar medicines markets

Oct 2020

Agenda

- Introduction
- Methodology
- Outputs
- Appendix
- Acronyms

Originator industry stipulates that reduction of its government protected monopolies has negative impacts on innovation

Context

- For many decades, the **originator pharma industry** has promoted the concept that a **reduction in government protection** could have **devastating effects on innovation** through **loss of financial incentives to reward it**
- This has posed a **considerable challenge to generic and biosimilar manufacturers**, and governments are **yet to find** an appropriate **balance** between **encouraging innovation** and **enabling access to less expensive medicines**, which could **enhance patient access and outcomes** and **reduce burden on healthcare systems**
- **Estimating medicine development cost** is an incredibly **challenging exercise**, and fundamentally, **outcomes** are expected to **vary considerably** based on the **agenda of the analysis**

- Instead of an exploration of the underpinning incentive structures of the originator vs. generic conundrum, we **reviewed the impact of originator-favouring government incentives** on the **success of generic and biosimilar medicines markets**
- In this study, we specifically focused on the **impact of FTAs** (free trade agreements) and **associated provisions protecting originator products** on generic and biosimilar medicines markets

Source: https://www.statnews.com/2019/10/02/trade-agreement-10-year-protection-obsolete/

We assessed the impact of free trade agreements (FTAs) on generics (Gx) and biosimilars (Bx), and articulated Gx / Bx value

Objectives

Overall project goal

Provide evidence of the value of generics and biosimilars and the potential impact of FTA provisions on generic and biosimilar medicines markets

Final Scope

- **EU-Korea FTA** – European Union-Korea Free Trade Agreement
- **KORUS** –United States-Korea Free Trade Agreement
- **NAFTA** – North American Free Trade Agreement (United States, Canada, Mexico)
- **EU-Andean FTA** – European Union-Andean Free Trade Agreement (European Union, Bolivia, Colombia, Ecuador and Peru)
- **TRIPS** – Word Trade Organisation (WTO) Agreement on the Trade-Related Aspects of Intellectual Property Rights
- **CETA** – Comprehensive Economic and Trade Agreement between the EU and Canada

Objective	Key questions
Identify impact of FTAs on market environments for generic and biosimilar products	• What has been the impact of implementation of FTAs for the generic and biosimilar medicines industries in terms of price, market share and new product approvals? • How have FTAs between larger and smaller countries, involving adopting standards and regulation from the larger market, impacted generic and biosimilar manufacturers?
Define the value of the generic and biosimilar medicines markets	• How can we measure and articulate the value that generics and biosimilars bring to healthcare systems and to patients?

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Overall, we used two pillars to illustrate the importance of the Gx / Bx markets, and the opportunities for protecting it

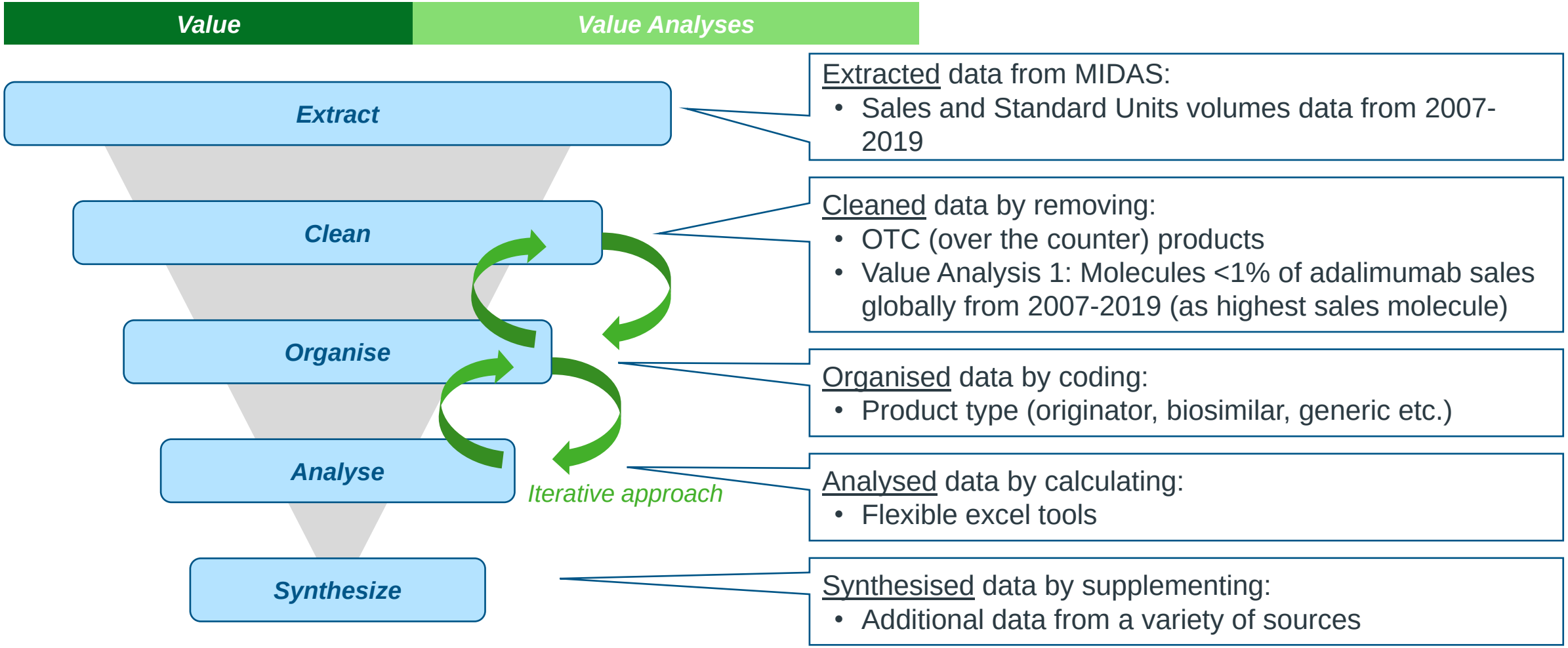
Methodology overview

***Value* of the Gx / Bx market s**	***Health* of the Gx / Bx markets**
What is the value of a Gx / Bx markets?	***What is the impact of FTA implementation?***
How can value be measured?	***How can the impact on the Gx/Bx markets be optimised?***

Our objective: Build a case for the importance of Gx / Bx to healthcare systems and patients, and review the negative impacts of FTAs on Gx / Bx markets health

For Value Analyses, data was ‘cleaned’ by removing OTC products and focusing on high sales molecules

Methodology deep-dive



A number of assumptions informed each step of the Value Analyses calculations

Methodology deep-dive

Value	*Value Analyses*
Value Analysis 1: Lost Cost Savings	• **Date of FTA implementation** (Secondary research) • **Number of quarters delay of generic entry** (Secondary research) • **Current generic entry and sales data** (IQVIA MIDAS data)
Value Analysis 2: Lost Patient Access	• **Price per month** (IQVIA Pricing insights / secondary research) • **Number of months treatment** (Secondary research)
Value Analysis 3: Lost Patient Outcomes	• **Number Needed to Treat - NNT** (Secondary research)

Value Analysis 1 focused on the 'lost' cost savings which could have been achieved, had LoEs not been delayed due to FTA terms

Methodology deep-dive

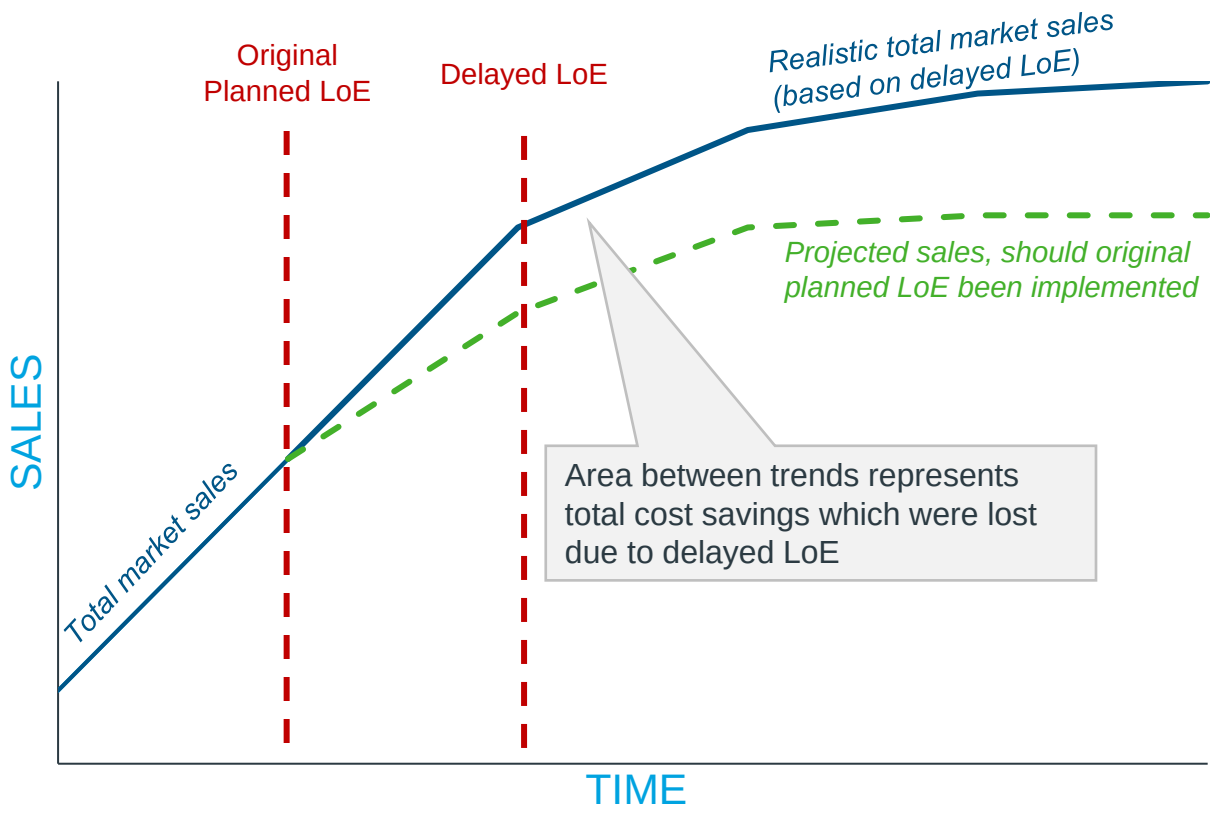
Value | **Value Analysis 1: Cost Savings**

Steps

- Obtained sales data from total market (Gx/Bx and originators) over time as a proxy for healthcare system expenditure
- Evaluated projected sales should 'original planned Loss of Exclusivity (LoE)' have been implemented
- Subtracted projected sales (based on original planned LoE) from realistic total market sales (based on delayed LoE) to obtain 'lost' cost savings due to delayed LoE

Please note that the analysis:

- Was conducted across prescription molecules only
- Did not measure impact of compounding / sequential FTAs
- Was conducted with sales based on list price
- Included data from 2007 onwards only
- Was unable to evaluate the impact of earlier LoE dates of molecules which have not yet gone off patent



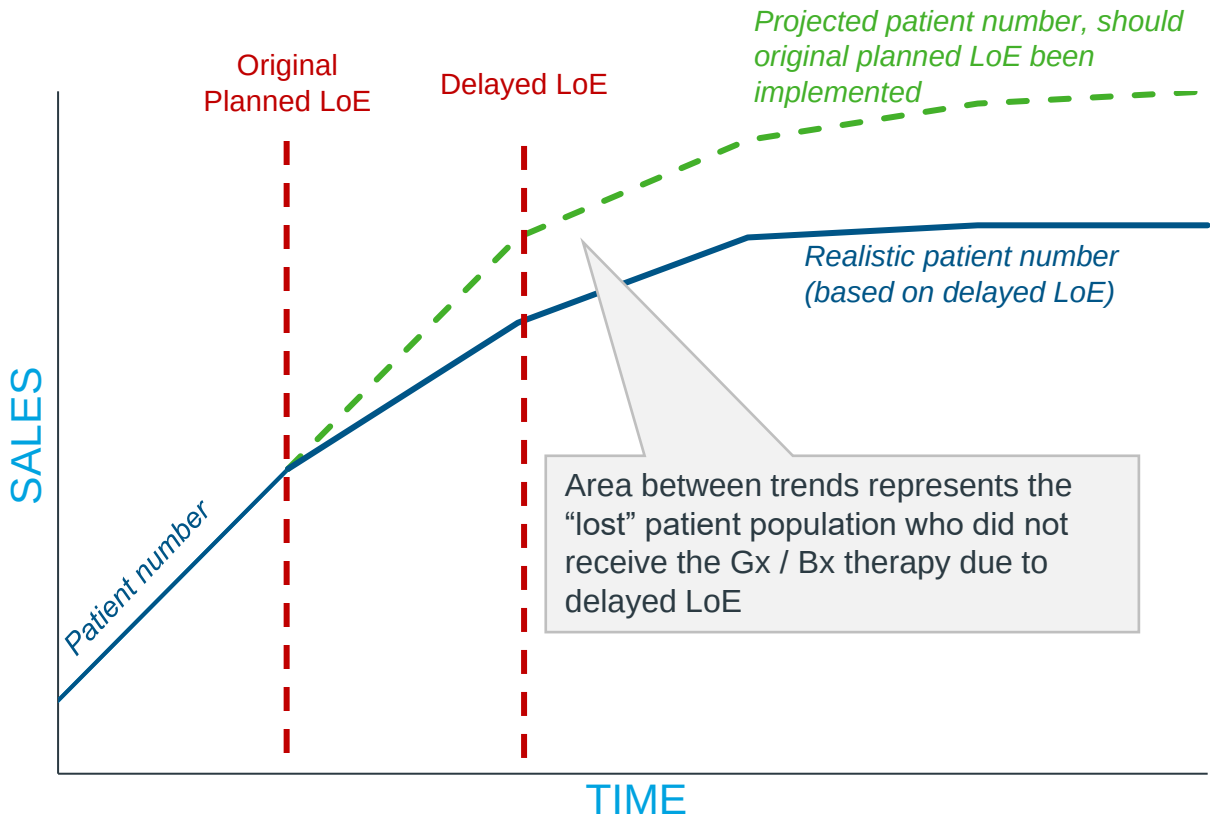
Value Analysis 2 translates 'lost' cost savings into no. of patients who could have accessed therapy, at molecule level

