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Health Canada's use of accelerated review pathways and therapeutic innovation, 1995-2016: a cohort study

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Structured summary

Objectives

This study examines the use of accelerated approval pathways by Health Canada over the period 1995 to 2016 inclusive and the relationship between the use of these pathways and the therapeutic gain offered by new products.

Design

Cohort study.

Data sources

Therapeutic Products Directorate, Biologics and Genetic Therapies Directorate, Notice of Compliance database, Notice of Compliance with conditions web site, Patented Medicine Prices Review Board, La revue Prescrire, World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) classification system.

Interventions

None

Primary and secondary outcomes

Percent of new drugs evaluated by Health Canada that went through an accelerated pathway between 1995 and 2016 inclusive. Kappa values comparing the review status to assessments of therapeutic value for individual drugs.

Results

438 (70.3%) drugs went through the standard pathway, 185 (29.7%) an accelerated pathway. Therapeutic evaluations were available for 509 drugs. Health Canada used an accelerated approval pathway for 159 of the 509 drugs whereas only 55 were judged to be therapeutically innovative. The Kappa value for the entire period for all 509 drugs was 0.276 (95% CI 0.194, 0.359) or fair.

Conclusion

Health Canada's use of accelerated approvals was stable over the entire time period. Its ability to predict which drugs will offer a major therapeutic gain is relatively poor. The findings in this study should provoke a discussion about whether Health Canada should continue to use these pathways and if so how their use can be improved.

Article Summary

Strengths and limitations of this study

- Examination of the use of accelerated approval pathways by Health Canada over an extended period of time.
- Comparison of use of accelerated approval pathways to independent assessment of therapeutic evaluation.
- Analysis of approvals and therapeutic value of therapeutic subgroups.
- Twenty percent of new drugs approved did not have therapeutic evaluations.

Introduction

In order to get a new active substance (NAS - a molecule never marketed before in Canada in any form) approved for marketing in Canada, companies typically file a New Drug Submission (NDS) which includes preclinical and clinical scientific information about the product's safety, efficacy and quality and information about its claimed therapeutic value, conditions for use and side effects (1). Health Canada then has a 300-day period to evaluate this information and make a decision about whether to allow the product to be sold, i.e., whether to issue a Notice of Compliance (NOC).

In an effort to ensure that promising therapies for serious, life-threatening or debilitating illnesses can reach Canadians in a timely manner, Health Canada has developed two other pathways for approving NAS. These are described in detail elsewhere (2), but briefly, the first of these is a priority review that involves the company submitting a complete NDS but with a review period of 180 days (3). The second is the Notice of Compliance with conditions (NOC/c) (4) whereby Health Canada will give a conditional approval based on limited evidence – Phase II clinical trials or trials with only surrogate markers. In return for NOC/c status, companies commit to further studies that definitively establish efficacy and submit the results of these to Health Canada. A failure to complete these studies or negative results from them could lead to the marketing authorization being cancelled.

Lexchin has examined how closely Health Canada's use of the two pathways (priority review and NOC/c, hereafter collectively termed accelerated review pathways) corresponds to independent assessments of the therapeutic innovation of drugs at the level of individual drugs. For the period 1997-2012, the Kappa value was 0.334 (95% CI 0.220, 0.447) or fair (5).

This current study is a further and more detailed look at how Health Canada uses its accelerated review pathways, by extending previous work in a number of ways. First it covers a wider time period – 1995 to 2016, inclusive. Second, it looks at the use of both of the accelerated review pathways over this entire time period for the entire sample of drugs as well as subgroups – small molecule drugs, biologics, and therapies for serious diseases. Third, it calculates the Kappa and positive and negative predictive values for the entire sample of drugs as well as the subgroups listed above. These subgroups were chosen because small molecules and biologicals have fundamentally different characteristics and these may influence a decision to use an accelerated review pathway and how accurately Health Canada can predict their therapeutic value. Similarly, when the treatment is for serious medical conditions, Health Canada may be more willing to use an accelerated review pathway and may be more likely to believe that the new product will provide a significant therapeutic benefit.

Methods

Data sources

All NAS approved from 1995 to 2016 inclusive were documented using the annual reports from the Therapeutic Products and the Biologics and Genetic Therapies Directorates that are in charge of reviewing applications for new small molecule drugs and biologicals and vaccines, respectively. (Reports are available by directly contacting the directorates at <publications@hc-sc.gc.ca>.) 1995 was the starting date as there are no annual reports from Health Canada prior to that year. Generic and brand names along with the specific approval pathway – standard, priority, NOC/c (only from 1998 onwards) – and whether the product

was a small molecule drug or biologic (information available only from 2000 onwards) were extracted from the annual reports.

Not all of the drugs with a NOC/c are documented in the annual reports and they were supplemented using four additional sources: articles by Lexchin (6) and Law (7), the Notice of Compliance database (http://webprod5.hc-sc.gc.ca/noc-ac/index-eng.jsp) and the Notice of Compliance with conditions web site (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/conditions/index-eng.php). Only drugs approved for the first time under a NOC/c were considered. Drugs can receive both a priority and NOC/c review and in this case they were only counted as receiving a priority review.

Assessment of therapeutic innovation

The therapeutic value of drugs was assessed using the ratings from the annual reports of the Canadian Patented Medicine Prices Review Board (PMPRB) <http://www.pmprb-cepmb.gc.ca/english/View.asp?x=91> and the French drug bulletin La revue Prescrire (8). The processes that these two organizations use in arriving at their decisions about therapeutically innovation have been previously described (5). For the purpose of this study, products that the PMPRB deemed breakthrough and substantial improvement were termed "innovative" and products in other categories were termed "not innovative" (category 3 = moderate, little or no improvement over existing medicines prior to 2010; slight or no improvement, moderate improvement – primary and moderate improvement – secondary from 2010 onward). Prescrire uses seven categories to rate therapeutic innovation. The first two, bravo (major therapeutic innovation in an area where previously no treatment was available); a real advance (important therapeutic innovation but has limitations) were defined as a significant therapeutic innovation and the other Prescrire categories (except judgment

reserved) were defined as no therapeutic advance.

If a drug was judged innovative by either the PMPRB and/or Prescrire, it was rated as innovative. If both organizations evaluated the drug and the ratings were discordant, i.e., one said it was not innovative and one said it was, the drug was still considered innovative. Table 1 shows that there is substantial agreement among the definitions used by Health Canada, the PMPRB and Prescrire in assessing therapeutic innovation. Ratings were current for PMPRB as of December 31, 2016 (the annual report for 2017 was not available at the time of writing) and for Prescrire as of February 20, 2018.

Table 1: Criteria used by Health Canada in determination of priority review or Notice of Compliance with conditions pathway and by Human Drug Advisory Panel and Prescrire in determining innovation status

Health Canada – criteria for priority review and NOC/c* pathway	**Human Drug Advisory Panel of Patented Medicine Prices Review Board – criteria for breakthrough and substantial improvement**	**Prescrire International – criteria for bravo and a real advance**
Priority review: A serious, life-threatening or severely debilitating illness or condition for which there is substantial evidence of clinical effectiveness that the drug provides: effective treatment, prevention or diagnosis of a disease or condition for which no drug is presently marketed in Canada	Breakthrough = first drug product to treat effectively a particular illness	Bravo = major therapeutic innovation in an area where previously no treatment was available
Priority review: A serious, life-threatening or severely debilitating illness or condition for which there is substantial evidence of clinical effectiveness that the drug provides: significant increase in efficacy and/or significant decrease in risk such that	Substantial improvement = provides a substantial improvement over existing drug products	A real advance = product is an important therapeutic innovation but has certain limitations

the overall benefit/risk profile is improved over existing therapies NOC/c pathway: Provides patients suffering from serious, life threatening or severely debilitating diseases or conditions with earlier access to promising new drugs		

Adapted from: (9)
*Notice of Compliance with conditions

Data analysis

The number and percent of drugs approved through the standard, priority and NOC/c pathways were calculated for each year and for the 22-year period.

Kappa values were used to compare the review status from Health Canada to the assessments for the same drug from the PMPRB/Prescrire for each year and for the 22-year period. Owing to the small number of drugs approved through the NOC/c pathway, numbers from the two accelerated review pathways were combined. Kappa scores measure whether there is more or less agreement between different evaluations than would be expected by chance. Levels of agreement were graded in accordance with the recommendations of Landis and Koch (10).

Subgroup analyses

The number and percent of small molecule drugs and biologics approved through the standard, priority and NOC/c pathways were calculate and compared using the Chi-square statistic. Similarly, the Kappa values were calculated separately for small molecule drugs and biologics.

All drugs were categorized using the second level of the World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) classification system (11). Drugs in three therapeutic groups – antineoplastic agents, antivirals for systemic use and immunosuppressants – were chosen for subgroup analyses because they are primarily used for serious life-threatening diseases and because there are sufficient numbers in each group to allow for statistical analyses. The number and percent of each subgroup that received an accelerated review was calculated as were the Kappa values on a drug-by-drug basis and for drugs in the "all other therapeutic groups". Distribution of approval pathways in the subgroups individually and for the three subgroups combined versus all other therapeutic groups was compared using the Chi-square statistic. Calculations were done using Excel 2016 for Macintosh (Microsoft) and Prism 7.0 (GraphPad Software).

Patient and public involvement

No patients were involved in any aspect of this study.

Ethics

No patients were involved in this study and only publicly available data was gathered. Therefore, ethics approval was not required.

Results

Review status

From January 1, 1995 to December 31, 2016 Health Canada approved a total of 623 NAS. Of these, 438 (70.3%) went through the standard pathway, 152 (24.4%) the priority pathway and 33 (5.3%%) received a NOC/c. Almost 30 percent (29.7%) went through the accelerated review pathways over the entire period, varying from a low of 9.1% in 2010 to a high of 47.8% in 2006 (Table 2). (Health Canada used both a priority and NOC/c approval for 11

drugs, data not shown.) Figure 1 shows that there is no trend to using accelerated review pathways more liberally or more conservatively over the time period. (Supplementary Tables 1 & 2, drugs with and without therapeutic evaluations, respectively, give all of the data extracted for the 623 drugs in question.)