Methodology deep-dive

Value | **Value Analysis 2: Patient Access**

Steps

- Molecule-level case studies were developed translating 'lost' cost savings into the number of patients who could have obtained access to the product, had the generic become available earlier:
  - 'Lost' cost savings were converted to patient number through use of price, dosing & compliance assumptions
  - As per the previous methodology, this enabled us to review the additional proportion of patients who could have accessed therapy, had these cost savings not been 'lost'
  - Case study choice was based on data availability – primarily, high 'lost' cost savings therapies were focused on, with the aim of achieving a range of hospital / retail products and IV / oral



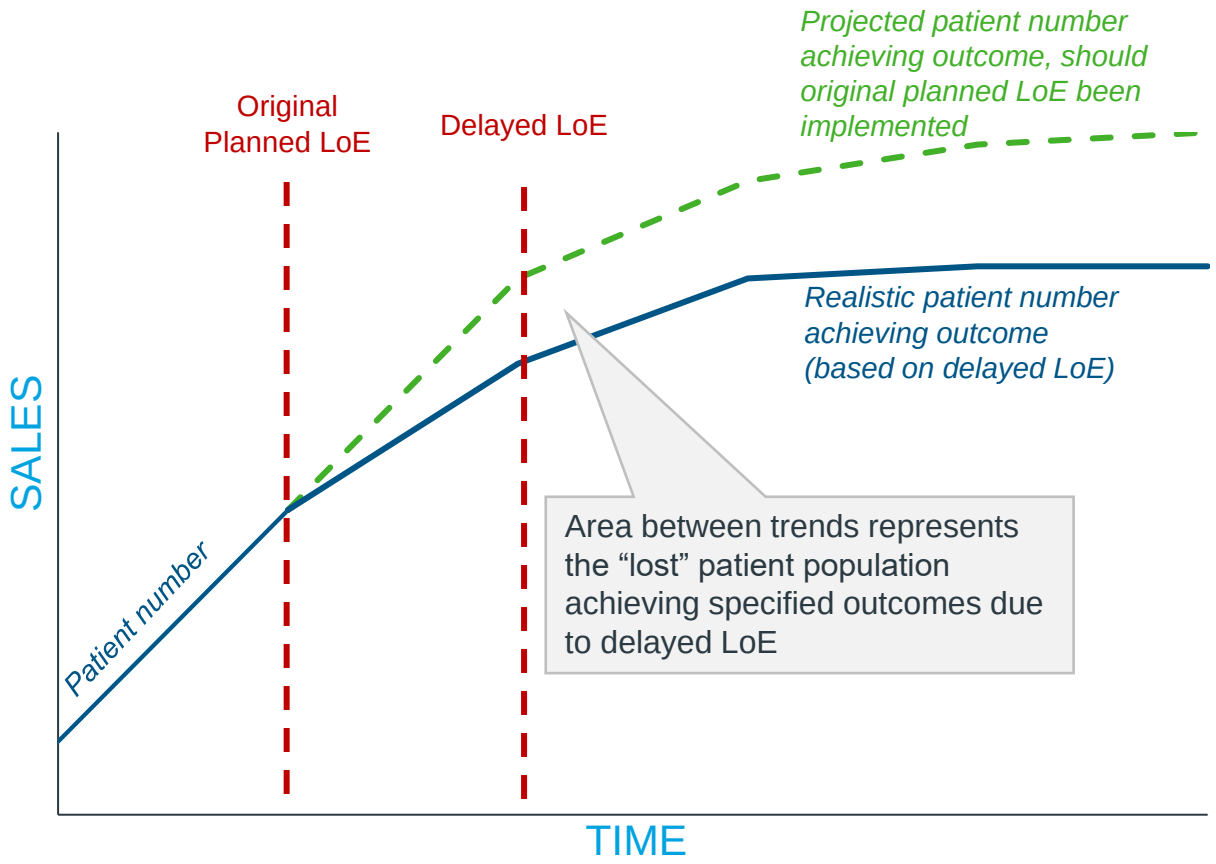
Value Analysis 3 translates enhanced patient access afforded by earlier LoE into a measure of improved patient outcomes

Methodology deep-dive

Value | **Value Analysis 3: Patient Outcomes**

Steps

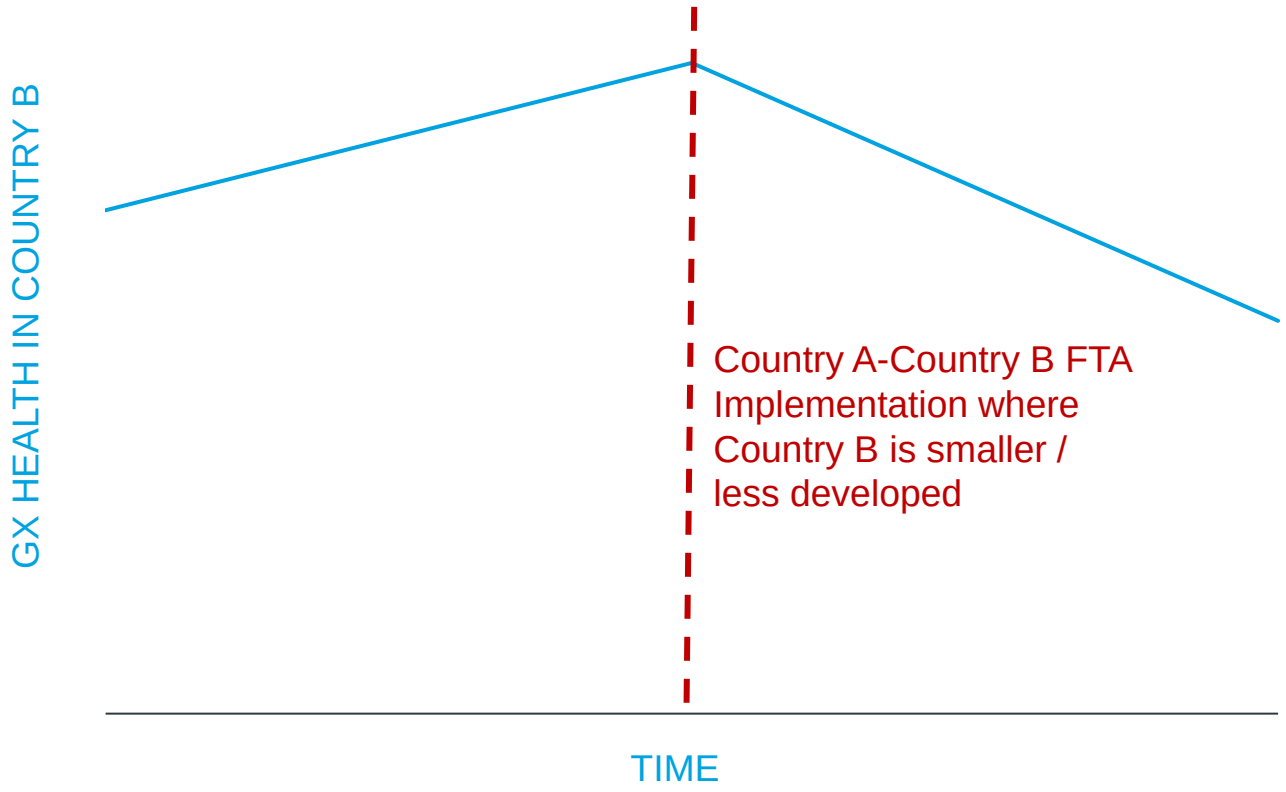
- Translated additional number of patients accessing therapy due to earlier LoE into a number of patients achieving specific outcomes (based on therapy area)
- Used NNT (Number Needed to Treat) to convert the patient number from Value Analysis 2 into a patient number achieving a pre-specified clinical outcome
- *Please note*: enhanced outcomes could result from confounding factors which are challenging to control for e.g. other line treatment / diagnostic innovation



Health Analysis 1 assessed FTA impact through review of number of Gx / Bx agents and manufacturers

Methodology deep-dive

Health | **Health Analysis 1: Market-level**



Steps

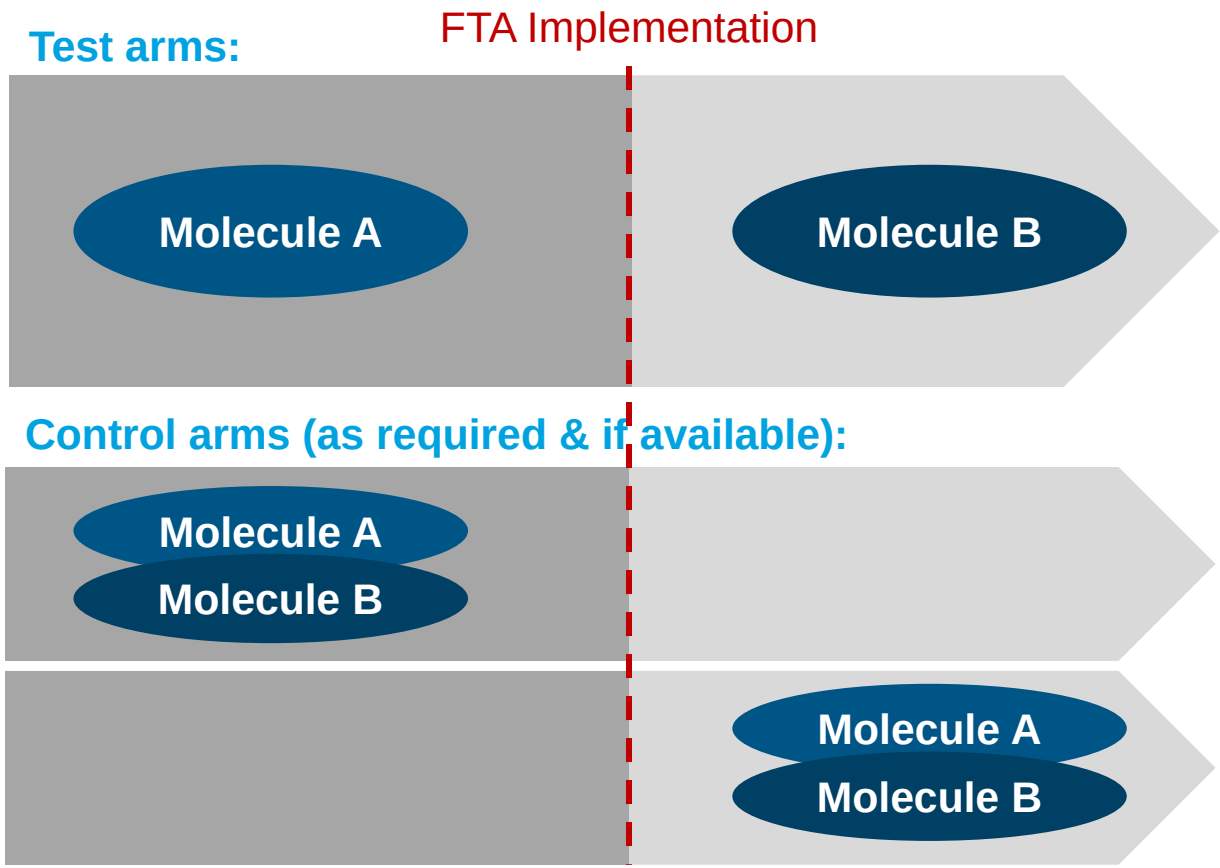
- Reviewed market-specific and global Gx/Bx trends to understand impact of FTA implementation through:
  - Volumes & volume share vs. originator
  - No. Gx/Bx agents
  - No. Gx/Bx manufacturers

NB: the multiple confounding factors associated with this analysis are challenging to control, thus positive trends, even with FTA implementation, are often observed

Health Analysis 2 assessed the performance of two comparable molecules; one genericised pre-FTA and the other post-FTA

Methodology deep-dive

Health | **Health Analysis 2: Case Studies**



Steps

- Identified suitable case studies with which to assess impact of FTA implementation (based on time of Gx / Bx launch):
  - Two molecules within the same class (ATC4 code) were identified, to ensure launch / uptake scenarios which are as similar as possible
  - One of the molecules had been genericised prior to FTA implementation, and the second was only genericised post-FTA implementation
  - Given that molecules were be taken from the same class, a potential limitation was the confounding impact of first vs. second in class success, which could not be controlled for

Note: molecules were considered "comparable" if belonging to the same ATC4 class. This system classifies the active ingredient of medicines according to the organ or system on which they act and their therapeutic, pharmacological and chemical properties.