Figure 1: Percent of drugs approved through different pathways

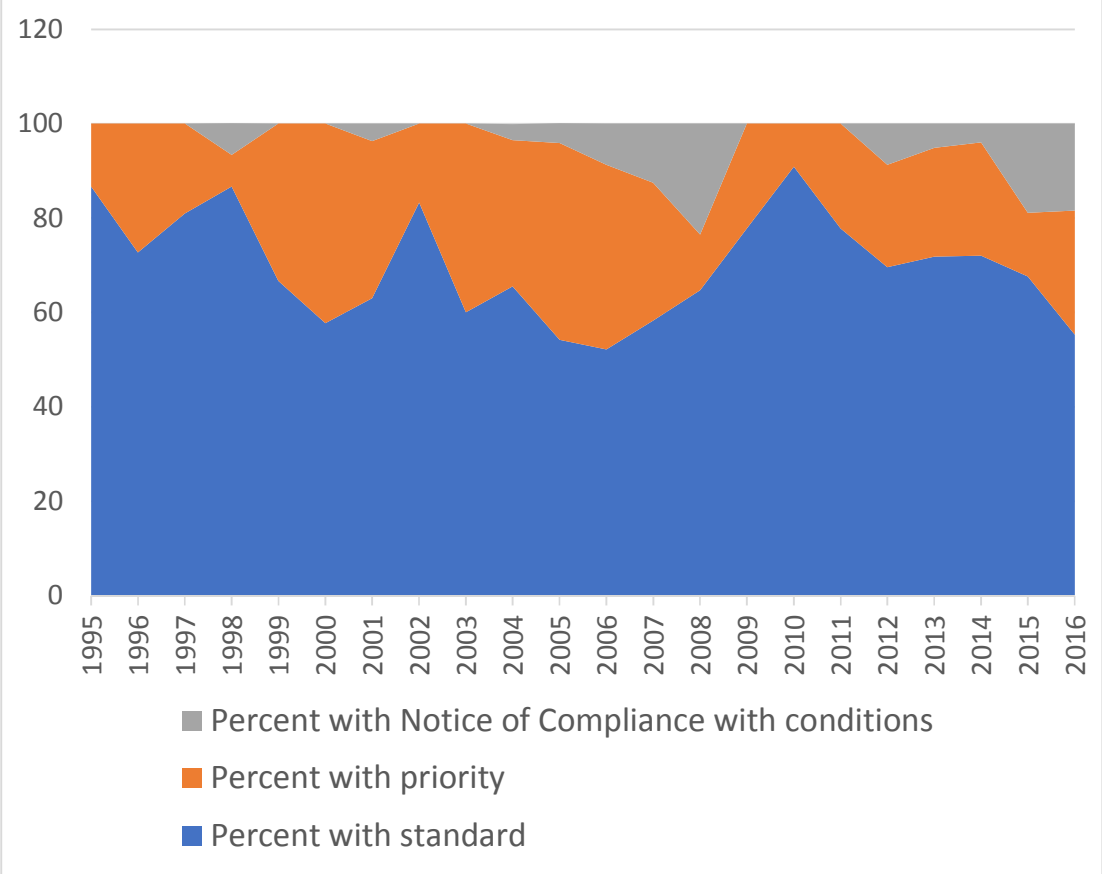

Table 2: Review status of new active substances approved 1995-2016

Year	Number of new active substances approved	Number (%) with standard review	Number (%) with priority review	Number (%) with NOC/c* review	Number (%) with any accelerated pathway review
1995	30	26 (86.7)	4 (13.3)	--	4 (13.3)
1996	33	24 (72.7)	9 (27.3)	--	9 (27.3)
1997	42	34 (81.0)	8 (19.0)	--	8 (19.0)
1998	30	26 (86.7)	2 (6.7)	2 (6.7)	4 (13.3)

1999	36	24 (66.7)	12 (33.3)	0 (0)	12 (33.3)
2000	26	15 (57.7)	11 (42.3)	0 (0)	11 (42.3)
2001	27	17 (63.0)	9 (33.3)	1 (3.7)	10 (37.0)
2002	24	20 (83.3)	4 (16.7)	0 (0)	4 (16.7)
2003	20	12 (60.0)	8 (40.0)	0 (0)	8 (40.0)
2004	29	19 (65.5)	9 (31.0)	1 (3.4)	10 (34.5)
2005	24	13 (54.2)	10 (41.7)	1 (4.2)	11 (45.8)
2006	23	12 (52.2)	9 (39.1)	2 (8.7)	11 (47.8)
2007	24	14 (58.3)	7 (29.2)	3 (12.5)	10 (41.7)
2008	17	11 (64.7)	2 (11.8)	4 (23.5)	6 (35.3)
2009	27	21 (77.8)	6 (22.2)	0 (0)	6 (22.2)
2010	22	20 (90.9)	2 (9.1)	0 (0)	2 (9.1)
2011	27	21 (77.8)	6 (22.2)	0 (0)	6 (22.2)
2012	23	16 (69.6)	5 (21.7)	2 (8.7)	7 (30.4)
2013	39	28 (71.8)	9 (23.1)	2 (5.1)	11 (28.2)
2014	25	18 (72.0)	6 (24.0)	1 (4.0)	7 (28.0)
2015	37	25 (67.6)	5 (13.5)	7 (18.9)	12 (32.4)
2016	38	21 (55.3)	10 (26.3)	7 (18.4)	17 (44.7)
Total	623	438 (70.3)	152 (24.4)	33 (5.3)	185 (29.7)

*Notice of Compliance with conditions
†Patented Medicine Prices Review Board

There were 126 biologics approved versus 323 small molecules (data only available from 2000 onward). There was no difference in the distribution of the approval pathways (p = 0.4867) (Table 3). There were 81 approvals for antineoplastic agents, 47 for antivirals for systemic use, 36 for immunosuppressants and 365 for drugs in the "all other therapeutic groups" (n = 67) (Supplementary Table 1). The distribution of approval pathways was significantly different for the three subgroups (p = 0.0018) and for the three subgroups combined versus "all other therapeutic groups" (p < 0.00001) (Table 3).

Table 3: Subgroup comparison of review pathways

Subgroup	**Standard**	**Priority**	**Notice of compliance with conditions**	**Total**

Small molecules	129	72	22	323
Biologics	73	45	8	126
Antineoplastic agents	34	26	21	81
Antivirals for systemic use	16	26	5	47
Immunosuppressants	22	13	1	36
All other therapeutic groups	365	89	5	459

Small molecules vs. biologics: chi-square = 1.4402 (p = 0.4867)
Antineoplastics vs. antivirals vs. immunosuppressants: chi-square = 17.1978 (p = 0.0018)
Antineoplastics + antivirals + immunosuppressants vs. all other therapeutic groups: chi-square = 97.4874 (p < 0.00001)

Therapeutic value

Out of the 623 NAS, 509 (81.7%) were evaluated for their therapeutic innovation either by the PMPRB and/or La revue Prescrire. Health Canada used an accelerated review pathway for 159 of the 509 drugs whereas only 55 were judged to be therapeutically innovative by one or both of the independent reviews (Table 4). The Kappa value for the entire period for all 509 drugs was 0.276 (95% CI 0.194, 0.359) or fair. Figure 2 presents the Kappa values for each year which generally ranged from 0 (poor) to 0.4 (fair).