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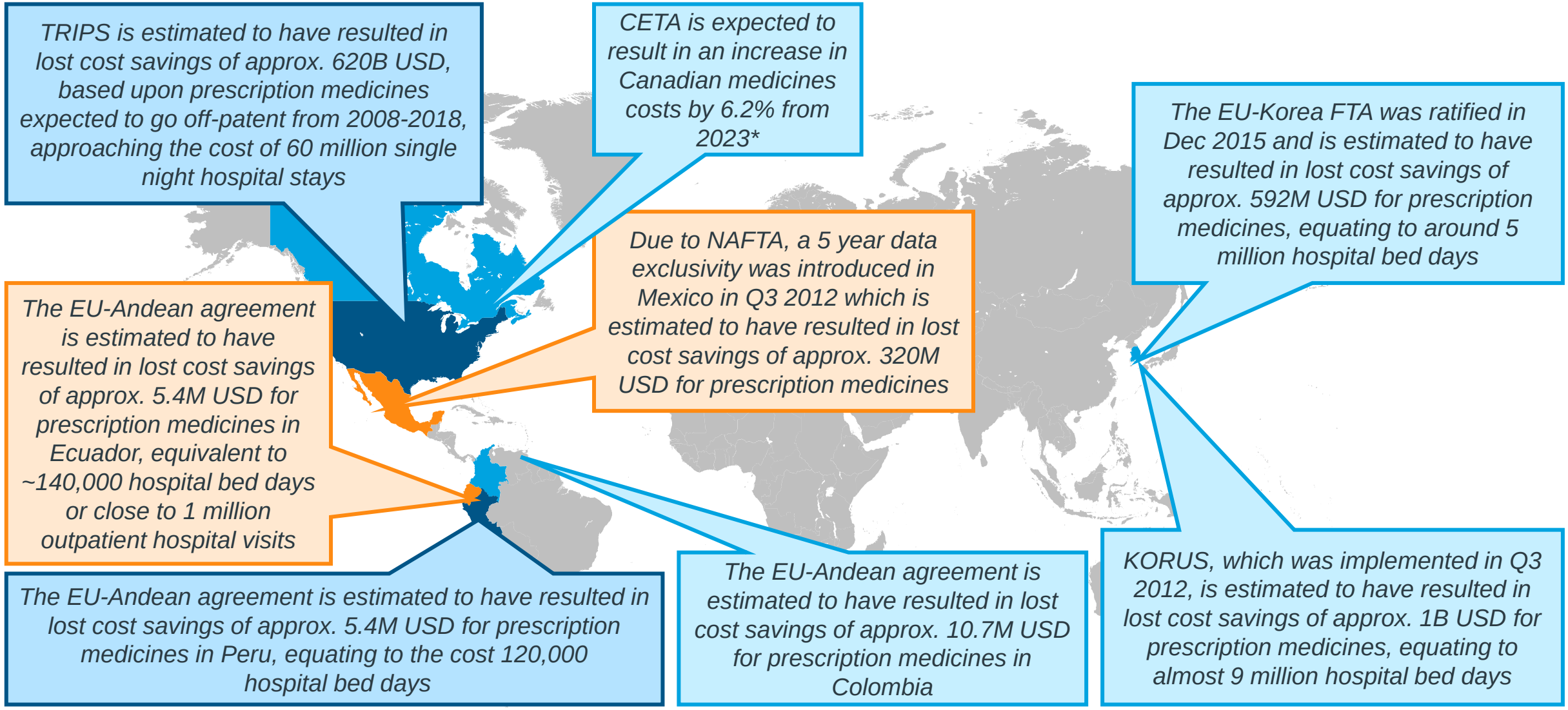

Note: Analysis includes all prescription molecules with global sales share >1%. * Sources: a) CETA and pharmaceuticals: Impact of the trade agreement between Europe and Canada on the costs of prescription drugs, May 2014, Lexchin & Gagnon; b) The Canada-EU Comprehensive Economic and Trade Agreement – A Prospective Analysis, Office of the Parliamentary Budget Officer, 2017; c) How will recent trade agreements that extend market protections for brand-name prescription pharmaceuticals impact expenditures and generic access in Canada? Beall RF, Hardcastle L, Clement F, Hollis A., Health Policy. 2019; d)The Canada-European Union Comprehensive Economic & Trade Agreement: An Economic Impact Assessment of Proposed Pharmaceutical Intellectual Property Provisions, Grootendorst & Hollis, 2011.
Sources for % estimates: WHO - Peru Primary Bed Day: 45.20 USD in 2005; https://www.businessinsider.com/most-expensive-health-conditions-hospital-costs-2018-2?r=US&IR=T; US hospital stay cost; WHO – Ecuador Primary Bed Day: 38.68 USD; WHO – Ecuador Outpatient visit: 5.42 USD; WHO – Korea Primary Bed Day: 113.35 USD

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FTA impact on Korea:
EU-Korea and US-Korea (KORUS) FTAs

KORUS was applied in Korea in Q3 2012, and led to a 3 year patent term extension: this has resulted in lost savings of up to 1B USD to date

To date, KORUS has resulted in lost cost savings in Korea of up to 1B USD

The greatest contributors to lost cost savings include…

- *Entecavir: 228.4 M USD*
- *Ibandronic acid: 100.8M USD*
- *Amlodipine-valsartan: 87.5M USD*
- *Trastuzumab: 78.5M USD*
- *Imatinib: 67.5M USD*
- *Fluticasone-salmeterol: 51.5M USD*

In 2018, lost cost savings amounted to 250 M USD, equating to approximately 0.75% of total pharma expenditure

Had patent term not been extended, lost cost savings could have been utilized effectively…

6,000 nurse wages for 1 year, or

1,700 physician wages for 1 year

Alternatively, had cost savings been diverted to enhancing patient access and outcomes…

- *Over 4,000 additional patients could have been treated with imatinib for Ph+ ALL (Acute Lymphoblastic Leukaemia), up to 1,000 of whom could have survived beyond 12 months*
- *Over 7,000 patients could have been treated with trastuzumab for HER-2 negative gastric cancer, with approximately 650 of these patients achieving disease free survival (DFS) for at least 1 year*

Note: Analysis includes all prescription molecules with global sales share >1%. Note: Molecules selected – a) from top lost approx.30 cost savings molecules per FTA; b) to obtain range of injectable / oral and indication coverage c) subject to availability / robustness of dosing & pricing assumptions, and NNT assumptions available d) to cover range of indications and indication types (i.e. high NNT and low NNT molecules).

The EU-KOREA FTA, implemented in Q4 2015, led to a 5 year extension of patent term: this has resulted in lost savings of up to 592M USD to date

The EU-KOREA FTA has resulted in lost cost savings in Korea of over 592M USD since its implementation in late 2015

The greatest contributors to lost cost savings include…

- *Dutasteride: 124.7M USD*
- *Oseltamivir: 110.5M USD*
- *Varenicline: 74.2M USD*
- *Tenofovir Disoproxil: 66.3M USD*
- *Amlodipine-Telmisartan: 64.1M USD*

In 2018, lost cost savings amounted to 215M USD, equating to over 0.64% of total prescription medicine expenditures in Korea

Had patent term not been extended, lost cost savings could have been utilized more effectively…

Over 6,500 nurse wages for 1 year, or

Over 1,400 physicians wages for 1 year

Alternatively, had cost savings been diverted to enhancing patient access and outcomes…

- *Over 7,300 patients could have been treated with dutasteride for benign prostatic hyperplasia, in a country where this condition's prevalence is increasing rapidly due to an ageing population*
- *Approx. 6,900 patients with smoking addiction could have been treated with varenicline*
- *200+ patients with relapsed multiple myeloma could have been treated with lenalidomide for almost a year until progression*

Note: Analysis includes all prescription molecules with global sales share >1%. Note: Molecules selected – a) from top lost approx.30 cost savings molecules per FTA; b) to obtain range of injectable / oral and indication coverage c) subject to availability / robustness of dosing & pricing assumptions, and NNT assumptions available d) to cover range of indications and indication types (i.e. high NNT and low NNT molecules).

The lost cost savings of 592M USD were the result of LoE delay of just 26 molecules

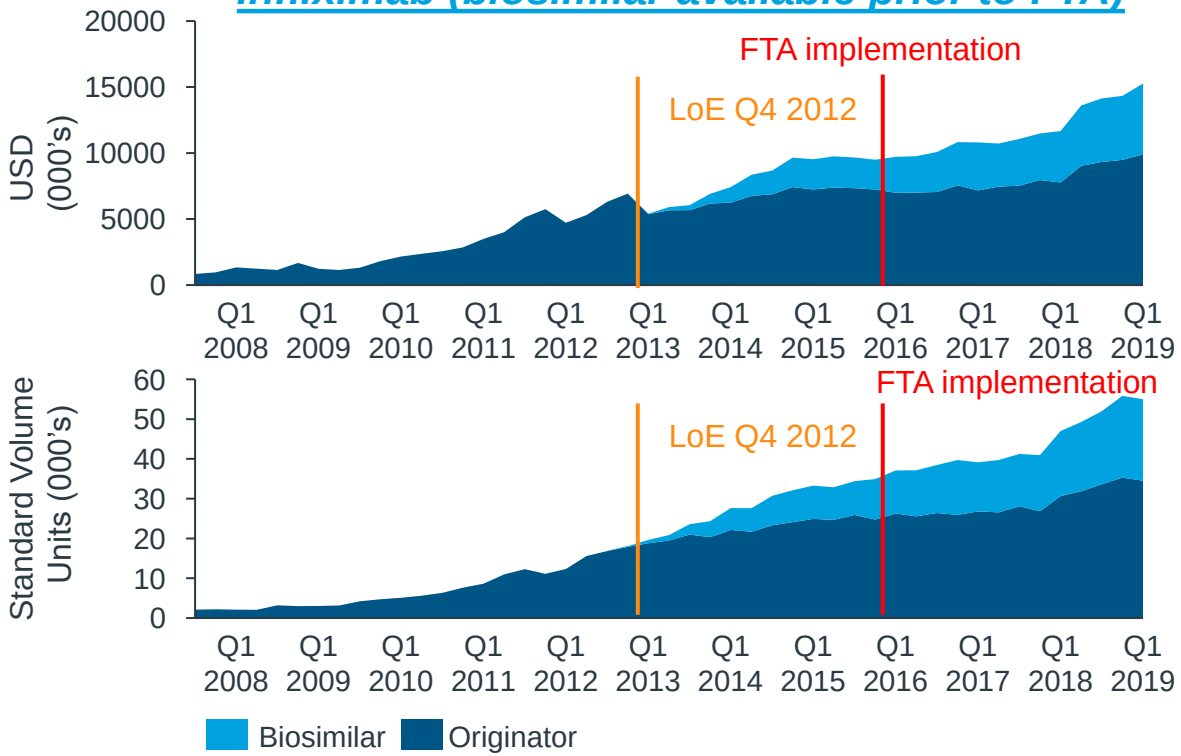
Molecule	Lost cost savings (USD)
dutasteride	124,685,650
oseltamivir	110,499,710
varenicline	74,155,850
tenofovir disoproxil	66,306,830
amlodipine-telmisartan	64,087,430
pirfenidone	35,809,060
amlodipine-hydrochlorothiazide-olmesartan medoxomil	22,211,590
temozolomide	21,903,810
dexmedetomidine	14,058,630
febuxostat	11,692,790
lenalidomide	10,271,780
buprenorphine	7,924,420
beclometasone-formoterol	6,537,910
omeprazole-sodium	5,459,450
loteprednol	2,412,450
valganciclovir	2,381,380
anagrelide	2,367,130
ezetimibe	2,101,320
deferasirox	1,911,580
decitabine	1,470,330
lacosamide	1,404,250
fluorouracil	1,242,170
voriconazole	1,218,160
cinacalcet	320,860
acetylsalicylic acid-dipyridamole	158,760
nitrofurantoin	22,620