Figure 2: Agreement between review status and therapeutic innovation (Kappa value)

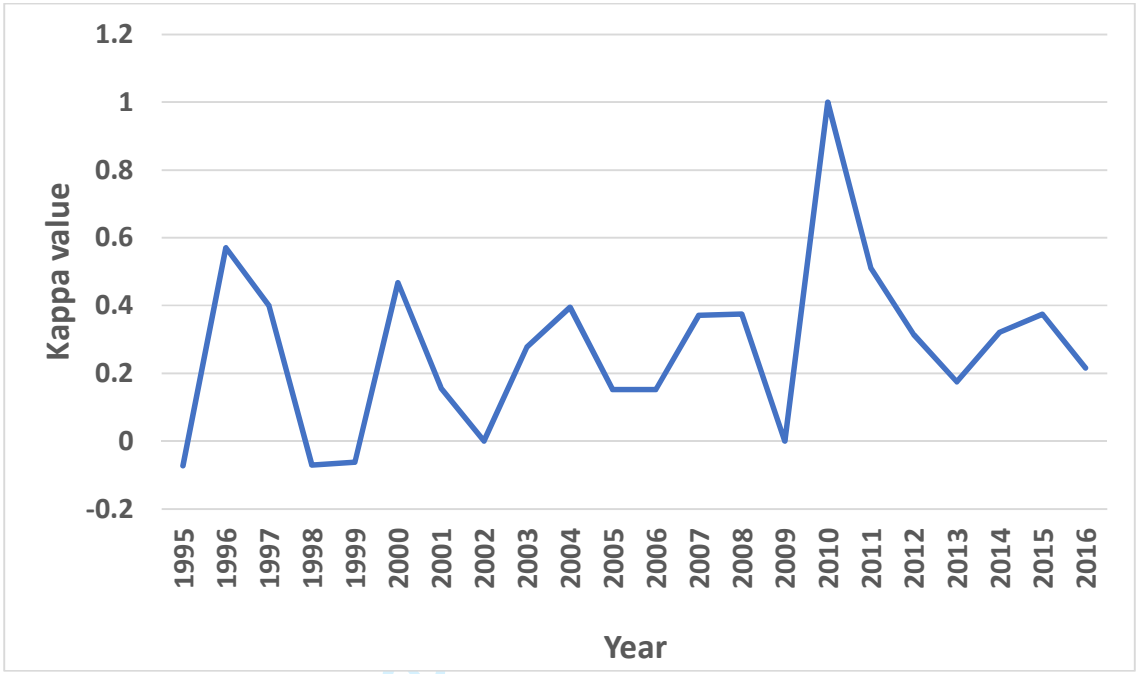

Table 4: Number of new active substances with an accelerated review and therapeutically innovative rating

Year	Number (%) of NAS* with a therapeutic assessment from Patented Medicine Prices Review Board and/or La revue Prescrire	Number of NAS with an accelerated review	Number of NAS rated as therapeutic innovation by either Patented Medicine Prices Review Board and/or La revue Prescrire
1995	22 (73.3)	3	1
1996	20 (60.6)	5	4
1997	24 (57.1)	4	4
1998	24 (80.0)	4	1
1999	31 (86.1)	10	1
2000	20 (76.9)	9	4
2001	23 (85.2)	8	1
2002	20 (83.3)	4	0
2003	19 (95.0)	8	2
2004	26 (89.7)	9	3
2005	21 (87.5)	9	3
2006	21 (91.3)	9	3
2007	22 (91.7)	9	3
2008	15 (88.2)	6	2
2009	26 (96.3)	7	0
2010	19 (86.4)	2	2
2011	23 (85.3)	5	2

2012	21 (91.3)	6	3
2013	36 (92.3)	11	6
2014	22 (88.0)	6	3
2015	30 (81.1)	12	4
2016	24 (63.2)	13	3
1995-2016	509 (81.7)	159	55

*New active substance
†Number of drugs rated as innovative as a percent of all drugs given an accelerated approval review by Health Canada
‡Number of drugs rated as not therapeutically innovative as a percent of all drugs given a standard review by Health Canada

There were 286 and 99 small molecule drugs and biologics, respectively, with therapeutic ratings. The Kappa values were 0.313 (95% CI 0.205, 0.420) (fair) and 0.233 (95% CI 0.061, 0.405) (fair), respectively. The overlapping 95% CIs indicate no difference in the Kappa values between the two groups (Table 5).

Table 5: Subgroup analyses: Kappa values

Subgroup	**Number (%)**	**Kappa value (95% CI)**
Small molecule drugs	286	0.313 (0.205, 0.420)
Biologics	99	0.233 (0.061, 0.405)
Antineoplastic agents	71	0.091 (0.017, 0.200)
Antivirals for systemic use	46	0.122 (0.011, 0.233)
Immunosuppressants	35	0.376 (0.075, 0.675)
All other therapeutic groups	357	0.385 (0.263, 0.506)

The 509 drugs were in 57 different second level ATC groups: antineoplastic agents (71), antivirals for systemic use (46), immunosuppressants (35) and “all other therapeutic groups” (357) (Supplementary Table 1). Kappa values for the four groups were: 0.091 (95% CI 0.017, 0.200) (poor), 0.200), 0.122 (95% CI 0.011, 0.233) (poor)), 0.376 (95% CI 0.075, 0.675) (fair) and (95% CI 0.263, 0.506)0.385 (fair), respectively. The 95% CIs for the Kappa values

for the antineoplastic agents, antivirals for systemic use and immunosuppressants overlapped indicating no difference among the groups but there was no overlap of any of these with the 95% CI for "all other therapeutic groups".

Discussion

Almost 30% of the new active substances that Health Canada reviewed between 1995 and 2016 went through one of two accelerated review pathways – priority review or NOC/c, primarily a priority review. There is no difference between small molecule drugs and biologics in the approval pathways used indicating that for these two groups Health Canada does not see one or the other being more likely to offer significant new therapeutic benefits. However, the same is not true for the therapeutic subgroups. The three specifically examined – antineoplastics, antivirals and immunosuppressants – were more likely to be assigned to an accelerated review pathway compared to all other therapeutic groups, possibly because of the nature of the diseases that they treat.

Just over 80% of the NAS approved had been assessed by the PMPRB and/or La revue Prescrire for their therapeutic benefit. The Kappa value for the 509 drugs was 0.276 meaning that Health Canada's ability to predict major therapeutic gain from these drugs was only fair. The relatively low Kappa value may relate to when Health Canada makes its decision about what type of approval pathway to use. This assignment is at the start of the review process when all of the data will not have been fully assessed. In contrast, the PMPRB and La revue Prescrire make their assessments after the drug has been marketed when more information about efficacy and safety is available.

As was the case with the assignment of an accelerated review pathway, there is no difference in how Health Canada evaluates the therapeutic value of small molecule drugs and biologics. Health Canada seems somewhat better at predicting the therapeutic value of drugs in the "all other therapeutic groups" than it does for drugs in the antineoplastic, antiviral and immunosuppressant groups although it is more likely to review these groups through an accelerated review pathway.