Just 26 molecules contributed to the approx. 592M USD lost cost savings in Korea due to the EU-Korea FTA

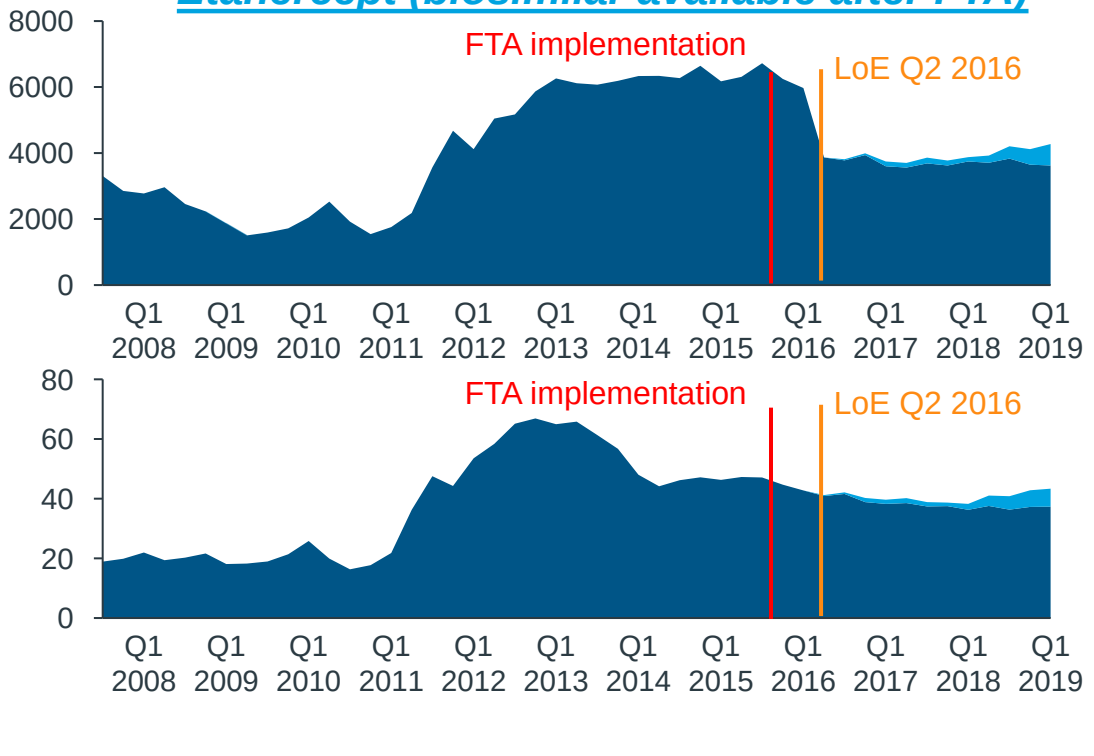
Note: Analysis includes all prescription molecules with global sales share >1%. Note: Molecules selected – a) from top lost approx.30 cost savings molecules per FTA; b) to obtain range of injectable / oral and indication coverage c) subject to availability / robustness of dosing & pricing assumptions, and NNT assumptions available d) to cover range of indications and indication types (i.e. high NNT and low NNT molecules).

Bx of molecules going off patent post-FTA implementation obtained significantly less share than comparable molecules which went off patent prior to FTA implementation, suggesting a negative impact caused by the EU-Korea FTA

Infliximab (biosimilar available prior to FTA)



Etanercept (biosimilar available after FTA)



- ***Infliximab biosimilar was available prior to the implementation of the EU-Korea FTA and obtained >10% of molecule market share value at 1 year***
- ***In contrast, biosimilar etanercept, which launched after implementation of the EU-Korea FTA was significantly less successful, obtaining <5% value share of the market at 1 year and failing to grow substantially beyond this***
- ***In combination, these two trends suggest that the EU-Korea FTA had a negative impact on the Bx market in Korea***

Note: these molecules are considered "comparable" in this situation as they belong to the same ATC4 class.

The compound effect of both KORUS and EU-Korea FTAs could have had resulted in even more considerable lost cost savings than either agreement when considered in isolation

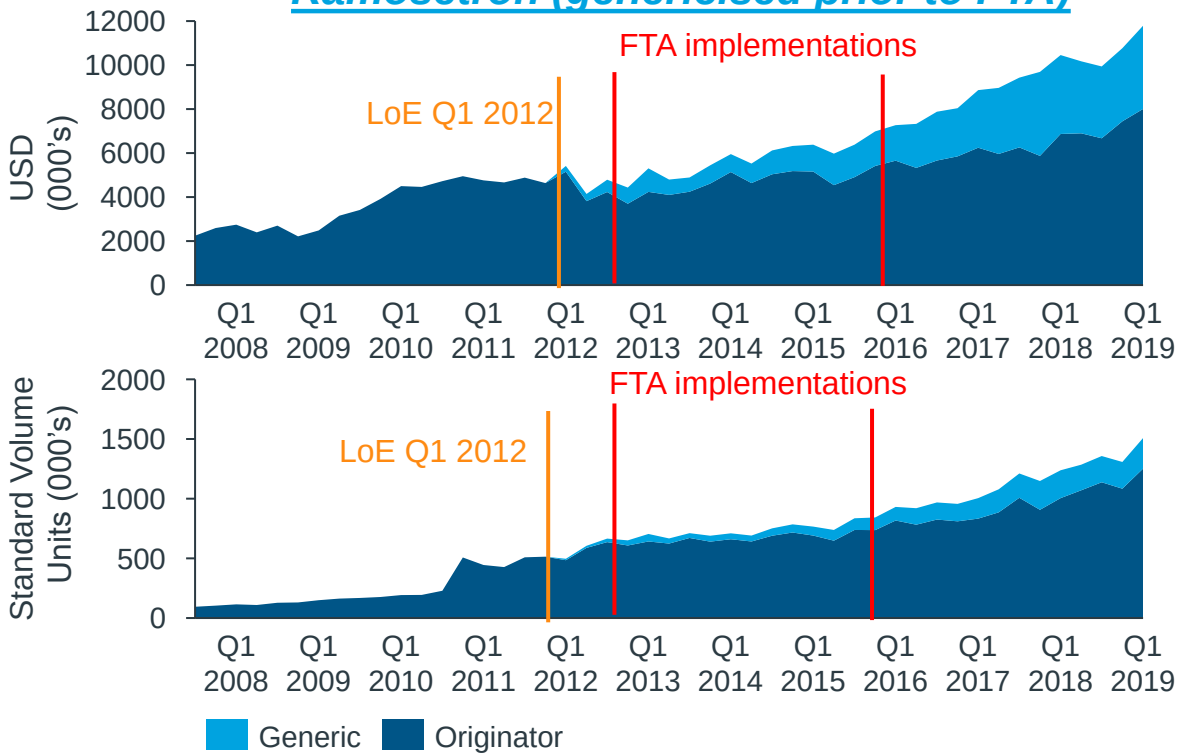
Combined, KORUS and EU-Korea FTAs are estimated to have resulted in lost cost savings of up to 1.2B USD

The greatest contributors to lost cost savings include;	
entecavir	223,937,100
ibandronic acid	146,560,290
trastuzumab	129,598,560
fluticasone-salmeterol	60,855,140
imatinib	60,345,710
erlotinib	52,351,020
rituximab	49,478,560
amlodipine-valsartan	49,073,580
palonosetron	47,788,710
lamivudine	46,986,030
hydrochlorothiazide-telmisartan	38,837,170
hydrochlorothiazide-olmesartan medoxomil	36,617,760
zoledronic acid	34,158,970
bosentan	25,276,640
olmesartan medoxomil	23,527,480

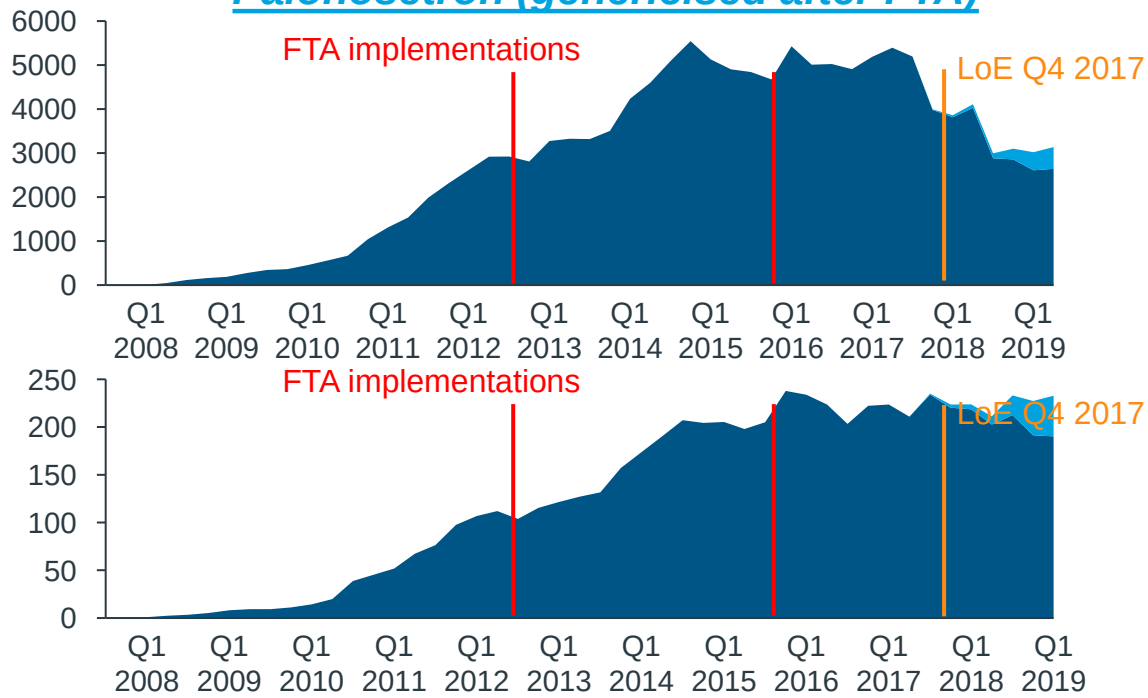
Note: Analysis includes all prescription molecules with global sales share >1%. Note: Molecules selected – a) from top lost approx.30 cost savings molecules per FTA; b) to obtain range of injectable / oral and indication coverage c) subject to availability / robustness of dosing & pricing assumptions, and NNT assumptions available d) to cover range of indications and indication types (i.e. high NNT and low NNT molecules).

Gx available only after EU-Korea and KORUS implementation achieved a significantly lower share of the molecule market in value and volume terms in comparison to Gx which were available prior to the implementation of both these FTAs

Ramosetron (genericised prior to FTA)



Palonosetron (genericised after FTA)



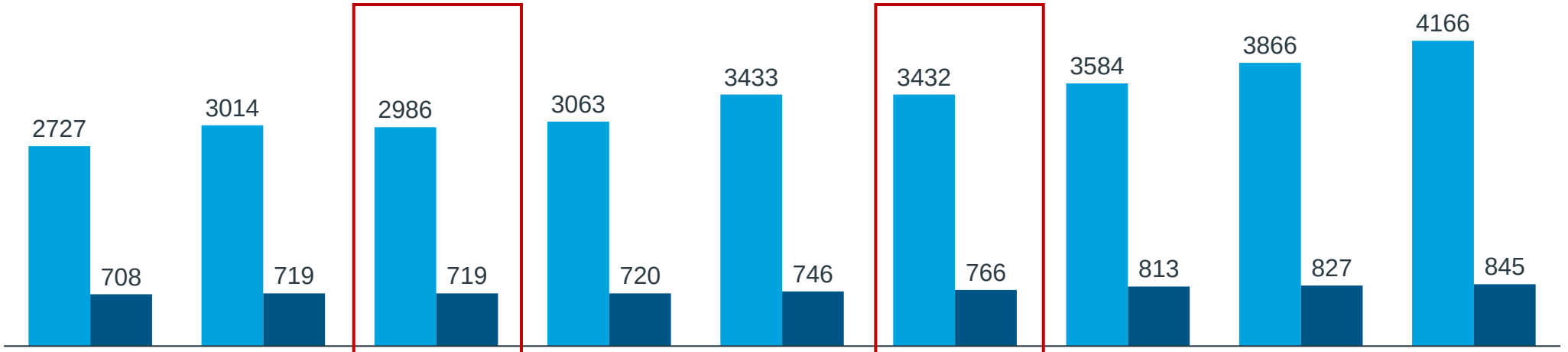
- ***Ramosetron genericised prior to implementation of both the EU-Korea and KORUS agreements; ramosetron generic was highly successful in Korea, taking a significant share of the molecule market by volume and value***
- ***By contrast, palonosetron (of the same class) genericised after both FTAs were implemented and has been significantly less successful, achieving just 12% molecule market share by value vs. ramosetron's 16%, and 5% vs. ramosetron's 9% since 1 year on the market; this suggests that both of these FTAs had a negative impact on Gx market health***

Note: these molecules are considered "comparable" in this situation as they belong to the same ATC4 class.