How Health Canada uses its accelerated review pathways is important for a number of reasons. First, their use may explicitly create an impression among clinicians and patients that these drugs are likely to deliver major new therapeutic benefits despite the fact that the likelihood that they will is only "fair" as measured by the Kappa value. Second, the NOC/c pathway requires companies to commit to conducting post-market studies to validate the efficacy of the product, but many of these studies are delayed (6, 7), leaving clinicians and patients uncertain about the value of these products. In at least one case, Health Canada did not suspend the sale of a drug and allowed it to stay on the market despite not fulfilling the conditions required under its NOC/c. In December 2003, Iressa (gefitinib) was approved as a third-line treatment for non-small cell lung cancer on the condition that the company submit a study showing that it improved survival (12). When the study results were submitted to Health Canada they showed no survival benefit for gefitinib compared to placebo (13). Health Canada recognized that the conditions had not been fulfilled, but rather than removing gefitinib from the market, in February 2005 it elected to allow it to continue to be sold (12). In 2009, the drug was deemed to have met its conditions after a new study showed non-inferiority, i.e., survival after taking it was no worse compared to another chemotherapeutic agent (14). Third, although the priority and standard approval pathways are equivalent in terms of the amount of data reviewed, the former is done in 180 days compared to 300 days

for the latter, meaning that the priority pathway is more resource intensive possibly drawing resources from other Health Canada activities. Finally, drugs reviewed through both accelerated review pathways are more likely to receive safety warnings once they are on the market compared to drugs with a standard approval (2, 15).

As Figure 1 indicates, Health Canada is not using the accelerated review pathways more liberally (or more conservatively) over time, but as Figure 2 shows it has not improved its ability to predict therapeutic innovation over the 22 years evaluated in this study. The Introduction describes the criteria that Health Canada uses to assign a drug to either a priority review or a NOC/c review but how those criteria are applied and whether Health Canada periodically reviews its performance are not known. The fact that it appears to be better at predicting therapeutic innovation for some therapeutic subgroups is encouraging.

Contrary to the situation in the United States (US) where the Food and Drug Administration (FDA) has been using an increasing number of expedited development or review programs, Health Canada's use of its programs has been relatively stable since 1995. Between 1987 and 2014, 43% received a priority review from the FDA and 19% were approved through the fast track program the equivalent of a NOC/c (16). (Drugs could be associated with both programs.) However, when it comes to approving oncology drugs through an accelerated pathway, Health Canada is only marginally better than the FDA. In the US, only 1 of 15 (6.7%) oncology drugs approved through an accelerated program from January 1, 2008, through December 31, 2012 had a proven survival benefit compared to the other 6 and 8 that either had no overall survival benefit or an unknown benefit, respectively (17). In this current study, out of 42 neoplastic agents that Health Canada gave an accelerated review to, only 6 (14.3%) were rated as therapeutically innovative. While Health Canada used accelerated

approvals less often than the FDA, it used these pathways more often than the European Medicines Association which applied them to only 70 (12.5%) of 558 new drugs it approved from 1995 to 2009 (18).

Limitations

Almost 20% of new drugs approved by Health Canada were not evaluated for their therapeutic innovation by either the PMPRB or La revue Prescrire. The absence of these evaluations may have skewed both the Kappa values in either a more positive or more negative direction.

Conclusion

Health Canada continues to use accelerated review pathways for about 30% of new drugs. The rationale for using accelerated review pathways is to get important therapeutic advances to patients in a timely manner, but Health Canada's ability to predict which of these drugs will fulfill this expectation has not improved over a 22-year period and remains relatively low. Moreover, using these pathways come with both health related and resource costs. The findings in this study should provoke a discussion about whether Health Canada should continue to use these pathways and if so how their use can be improved.

Acknowledgements

None

Competing Interests

In 2015-2017, Joel Lexchin received payment from two non-profit organizations for being a consultant on a project looking at indication based prescribing and a second looking at which drugs should be distributed free of charge by general practitioners. In 2015, he received payment from a for-profit organization for being on a panel that discussed expanding drug insurance in Canada. He is on the Foundation Board of Health Action International.

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Data sharing

Full data that was extracted is available from the online data repository Dryad http://datadryad.org with the DOI:

Author Contributions

JL came up with the idea for this study, gathered and analyzed the data and wrote the manuscript.

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Supplementary Table 1: All drugs approved between 1995-2016 that received therapeutic assessment

Generic name	Brand name	PMPRB	PMPRB	Review status		
		breakthrough, substantial improvement and/or	and/or Prescrire no significant therapeutic	Standard	Priority	Notice of compliance with conditions
Adapalene	Differin		1	1		
Dexrazoxane	Zinecard	1		1		
Bambuterol	Bambec		1	1		
Naltrexone	Revia		1	1		
Cefprozil	Cefzil		1	1		
Zuclopenthixol	Clopixol		1	1		
Zuclopenthixol	Clopixol acuphase		1	1		
Zuclopenthixol	Clopixol depot		1	1		
Lansoprazole	Prevacid		1	1		
Cefepime	Maxipime		1	1		
Interferon Beta-1B	Betaseron		1		1	
Famciclovir	Famvir		1	1		
Cefpodoxime	Orelox		1	1		
Sevoflurane	Sevorane		1	1		
Losartan	Cozaar		1	1		
Iotrolan	Osmovist 280		1	1		
Bicalutamide	Casodex		1	1		
Acarbose	Prandase		1	1		
Mycophenolate	Cellcept		1	1		
Tacrolimus	Prograf		1		1	
Lamivudine	3TC		1		1	
Alendronate	Fosamax		1	1		
Stavudine	Zerit		1	1		
Acellular pertussis vaccine adsorbed	Acel-P		1		1	
Dorzolamide	Trusopt		1	1		
Amifostine	Ethyol	1			1	