The number of generic products available on the Korean market declined at the point of KORUS and EU-Korea FTA implementation

The number of generics available on the Korean market declined in 2012 (year of KORUS implementation) and 2015 (year of EU-Korea implementation); these trends were not observed in the originator market or in the US generic market as a control, suggesting that both FTAs had a direct impact on the health of the Korean generic market

Number of Generic / Originator products available on the Korean market



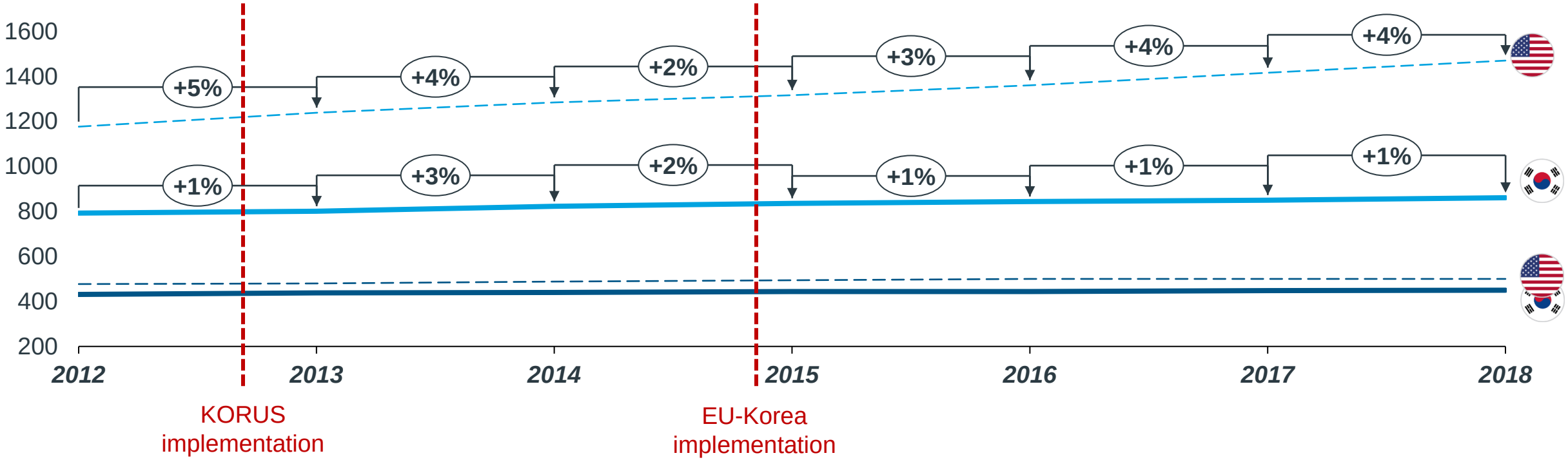
	2010	2011	2012	2013	2014	2015	2016	2017	2018
	11%	-1%	3%	12%	0%	4%	8%	8%
	2%	0%	0%	4%	3%	6%	2%	2%
	4%	5%	7%	6%	7%	6%	7%	6%
	0%	0%	3%	1%	1%	1%	0%	1%

Prior to FTA = 2008, 2009, 2010; During FTA = 2011, 2012, 2013; Post FTA = 2014, 2015, 2016

Note: Analysis includes all prescription molecules with global sales share >1%. YoY = Year on Year Growth. Generic Originator

The growth rate in number of manufacturers in the Korean market also dropped at the time of KORUS implementation, and has continued to be low vs. US trends to the present day

Number of Generic / Originator manufacturers with products on the Korean market



Generic market size and growth in Korea is considerably more limited vs. USA from 2012 onwards, suggesting an accumulating impact of both FTAs on Korea's generic medicines market

- Originator manufacturers in USA
- Originator manufacturers in Korean market
- Generic manufacturers in Korean market
- Generic manufacturers in USA

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FTA impact on Mexico:
NAFTA (North American FTA)

A 5 year data exclusivity term was applied in Mexico via NAFTA in Q3 2012, resulting in lost cost savings of 320M USD to date

To date, the amendment of data exclusivity terms within NAFTA has resulted in lost cost savings in Mexico of 320M USD

The greatest contributors to lost cost savings include;

- *Ipratropiumbromide-salbutamol:* *110.4M USD*
- *Etoricoxib:* *56.3M USD*
- *Tadalafil:* *36.0M USD*
- *Hydrochlorothiazide-valsartan:* *35.9M USD*
- *Hydrochlorothiazide-irbesartan:* *19.2M USD*

In 2018, lost cost savings amounted to almost 80M USD, representing approximately 0.25% of annual pharmaceutical expenditure

Had patent term not been extended, lost cost savings could have been utilized effectively…

Almost 7,000 nurse wages for 1 year, or

Over 2,000 physician wages for 1 year

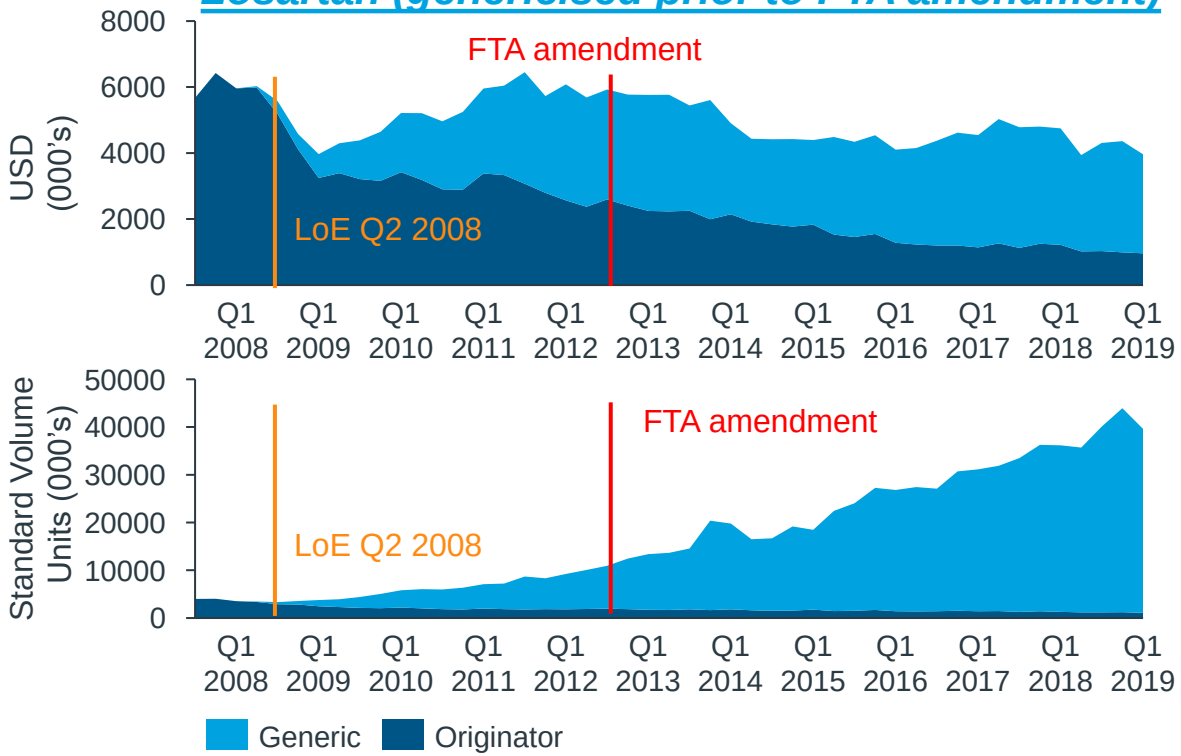
Alternatively, had cost savings been diverted to enhancing patient access and outcomes…

- *Over 150,000 patients could have been treated with filgrastim (12th greatest lost cost savings) for low neutrophil count due to HIV / AIDS or following chemotherapy poisoning*
- *Approx. 450 metastatic / recurrent RCC, GBM or CRC patients could have been treated with bevacizumab*

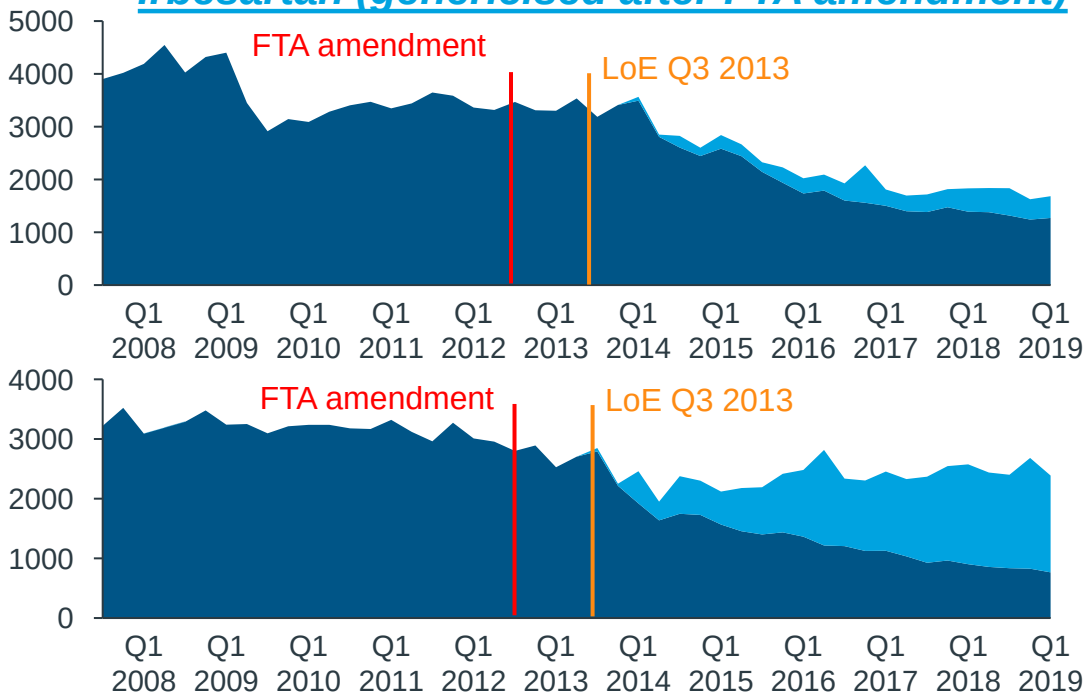
Note: Analysis includes all prescription molecules with global sales share >1%. Note: Molecules selected – a) from top lost approx.30 cost savings molecules per FTA; b) to obtain range of injectable / oral and indication coverage c) subject to availability / robustness of dosing & pricing assumptions, and NNT assumptions available d) to cover range of indications and indication types (i.e. high NNT and low NNT molecules).

Gx available prior to the amendment of data exclusivity terms in NAFTA were highly successful, obtaining significant share of the molecule market by value and volume; this success was not mirrored by Gx available after the addition of this data exclusivity term, suggesting it had a negative impact on the Gx market

Losartan (genericised prior to FTA amendment)



Irbesartan (genericised after FTA amendment)



- *Losartan was genericised prior to the NAFTA 5 year data exclusivity term application in Mexcio; the generic was highly successful, obtaining close to 100% share of the molecule market in volume share, and a considerable proportion of value share*
- *By contrast, irbesartan (of the same class) was genericised after the data exclusivity amendment had been applied and has been considerably less successful than losartan, obtaining just 27% of the molecule market by volume share at 1 year vs. 42%*
- *Together, these findings suggest that the application of a data exclusivity term negatively impacted the Gx market in Mexico*

Note: these molecules are considered "comparable" in this situation as they belong to the same ATC4 class

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FTA impact on South America: *EU-Andean FTA*

A 5 year data exclusivity term was applied in Ecuador through the EU-Andean FTA implemented in Q1 2017; this is estimated to have resulted in lost cost savings in Ecuador of up to 3.2M USD to date

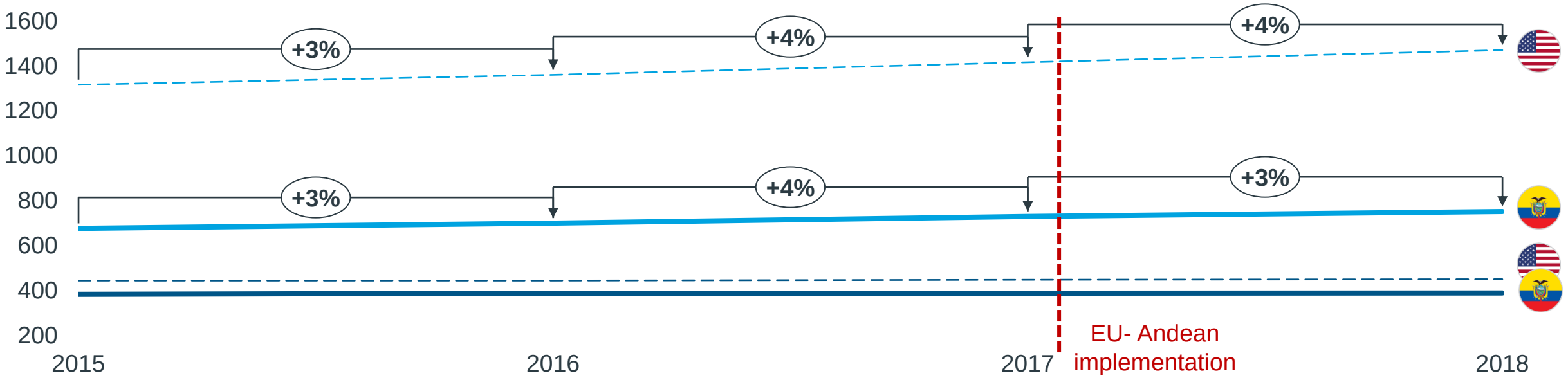
To date, the implementation of the EU-Andean FTA has resulted in lost cost savings in Ecuador of 3.2M USD

The greatest contributors to lost cost savings include (USD);	
rituximab	689,039
amlodipine-telmisartan	673,976
dabigatran etexilate	469,004
ipratropium bromide	364,428
solifenacin	240,001
apixaban	178,866
sevelamer	119,114
sumatriptan	111,369
imiquimod	92,678
budesonide-formoterol	77,561
oseltamivir	58,581
emtricitabine-tenofovir disoproxil	6,541

Note: Analysis includes all prescription molecules with global sales share >1%. Note: Molecules selected – a) from top lost approx.30 cost savings molecules per FTA; b) to obtain range of injectable / oral and indication coverage c) subject to availability / robustness of dosing & pricing assumptions, and NNT assumptions available d) to cover range of indications and indication types (i.e. high NNT and low NNT molecules).

The implementation of this FTA negatively impacted the growth in number of Gx manufacturers with Gx products launched on the Ecuadorian market

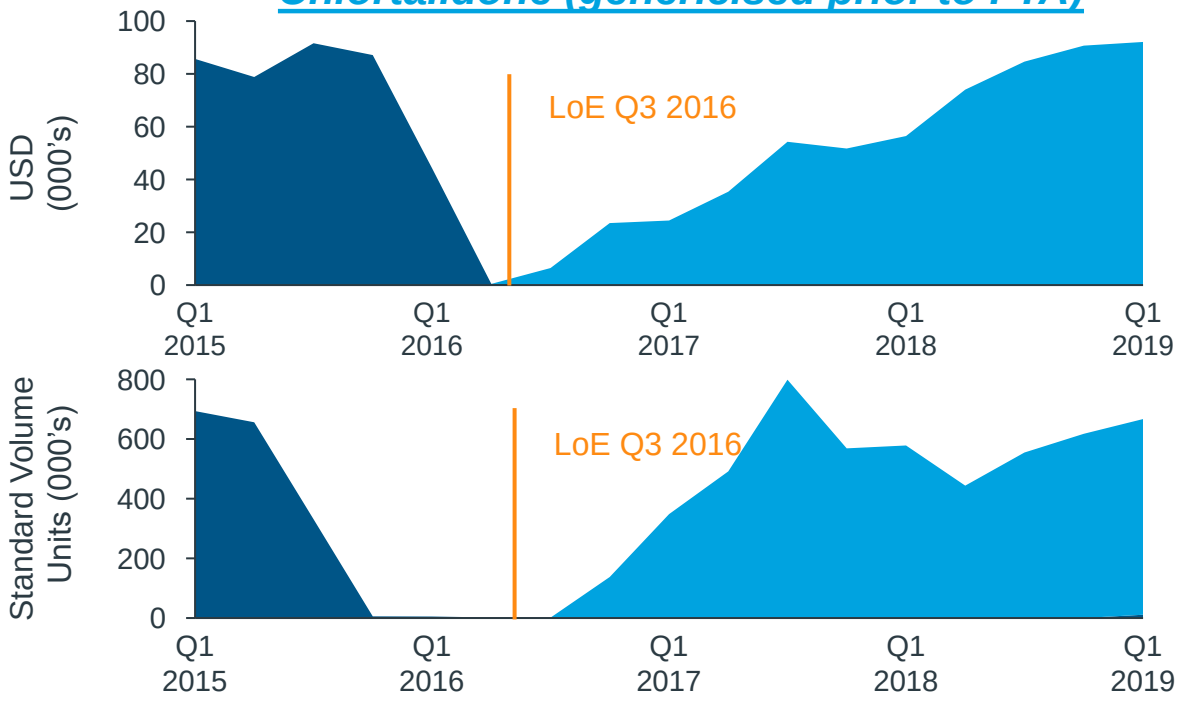
Number of Generic / Originator manufacturers with products on the Ecuador market



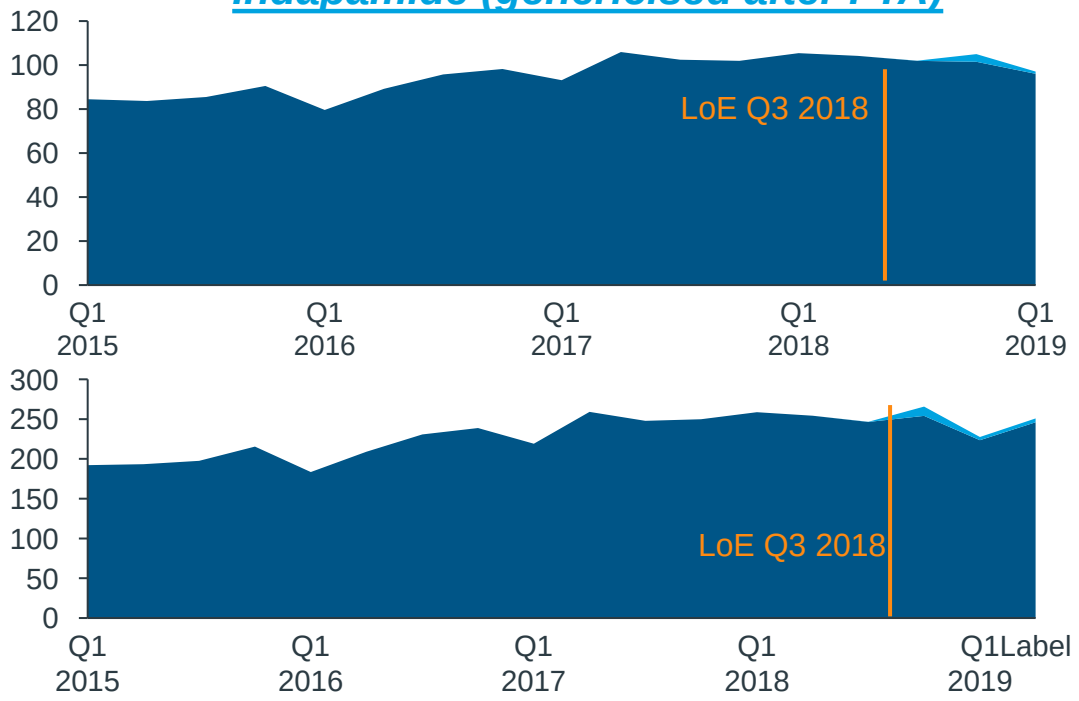
Prior to implementation of the EU-Andean FTA, Ecuadorian Gx market growth had been in-step with that of the US based on the number and proportion of Gx manufacturers with products available in the market; however, once this FTA was implemented, Ecuadorian Gx growth rate reduced moderately

Implementation of this FTA may also have reduced the success and market share of Gx launching after its application

Chlortalidone (genericised prior to FTA)



Indapamide (genericised after FTA)



- *In Ecuador, chlortalidone genericised prior to implementation of the EU-Andean agreement, and was highly successful, entirely displacing the originator market*
- *However, indapamide (of the same class) genericised after EU-Andean agreement implementation and has failed so far to capture a substantial segment of originator share*
- *Together, these trends suggest that the EU-Andean FTA had a negative impact on the Gx market in Ecuador upon implementation*

Note: these molecules are considered “comparable” in this situation as they belong to the same ATC4 class.

A 5 year data exclusivity term was applied in Peru through the EU-Andean FTA implemented in Q1 2013; this is estimated to have resulted in lost cost savings in Peru of up to 5.4M USD to date

To date, the EU-Andean FTA has resulted in lost cost savings in Peru of 5.4M USD

The greatest contributors to lost cost savings include (USD);	
amlodipine-valsartan	1,372,315
nepafenac	1,257,454
tolterodine	354,728
amlodipine-hydrochlorothiazide-valsartan	238,766
clonidine	229,507
bisoprolol-hydrochlorothiazide	86,337
pazopanib	78,050
exemestane	55,593
imiquimod	52,151
solifenacin	38,109
azacitidine	37,897
dasatinib	25,640

Note: Analysis includes all prescription molecules with global sales share >1%. Note: Molecules selected – a) from top lost approx.30 cost savings molecules per FTA; b) to obtain range of injectable / oral and indication coverage c) subject to availability / robustness of dosing & pricing assumptions, and NNT assumptions available d) to cover range of indications and indication types (i.e. high NNT and low NNT molecules).

A 5 year data exclusivity term was applied in Colombia through the EU-Andean FTA implemented in Q3 2013; this is estimated to have resulted in lost cost savings in Colombia of up to 10.7M USD to date

To date, the EU-Andean FTA has resulted in lost cost savings in Colombia of 10.7M USD

The greatest contributors to lost cost savings include (USD);	
tolterodine	3,601,602
dutasteride-tamsulosin	3,526,911
agomelatine	740,798
caspofungin	608,643
ciclesonide	514,892
lubiprostone	330,912
linezolid	256,539
emtricitabine-tenofovir disoproxil	160,651
filgrastim	159,366
baclofen	132,255
bortezomib	112,819
dexmedetomidine	99,011
febuxostat	91,977
dapsone	80,782
lacosamide	65,427
pemetrexed	51,561
epoetin alfa	46,857
valganciclovir	43,209
rocuronium bromide	30,076
temozolomide	21,941
vasopressin	6,337
vinorelbine	4,342
bosentan	3,975
epirubicin	2,950

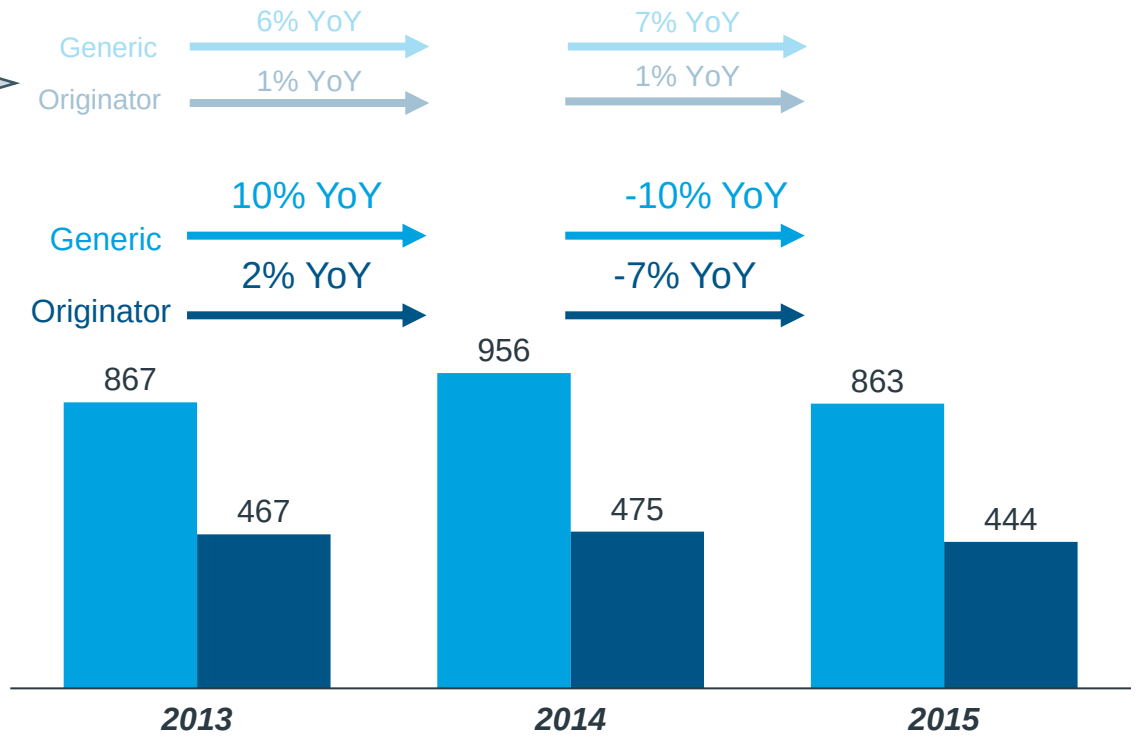
Note: Analysis includes all prescription molecules with global sales share >1%. Note: Molecules selected – a) from top lost approx.30 cost savings molecules per FTA; b) to obtain range of injectable / oral and indication coverage c) subject to availability / robustness of dosing & pricing assumptions, and NNT assumptions available d) to cover range of indications and indication types (i.e. high NNT and low NNT molecules).