Valacyclovir	Valtrex		1	1	
Quinagolide	Norprolac		1	1	
Meropenem	Merrem		1	1	
Abciximab	Reopro	1		1	
Anastrozole	Arimidex		1	1	
Ritonavir	Norvir	1			1
Raltitrexed	Tomudex		1		1
Indinavir	Crixivan	1			1
Insulin lispro	Humalog		1	1	
Dirithromycin	Dynabac		1	1	
Olanzapine	Zyprexa		1	1	
Nalmefene	Revex		1	1	
Zolpidem	Ambien		1	1	
Desflurane	Suprane		1	1	
Gemcitabine	Gemzar		1	1	
Ropivacaine	Naropin injections		1	1	
Imiglucerase	Cerezyme	1			1
Atorvastatin	Lipitor		1		1
Topiramate	Topamax		1	1	
Formoterol	Foradil dry powder capsules		1	1	
Epoprostenol	Flolan		1		1
Coagulation factor IX	Benefix	1			1
Topotecan	Hycamtin		1	1	
Dolasetron	Anzemet		1	1	
Letrozole	Femara		1	1	
Fexofenadine	Allegra		1	1	
Latanoprost	Xalatan		1	1	
Carbetocin	Duratocin		1	1	
Follitropin beta	Puregon		1	1	
Irinotecan	Camptosar	1		1	
Donepezil	Aricept	1		1	
Ropinirole	Requip		1	1	

Ibandronate	Bondronat		1	1		
Glatiramer	Copaxone for injection		1	1		
Tolcapone	Tasmar		1	1		
Zafirlukast	Accolate		1	1		
Valsartan	Diovan		1	1		
Levofloxacin	Levaquin		1	1		
Brimonidine	Alphagan opthalmic solution		1	1		
Quetiapine	Seroquel		1	1		
Pramipexole	Mirapex		1	1		
Interferon Beta-1A	Rebif		1	1		
Emedastine	Emadine ophthalmic		1	1		
Cerivastatin	Baycol		1	1		
Grepafloxacin	Raxar		1	1		
Naratriptan	Amerge		1	1		
Bupropion	Wellbutrin SR		1	1		
Irbesartan	Avapro		1	1		
Tamsulosin	Flomax		1	1		
Montelukast	Singulair		1	1		
Delavirdine	Rescriptor		1	1		1
Nelfinavir	Viracept		1		1	
Zolmitriptan	Zomig		1	1		
Capecitabine	Xeloda		1		1	
Nevirapine	Viramune		1	1		1
Clopidogrel	Plavix		1	1		
Brinzolamide	Azopt ophthalmic suspension		1	1		
Raloxifene	Evista		1	1		
Candesartan	Atacand		1	1		
Tolterodine	Detrol		1	1		
Varicella vaccine	Varivax	1		1		

Alatrofloxacin	Trovan (IV)		1	1		
Trovafloxacin	Trovan (tablets)		1	1		
Becaplermin gel	Regranex		1	1		
Tizanidine	Zanaflex		1	1		
Penciclovir	Denavir		1	1		
Citalopram	Celexa		1	1		
Recombinant factor VIIa	Niastase		1		1	1
Modafinil	Alertec		1	1		
Sildenafil	Viagra	1		1		
Recombinant-methionyl interferon consensus 1	Infergen		1		1	
Efavirenz	Sustiva		1		1	
Repaglinide	Gluconorm		1	1		
Celecoxib	Celebrex		1		1	
Triptorelin	Trelstar		1	1		
Ancestim	Stemgen		1	1		
Orlistat	Xenical		1	1		
Abacavir	Ziagen		1		1	1
Eptifibatide	Integrilin		1	1		
Eprosartan	Teveten		1	1		
Cidofovir	Vistide		1	1		
Rizatriptan	Maxalt		1	1		
Trastuzumab	Herceptin		1		1	
Telmisartan	Micardis		1	1		
Risedronate	Actonel		1	1		
Tirofiban	Aggrastat		1	1		
Icodextrin	Extraneal		1	1		
Varicella zoster vaccine	Varilrix		1		1	
Temozolomide	Temodal		1	1		
Rofecoxib	Vioxx		1		1	

Zanamivir	Relenza		1		1	1
Melanoma theracine	Melacine		1		1	
Gadobutrol	Gadovist		1	1		
Dalfopristin	Synercid		1	1		
Oseltamivir	Tamiflu		1	1		
Daclizumab	Zenaprax		1		1	
Leflunomide	Arava		1	1		
Rituximab	Rituxan	1			1	
Rosiglitazone	Avandia		1		1	
Oxcarbazepine	Trileptal		1	1		
Rivastigmine	Exelon		1	1		
Zaleplon	Starnoc		1	1		
Verteporfin	Visudyne	1			1	
Cabergoline	Dostinex		1	1		
Exemestane	Aromasin		1	1		
Pioglitazone	Actos		1		1	
Zoledronic acid	Zometa		1		1	
Riluzole	Rilutek	1			1	1
Meloxicam	Mobic		1	1		
Basiliximab	Simulect		1		1	
Moxifloxacin	Avelox		1	1		
Peginterferon Alfa-2b	Peg-intron		1	1		
Etanercept	Enbrel	1			1	
Gadoversetamide	Optimark		1	1		
Sibutramine	Meridia		1	1		
Sirolimus	Rapamune		1	1		
Gatifloxacin	Tequin		1	1		
Glucagon, rDNA origin	Glucagon		1		1	
Mequinol/tretinoin	Solage		1	1		
Amprenavir	Agenerase		1	1		1
Lopinavir/ritonavir	Kaletra		1		1	
Linezolid	Zyvoxam		1	1		
Iron	Venofer		1		1	