The implementation of the EU-Andean FTA resulted in Q3 2013 may have caused the considerable decrease in number of Gx products available in Colombia from 2014 onwards

While both the number of generic and originator products available in Colombia decreased after EU-Andean agreement implementation, the impact on the generic medicines market was more considerable vs. originator trends and vs. US Gx trends as a control

Number of Generic / Originator products available on the Colombian market

In contrast, the US generic medicines market demonstrated mild growth



Prior to FTA = 2008, 2009, 2010; During FTA = 2011, 2012, 2013; Post FTA = 2014, 2015, 2016
Note: Analysis includes all prescription molecules with global sales share >1%. YoY = Year on Year Growth. Generic Originator

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FTA impact on the USA:
TRIPS (WTO Agreement on Trade-Related Aspects of IP Rights)

TRIPS resulted in an extension of patent term from 17 to 20 years in the USA; this led to estimated lost cost savings of up to 620B USD between 2008 and 2018

TRIPS is estimated to have resulted in lost cost savings of approx. 620B USD, based upon prescription medicines expected to go off-patent from 2008-2018

The greatest contributors to lost cost savings include…

- *Atorvastatin: 23.4B USD*
- *Esomeprazole: 18.5B USD*
- *Clopidogrel: 16.5B USD*
- *Quietapine: 13.9B USD*
- *Montelukast: 11.2B USD*

In 2018, implementation of TRIPS resulted in 78B USD worth of lost cost savings, equating to over 20% of total US prescription medicine expenditures that year

Had patent term not been extended, lost expenditure could have been utilized more effectively…

Over 1,000 nurse wages for 1 year

Alternatively, had cost savings been diverted to enhancing patient access and outcomes…

- *Approx. 10 million more patients could have received a 10 year course of treatment with max. dose atorvastatin, in a market in which approx. 35 million patients are currently on statins and over 100 million people are estimated to suffer from high cholesterol*
- *Approx. 50 million additional patients could have received a 10 year course of clopidogrel treatment to reduce blood clots / stroke risk leading to prevention of death in 150,000 patients / year, in a country where stroke kills around 140,000 patients every year*

Note: Analysis includes all prescription molecules with global sales share >1%. Note: Molecules selected – a) from top lost approx.30 cost savings molecules per FTA; b) to obtain range of injectable / oral and indication coverage c) subject to availability / robustness of dosing & pricing assumptions, and NNT assumptions available d) to cover range of indications and indication types (i.e. high NNT and low NNT molecules).

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FTA impact on Canada: *CETA (Comprehensive Economic and Trade Agreement with EU)*

CETA is expected to compound rising medicine costs in Canada, risking quality of care and patient access to medicines

Current Position

Canada has **high regulated medicine costs** (832 USD / patient / year[1]) vs. global, with prices rising rapidly from an **absolute perspective** and **relative to other health expenditures in the country**

CETA Provisions

- **For Canada, CETA's provisions will result in:**
  - ***Certificates of supplementary protection*** leading to delayed generic and biosimilar entry by up to 2 years
  - ***Originator exclusivity periods locked-in*** for both synthetic and biologic medicines, preventing reversals in the future
  - ***New right of appeal*** for the patent linkage system, which may further **delay generic and biosimilar entry**

CETA Impacts

- Studies estimate that the **recently implemented CETA** between the **EU and Canada** will result in an **increase in Canadian medicine costs by 6.2% from 2023**[2]
- Increasingly, **public and employer-sponsored health benefit plans could face** significant **economic pressures** exerted by rising medicine costs, inevitably negatively impacting the quality of care in Canada through:
  - **Access restrictions** may be applied to public plans to limit costs
  - **Costs transfers** to old / sick patients leading to affordability challenges
  - **Finances diversions** from other important parts of the health system

Sources: 1. OECD; pharmaceutical spending 2019; 2. a) CETA and pharmaceuticals: Impact of the trade agreement between Europe and Canada on the costs of prescription drugs, May 2014, Lexchin & Gagnon; b) The Canada-EU Comprehensive Economic and Trade Agreement – A Prospective Analysis, Office of the Parliamentary Budget Officer, 2017; c) How will recent trade agreements that extend market protections for brand-name prescription pharmaceuticals impact expenditures and generic access in Canada? Beall RF, Hardcastle L, Clement F, Hollis A., Health Policy. 2019; d)The Canada-European Union Comprehensive Economic & Trade Agreement: An Economic Impact Assessment of Proposed Pharmaceutical Intellectual Property Provisions, Grootendorst & Hollis, 2011.

CETA has impacted only Canada, leading to even higher structural IP laws for pharmaceuticals

	TRIPS requirement	USA	Current EU (pre- & post-CETA)	Canada (pre-CETA)	Canada (post-CETA)
Patent term	20 yrs	20 yrs	20 yrs	20 yrs	20 yrs
Supplementary protection	NA	0-5 yrs (PTE)	0-5 yrs (SPC)	NA	0-2 yrs (CSP)
Data exclusivity	Allowed	5 yrs (synthetic) 4-8 yrs (biologic)	8+2+1 yrs	6+2+0.5 yrs	6+2+0.5 yrs
Patent linkage	NO	YES (synthetic) NO (biologic)	NO	YES (synthetic) YES (biologic)	YES (synthetic) YES (biologic)
Finality to patent linkage proceedings	NA	YES	NA	NO	YES
Incentives for generic patent challenge	NA	180-day exclusivity	NA	NO	NO

Higher structural / legislative protection

Source: IGBA

Introduction of Supplementary Protection could result in 2 years of generic and biosimilar entry delay

CETA Provisions	Sui generis protection

Provision

- In addition to TRIPs, which provides 20 years of protection from time of patent application filing, **CETA now allows for up to 2 additional years of protection** beyond the patent protection period. This sui generis protection is called “Certificates of Supplementary Protection” in Canada.
- The term of additional protection is calculated by **taking the time between patent application and product marketing** and **subtracting five years;** provided the **result is capped at 2 years**

Rationale

- **Concession by Canada in CETA negotiations**

Delay in generic and biosimilar entry, which could lead to increasing pricing pressure for Canadian patients and payers

Originator exclusivity periods now locked-in for both new chemical entities and biologics

CETA Provisions	*Data protection lock-in*

Provision

- In 2006, **Canada extended market exclusivity for pharmaceuticals to 8 years** (vs. original 5 years outlined in TRIPs and NAFTA), with an **additional 6 month extension** if the medicine is studied **in a paediatric population.**
- As a result, **generic and biosimilar manufacturers are not allowed to make use of an originator's data** in their applications for a **minimum of 6 years**
- While **CETA does not extend the period of exclusivity**, Canada has agreed to **lock-in this current practice** by way of a treaty obligation, making it **very difficult for future governments to shorten this period**

Rationale

- **Concession by Canada in CETA negotiations**

No ability to alter policy to favor generic / biosimilar entrants in the future

CETA required changes to patent linkage system by providing right of appeal which could further delay generic, biosimilar entry

CETA Provisions	*Patent Linkage Appeal Rights*

Provision

- **CETA allows originator to appeal decisions** made under Canada's patent linkage system
- **CETA does not require the EU to use a patent linkage system**, thus it is only applicable to Canada

Rationale

- **Concession by Canada in CETA negotiations**

Addition of right of appeal under patent linkage system could create further delays for generic and biosimilar entry

CETA provisions support originators, largely based outside of Canada, and may negatively impact Canada's generic manufacturing industry

CETA may damage Canadian Gx industry…

- Increased IP complexity, longer structural protection and resulting delays in domestic generic entry could make Canada a **less attractive place to locate and maintain manufacturing plants**
- Canadian plants may be **less competitive in attracting for global supply mandates**

…and increase revenues for EU originators

- CETA provisions strongly **support originators**, many of which are **headquartered in the EU**
- Increased imports from Europe will **negatively impact Canada's trade deficit for pharmaceuticals,** and lead to **potential for higher import costs** for longer periods

On both sides of the equation, Canada's pharma economy could be severely impacted by CETA

While studies vary numerically, all point to a substantial negative impact of CETA

Multiple sources have evaluated the potential impact of CETA, offering different quantifications of impact

- ***How will recent trade agreements that extend market protections for brand-name prescription pharmaceuticals impact expenditures and generic access in Canada?*** Beall RF, Hardcastle L, Clement F, Hollis A., Health Policy. 2019.
- ***The Canada-EU Comprehensive Economic and Trade Agreement – A Prospective Analysis***, Office of the Parliamentary Budget officer, 2017.
- ***CETA and pharmaceuticals: impact of the trade agreement between Europe and Canada on the costs of prescription drugs***, Lexchin & Gagnon, May 2014.
- ***The Canada-European Union Comprehensive Economic & Trade Agreement: An Economic Impact Assessment of Proposed Pharmaceutical Intellectual Property Provisions***, Grootendorst & Hollis, 2011.

While estimates may vary, all sources point to the significant negative impact CETA is expected to have on the Canadian generic and biosimilar markets

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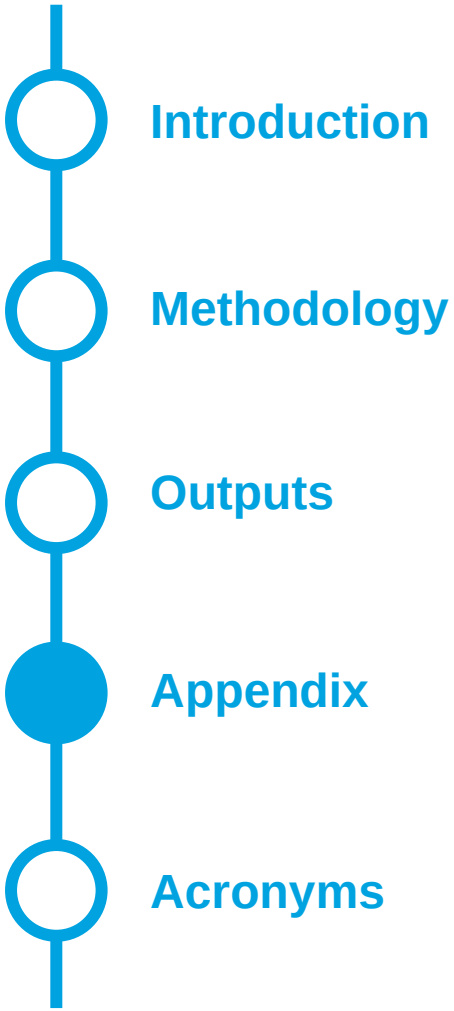
Appendix

Agenda



Introduction

Methodology

Outputs

Appendix

Acronyms

Certificates of supplementary protection issued by Health Canada

Molecule	Patent Expiry Date	CSP Term Ends
abemaciclib	15/12/2029	15/12/2031
acalabrulinib	11/07/2032	11/07/2034
alpelisib	08/09/2029	08/09/2031
antihemophilic factor / damoctocog alfa pegol	14/11/2025	14/11/2027
apalutamide	04/06/2033	04/07/2033
baricitinib	10/03/2029	10/03/2031
benralizumab	14/05/2028	14/05/2030
brigatinib	21/05/2029	21/05/2031
brodalumab	01/10/2027	01/10/2029
brolucizumab	25/06/2029	25/06/2031
cabotegravir	28/04/2026	28/04/2028
crisaborole	16/02/2026	16/02/2028
dacomitinib	25/04/2025	25/04/2027
darunavir ethanolate / cobicistat / emtricitabine / tenofovir alafenamide hemifumarate	22/02/2028	22/02/2030
dolutegravir / lamivudine	24/01/2031	24/01/2033
doravirine	28/03/2031	28/03/2033
dupilumab	27/10/2029	27/10/2031
durvalumab	24/11/2030	04/11/2032
emicizumab	17/11/2031	03/08/2033