Doxercalciferol	Hectorol		1	1		
Rabeprazole	Pariet		1	1		
Entacapone	Comtan		1	1		
Eflornithine	Vaniqa		1	1		
Mirtazapine	Remeron		1	1		
Desloratadine	Aerius		1	1		
Infliximab	Remicade		1	1		
Caspofungin	Cancidas		1		1	
Galantamine	Reminyl		1	1		
Esomeprazole	Nexium		1	1		
Imatinib	Gleevec	1			1	1
Tenecteplase	Tnkase		1	1		
Travoprost	Travatan		1	1		
Bosentan	Tracleer		1		1	
Meningococcal group C polysaccharide, tetanus toxoid	Neisvac-C		1		1	
Glimepiride	Amaryl		1	1		
Nateglinide	Starlix		1	1		
Alfuzosin	Xatral		1	1		
Tegaserod	Zelnorm		1	1		
Ganirelix	Orgalutran		1	1		
Valganciclovir	Valcyte		1	1		
Palivizumab	Synagis		1	1		
Docosanol	Abreva		1	1		
Bimatoprost	Lumigan		1	1		
Anakinra	Kineret		1		1	
Moroctocog alpha	Refacto		1		1	
Peginterferon Alfa-2b ribavirin	Pegetron		1	1		
Fondaparinux	Arixtra		1		1	
Hetastarch	Hextend		1	1		
Darbepoetin alpha	Aranesp		1	1		

Norelgestromin/ethinyl estradiol	Evra		1	1		
Treprostinil	Remodulin		1		1	
Bivalirudin	Angiomax		1	1		
Tiotropium	Spiriva		1	1		
Valdecoxib	Betra		1	1		
Drotrecogin Alfa	Xigris	1			1	
Rosuvastatin	Crestor		1	1		
Recombinant cholera toxin B subunit	Dukoral		1		1	
Levetiracetam	Keppra		1	1		
Tenofovir	Viread		1		1	1
Pimecrolimus	Elidel		1	1		
Ertapenem	Invanz		1	1		
Ezetimibe	Ezetrol		1	1		
Telithromycin	Ketek		1	1		
Enfuvirtide	Fuzeon	1			1	
Dutasteride	Avodart		1	1		
Peginterferon Alfa-2a	Pegasys		1	1		
Cetrorelix	Cetrotide		1	1		
Adefovir	Hepsera		1		1	
Tadalafil	Cialis		1	1		
Almotriptan	Axert		1	1		
Rasburicase	Fasturtec		1		1	
Atazanavir	Reyataz		1		1	
Gefitinib	Iressa		1		1	1
Agalsidase Beta	Fabrazyme		1		1	
Agalsidase	Replagal	1			1	1
Fulvestrant	Faslodex		1	1		

Gemifloxacin	Factive		1	1		
Pegfilgrastim	Neulasta		1	1		
Vardenafil	Levitra		1	1		
Gadobenate	Multihance		1	1		
Miglustat	Zavesca		1		1	
Botulinum Toxin Type B	Myobloc		1	1		
Peginterferon Alfa-2A Ribavirin	Pegasys RBV		1		1	
Ethinyl estradiol/etonogestrel	Nuvaring		1	1		
Pemetrexed	Alimta		1		1	
Laronidase	Adlurazyme	1			1	
Teriparatide	Forteo		1		1	
Cinacalcet	Sensipar	1			1	
Eletriptan	Relpax		1	1		
Voriconazole	Vfend		1	1		
Frovatriptan	Frova		1	1		
Adalimumab	Humira		1	1		
Alefacept	Amevive		1	1		
Omalizumab	Xolair		1	1		
Memantine	Ebixa		1	1		1
Fosamprenavir	Telzir		1	1		
Drospirenone/ethinyl estradiol	Yasmin 21/28		1	1		
Atomoxetine	Strattera		1	1		
Escitalopram	Cipralex		1	1		
Bortezomib	Velcade		1	1		1
Paricalcitol	Zemplar		1	1		
Pantoprazole	Pantaloc M		1	1		
Pegaptanib	Macugen	1			1	
Ibritumomab	Zevalin		1		1	
Pregabalin	Lyrica		1	1		

Lutropin Alfa	Luveris		1	1		
Erlotinib	Tarceva		1		1	
Tramadol	Tramacet		1	1		
Sodium oxybate	Xyrem		1	1		
Perindopril	Coversyl		1	1		
Bevacizumab	Avastin		1		1	
Cetuximab	Erbitux		1		1	
Insulin detemir	Levemir		1	1		
Pegvisomant	Somavert		1		1	
Efalizumab	Raptiva		1	1		
Darifenacin	Enablex		1	1		
Emtricitabine	Emtriva		1	1		
Tipranavir	Aptivus		1		1	
Alemtuzumab	Mabcampath	1		1		
Palifermin	Kepivance	1			1	
Trospium	Trosec		1	1		
Solifenacin	Vesicare		1	1		
Histrelin	Vantas		1	1		
Insulin glulisine	Apidra		1	1		
Sunitinib	Sutent		1		1	1
Entecavir	Baraclude		1		1	
Abatacept	Orencia		1		1	
Recombinant human papillomavirus	Gardasil	1			1	
Lanreotide	Somatuline autogel		1	1		
Sorafenib	Nexavar		1	1		
Darunavir	Prezista		1	1		1
Rotaviruses	Rotateq	1		1		
Alglucosidase Alfa	Myozyme	1			1	
Rasagiline	Azilect		1	1		
Ciclesonide	Alvesco		1	1		

Tigecycline	Tygacil		1	1		
Natalizumab	Tysabri		1		1	
Lanthanum	Fosrenol		1	1		
Deferasirox	Exjade		1		1	1
Gadofosveset	Vasovist		1	1		
Telbivudine	Sebivo		1		1	
Varenicline	Champix		1	1		
Acamprosate	Campral		1	1		
Dasatinib	Sprycell	1		1		1
Posaconazole	Spriafil (Posanol)	1			1	
Micafungin	Mycamine		1	1		
Sitaxentan	Thelin		1	1		
Idursulfase	Elaprase		1		1	
Oxaliplatin	Eloxatin		1		1	
Ranibizumab	Lucentis	1			1	
Fluticasone	Avamys		1	1		
Aprepitant	Emend		1	1		
Maraviroc	Celsentri		1		1	
Daptomycin	Cubicin		1	1		
Paliperidone	Invega		1	1		
Duloxetine	Cymbalta		1	1		
Nesiritide	Natrecor		1	1		1
Aliskiren	Rasilez		1	1		
Anidulafungin	Eraxis		1	1		
Raltegravir	Isentress		1		1	1
Rivastigmine	Exelon patch		1	1		
Sitagliptin	Januvia		1	1		
Temsirolimus	Torisel		1		1	
Lenalidomide	Revlimid	1		1		1
Ambrisentan	Volibris		1	1		
Etravirine	Intelence		1		1	