Source: Health Canada Register of Certificates of Supplementary Protection, accessed October 11, 2020

Certificates of supplementary protection issued by Health Canada

Molecule	Patent Expiry Date	CSP Term Ends
entrectinib	08/07/2028	08/07/2030
erenumab	18/12/2029	18/12/2031
ertugliflozin	17/08/2029	17/082031
fluticasone furoate, umeclidinium, vilanterol	29/11/2031	29/11/2029
galcanezumab	07/06/2031	07/06/2033
gilteritinib fumarate	06/05/2030	06/05/2032
glasdegib	16/06/2028	16/06/2030
guselkumab	28/12/2026	28/12/2028
inotersen	29/04/2031	29/04/2033
insulin glargine / lixisenatide	09/10/2029	09/10/2031
lanadelumab	06/01/2031	06/01/2033
larotrectinib	21/10/2029	21/10/2031
letermovir	17/04/2024	17/04/2026
lifitegrast	17/05/2026	17/05/2028
lorlatinib	20/02/2033	23/02/2034
neisseria meningitidis grp B recombinant lipoprotein 2086 subfamily A / Neisseria meningitidis grp B recombinant lipoprotein 2086 subfamily B	11/10/2022	11/10/2024
olaratumab	19/06/2026	19/06/2028
ribociclib	20/08/2029	20/09/2031

Source: Health Canada Register of Certificates of Supplementary Protection, accessed October 11, 2020

Certificates of supplementary protection issued by Health Canada

Molecule	Patent Expiry Date	CSP Term Ends
risankizumab	02/11/2031	02/11/2033
romosozumab	28/04/2026	28/04/2028
semaglutide	02/03/2026	02/03/2028
simponimod	21/12/2029	21/12/2031
talazoparib	27/07/2029	27/07/2031
tezacaftor / ivacaftor	12/11/2028	12/11/2030
tisagenlecleucel	09/12/2031	09/12/2033
upadacitinib	01/12/2030	01/12/2032

Source: Health Canada Register of Certificates of Supplementary Protection, accessed October 11, 2020

Value Analysis 1: Market Level Outputs

Lost cost savings due to FTA-based patent term extension: Market Level

FTA	Analysis of impact on	Date of implementation	Implementation type	Period reviewed	Patent term extension (QTRs)	Lost cost savings (USD)
KORUS	Korea	Q3 2012	Entered into force	Implementation-2018	12	***1.00 B***
NAFTA	Mexico	Q3 2012	Implementation of 5 year exclusivity rule	Implementation-2018	20*	***332 M***
TRIPS	USA	1995-2000**	Implementation	2008-2018	12*	***600 B***
EU-Korea	Korea	Q4 2015	Entered into force	Implementation-2018	20	***592 M***
EU-Andean	Colombia	Q3 2013	Entered into force	Implementation-2018	20	***10.7 M***
EU-Andean	Peru	Q1 2013	Entered into force	Implementation-2018	20	***5.4 M***
EU-Andean	Ecuador	Q1 2017	Entered into force	Implementation-2018	20	***3.2 M***

Sources: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4108121/-targetText=The%20model%20used%20by%20Hollis,when%20pediatric%20trials%20were%20conducted); https://www.insideeulifesciences.com/2013/06/10/drug-patent-protection-in-korea-under-the-eu-korea-free-trade-agreement/; https://ec.europa.eu/trade/policy/countries-and-regions/countries/south-korea/. *IGBA inputs.
**Note: Tool data goes back to 2007, thus impact from 1995-2007 is not captured.

Value Analysis 1: Molecule Level Outputs

Lost cost savings due to FTA-based patent term extension: Top 5 Molecules

Molecule	*Lost cost savings (USD)*
entecavir	**228,381,243**
ibandronic acid	**100,859,037**
amlodipine-valsartan	**87,477,308**
trastuzumab	**78,492,571**
imatinib	**67,478,377**
fluticasone-salmeterol	**51,455,853**
hydrochlorothiazide-telmisartan	**47,378,750**
erlotinib	**37,576,968**
hydrochlorothiazide-olmesartan medoxomil	**36,219,889**
lamivudine	**35,796,558**

Value Analysis 1: Molecule Level Outputs

Lost cost savings due to FTA-based patent term extension: Top 10 Molecules

Molecule	*Lost cost savings (USD)*
atorvastatin	**24,259,589,592**
esomeprazole	**18,791,245,406**
clopidogrel	**18,319,723,611**
quetiapine	**15,283,353,560**
montelukast	**12,308,453,780**
aripiprazole	**10,861,355,356**
rosuvastatin	**10,779,738,603**
pioglitazone	**10,597,190,714**
salbutamol	**10,281,008,148**
olanzapine	**10,273,271,581**

Value Analysis 1: Molecule Level Outputs

Lost cost savings due to FTA-based patent term extension: Top 10 Molecules

Molecule	*Lost cost savings (USD)*
ipratropiumbromid-salbutamol	**110,425,321**
etoricoxib	**56,338,955**
tadalafil	**35,978,472**
hydrochlorothiazide-valsartan	**35,852,935**
hydrochlorothiazide-irbesartan	**19,169,162**
irbesartan	**10,116,214**
omeprazole-sodium	**8,868,887**
solifenacin	**8,020,283**
amlodipine-atorvastatin	**5,020,108**
travoprost	**4,118,332**

Value Analysis 1: Molecule Level Outputs

Lost cost savings due to FTA-based patent term extension: Top 10 Molecules

Molecule	*Lost cost savings (USD)*
dutasteride	**113,086,597**
oseltamivir	**106,484,670**
varenicline	**71,442,451**
tenofovir disoproxil	**65,142,632**
amlodipine-telmisartan	**51,427,172**
pirfenidone	**35,809,062**
amlodipine-hydrochlorothiazide	**22,211,593**
temozolomide	**21,903,808**
dexmedetmoidine	**14,058,626**
febuxostat	**11,692,794**

Value Analysis 1: Molecule Level Outputs

Lost cost savings due to FTA-based patent term extension: Top 10 Molecules

Molecule	*Lost cost savings (USD)*
rituximab	**689,039**
amlodipine-telmisartan	**673,976**
dabigatran etexilate	**469,004**
ipratropium bromide	**364,428**
solifenacin	**240,001**
apixaban	**178,866**
sevelamer	**119,114**
sumatriptan	**111,369**
Imiquimod	**92,678**
budesonide-formoterol	**77,561**

Value Analysis 1: Molecule Level Outputs

Lost cost savings due to FTA-based patent term extension: Top 10 Molecules

Molecule	*Lost cost savings (USD)*
amlodipine-valsartan	**1,372,315**
nepafenac	**1,257,454**
tolterodine	**354,728**
amlodipine-hydrochlorothiazide-valsartan	**238,766**
clonidine	**229,507**
bisoprolol-hydrochlorothiazide	**86,337**
pazopanib	**78,050**
exemestane	**55,593**
imiquimod	**52,151**
solifenacin	**38,109**

Value Analysis 1: Molecule Level Outputs

Lost cost savings due to FTA-based patent term extension: Top 10 Molecules

Molecule	*Lost cost savings (USD)*
tolterodine	**3,601,602**
dutasteride-tamsulosin	**3,526,911**
agomelatine	**740,798**
caspofungin	**608,643**
ciclesonide	**514,892**
lubiprostone	**330,912**
linezolid	**256,539**
emtricitabine-tenofovir disoproxil	**160,651**
filgrastim	**159,366**
baclofen	**132,255**

Value Analysis 2: Molecule Level Outputs

Selected case studies for "Lost Access"

FTA	Molecule	Price / mo (USD)	Dosing	Duration of tx (mo)	"Lost Access" Patients
KORUS	imatinib	2300.00	600mg / day	7.2	**4,076 Ph+ ALL pts**
KORUS	trastuzumab	1076.95	6mg / kg / 3wk	10.0	**7,289 HER2 positive gastric cancer pts**
TRIPS (US)	atorvastatin	18.09	80mg / day	120.0	**10,781,582 hypercholesterolaemia pts**
TRIPS (US)	clopidogrel	2.70	75mg / day	120.0	**50,925,926 pts requiring blood thinning**
NAFTA	filgrastim	17.82	5mcg / kg / day	0.5	**183,300 pts with low neutrophil count**
NAFTA	bevacizumab	5239.50	10mg / kg / 2wk	5.0	**435 pts with RCC / GBM / CRC**
EU-KOREA	dutasteride	23.41	0.5mg / day	24.0	**7,300 benign prostatic hyperplasia pts**
EU-KOREA	varenicline	58.98	0.5mg twice daily	3.0	**6,900 smoking cessation pts**

Price source: Country websites, IQVIA Pricing Insights
Dosing source: Prescribing Information
Duration of Treatment: Prescribing Information (if specified time period); PFS assumed as treatment duration for oncology products
Note: Molecules selected – a) from top lost approx.30 cost savings molecules per FTA; b) to obtain range of injectable / oral and indication coverage c) subject to availability / robustness of dosing & pricing assumptions, and NNT assumptions available d) to cover range of indications and indication types (i.e. high NNT and low NNT molecules).

Value Analyses 2 & 3: Molecule Level Outputs

Selected case studies for "Lost Outcomes"

FTA	Molecule	"Lost Access" Patients	NNT	Outcome	"Lost Outcomes" Patients
KORUS	imatinib	**4,076 Ph+ ALL pts**	3.8	No. patients alive at 1 year	**1,060 pts**
KORUS	trastuzumab	**7,289 HER2 positive gastric cancer pts**	11.1	No. patients disease-free at 1 year	**656 pts**
TRIPS (US)	clopidogrel	**50,952,926 CV risk pts**	19.0	No. patients event-free at 1 year	**152,931 pts**
EU-KOREA	dutasteride	**7,300 benign prostatic hyperplasia pts**	7	No. patients progressed at 1 year	**1043 pts**
EU-KOREA	varenicline	**6,900 smoking cessation pts**	11	No. patients with smoking cessation	**627 pts**

Price source: Country websites, IQVIA Pricing Insights
Dosing source: Prescribing Information
Duration of Treatment: Prescribing Information (if specified time period); PFS assumed as treatment duration for oncology products
Note: Molecules selected – a) from top lost approx.30 cost savings molecules per FTA; b) to obtain range of injectable / oral and indication coverage c) subject to availability / robustness of dosing & pricing assumptions, and NNT assumptions available d) to cover range of indications and indication types (i.e. high NNT and low NNT molecules).

IQVIA MIDAS Data Coverage

IQVIA Data Coverage

Market	*Retail coverage*	*Hospital coverage*
Australia	96%	96%
Korea	52%	17%
USA	98%	87%
Mexico	92%	70%
Colombia	71%	-
Peru	67%	-
Ecuador	73%	-

This table outlines the coverage IQVIA data has across retail and hospital channels

IQVIA MIDAS Data Coverage

Coverage by molecule (where molecule case studies outlined)

Market	Molecule	Formulation	Retail / hospital split
Korea	imatinib	Oral	100% / 0%
Korea	trastuzumab	Injectable	100% / 0%
Korea	filgrastim	Injectable	100% / 0%
Korea	bevacizumab	Injectable	100% / 0%
Korea	infliximab	Injectable	100% / 0%
Korea	etanercept	Injectable	100% / 0%
Korea	ramosetron	Oral	100% / 0%
Korea	palonosetron	Oral	100% / 0%
Mexico	losartan	Oral	100% / 0%
Mexico	irbesartan	Oral	100% / 0%
Mexico	dutasteride	Oral	100% / 0%
Mexico	varenicline	Oral	100% / 0%
Ecuador	chlortalidone	Oral	100% / 0%
Ecuador	indapamide	Oral	100% / 0%
USA	atorvastatin	Oral	89% / 11%
USA	clopidogrel	Oral	83% / 17%

This table outlines the coverage IQVIA data has across retail and hospital channels for specific molecules.

Agenda

- Introduction
- Methodology
- Outputs
- Appendix
- Acronyms

Acronyms

Acronym	Meaning
Bx	Biosimilars
CETA	Comprehensive Economic and Trade Agreement (between the European Union and Canada)
CRC	Colorectal carcinoma
FTA	Free Trade Agreement
GBM	Glioblastoma multiforme
Gx	Generics
IQVIA	Company that is a world leader in health data, technology and advanced analytics
IV	Intravenous
KORUS	United States-Korea Free Trade Agreement
LoE	Loss of Exclusivity
MIDAS®	Database provided by IQVIA; gold standard for global pharmaceutical market information
NAFTA	North American Free Trade Agreement (between the United States, Canada and Mexico)
OTC	Over-the-Counter medicines
TRIPS	Agreement on the Trade-Related Aspects of Intellectual Property Rights (between World Trade Organisation (WTO) member states)
RCC	Renal cell carcinoma