Methylnaltrexone	Relistor	1			1	
Panitumumab	Vectibix		1	1		1
Nepafenac	Nevanac		1	1		
Dabigatran	Pradaxa		1	1		
Ceftobiprole	Zeftera		1	1		
Idebenone	Catena		1	1		1
Nilotinib	Tasigna		1	1		1
Rivaroxaban	Xarelto		1	1		
Olmesartan	Olmetec		1	1		
Capsular polysaccharide	Synflorix		1	1		
Ustekinumab	Stelara		1	1		
Loteprednol	Alrex		1	1		
Eculizumab	Soliris		1		1	
Desvenlafaxine	Pristiq		1	1		
Lisdexamfetamine	Vyvanse		1	1		
Romiplostim	Nplate		1		1	
Methyl aminolevulinate	Metvix		1	1		
Eplerenone	Inspra		1	1		
Fosaprepitant	Emend IV		1	1		
Golimumab	Simponi		1	1		
Lapatinib	Tykerb		1	1		
Vorinostat	Zolinza		1	1		
Aripiprazole	Abilify		1	1		
Clofarabine	Clolar		1	1		
Dronedarone	Multaq		1		1	
Certolizumab	Cimzia		1	1		
Doripenem	Doribax		1	1		
Aztreonam	Cayston		1		1	1
Saxagliptin	Onglyza		1	1		
Besifloxacin	Besivance		1	1		
Azacitidine	Vidaza		1		1	
Japanese encephalitis vaccine	Ixiaro		1	1		
Alitretinoin	Toctino		1	1		
Degarelix	Firmagon		1	1		

Dexmedetomidine	Precedex		1	1		
Everolimus	Afinitor		1	1		1
Thrombin alfa	Recothrom		1	1		
Pneumococcal conjugate	Prevnar		1		1	
Gadoxetate	Primovist		1	1		
Recombinant human papillomavirus	Cervarix		1	1		
Canakinumab	Ilaris	1			1	
Prasugrel	Effient		1	1		
Tocilizumab	Actemra		1	1		
Sapropterin	Kuvan	1			1	
Trabectedin	Yondelis		1	1		
Liraglutide	Victoza - 1.2 mg pen-injector		1	1		
Meningococcal oligosaccharides conjugated	Menveo		1	1		
Pazopanib	Votrient		1	1		
Paliperidone	Invega sustenna		1	1		
Sevelamer	Renvela		1	1		
Dexlansoprazole	Dexilant		1	1		
Denosumab	Prolia		1	1		
Febuxostat	Uloric		1	1		
Lacosamide	Vimpat		1	1		
Velaglucerase alfa	VPRIV		1	1		
Roflumilast	Daxas		1	1		
Tapentadol	Nucynta CR		1	1		
Silodosin	Rapaflo		1	1		
Eltrombopag	Revolade		1	1		
Exenatide	Byetta		1	1		
Fingolimod	Gilenya		1	1		
Ticagrelor	Brilinta		1		1	
Cabazitaxel	Jevtana		1	1		
Rufinamide	Banzel		1	1		
Belimumab	Benlysta		1	1		

Rilpivirine	Edurant		1	1	
Tolvaptan	Samsca		1	1	
Abiraterone	Zytiga		1		1
Linagliptin	Trajenta		1	1	
Boceprevir	Victrelis	1			1
Boceprevir, peginterferon alfa-2b, ribavirin	Victrelis Triple	1			1
Telaprevir	Incivek		1		1
Colesevelam	Lodalis		1	1	
Senapine	Saphris		1	1	
Dienogest	Visanne		1	1	
Indacaterol	Onbrez breezhaler		1	1	
Prucalopride	Resotran		1	1	
Plerixafor	Mozobil		1	1	
Eribulin	Halaven		1	1	
Apixaban	Eliquis		1	1	
Vandetanib	Caprelsa		1	1	
Ipilimumab	Yervoy		1	1	
Fesoterodine	Toviaz		1	1	
Fampridine	Fampyra		1	1	
Vemurafenib	Zelboraf	1			1
Azilsartan	Edarbi		1	1	
Ofatumumab	Arzerra		1	1	
Palonosetron	Aloxi		1	1	
Crizotinib	Xalkori		1	1	1
Fidaxomicin	Dificid		1	1	
Lurasidone	Latuda		1	1	
Ruxolitinib	Jakavi		1		1
Collagenase clostridium histolyticum	Xiaflex	1		1	
Axitinib	Inlyta		1	1	
Catridecacog	Tretten		1		1
Bendamustine	Treanda		1	1	
Pirfenidone	Esbriet		1		1

Elvitegravir, emtricitabine, tenofovir,	Stribild		1	1		
Ivacaftor	Kalydeco	1			1	
Stiripentol	Diacomit		1	1		
Nebivolol	Bystolic		1	1		
Ingenol	Picato		1	1		
Brentuximab	Adcetris		1	1		1
Meningococcal polysaccharide groups A,C,W-135 & Y conjugate vaccine, Tetanus toxoid	Nimenrix		1	1		
Mirabegron	Myrbetriq		1	1		
Regorafenib	Stivarga		1		1	
Rotigotine	Neupro		1	1		
Dimethyl	Tecfidera		1	1		
Perampanel	Fycompa		1	1		
Pertuzumab	Perjeta	1			1	
Enzalutamide	Xtandi		1		1	
Ulipristal	Fibristal		1	1		
Vismodegib	Erivedge		1	1		
Dabrafenib	Tafinlar		1	1		
Trametinib	Mekinist		1	1		
Fluticasone and vilatnerol	Breo ellipta		1	1		
Aclidinium	Tudorza genuair		1	1		
Rifaximin	Zaxine		1		1	
Ocriplasmin	Jetrea	1			1	
Trastuzumab emtansine	Kadcyla		1		1	
Galsulfase	Naglazyme	1		1		
Riociguat	Adempas		1		1	

Pasireotide	Signifor	1		1		
Efinaconazole	Jublia		1	1		
Romidepsin	Istodax		1	1		1
Dolutegravir	Tivicay		1	1		
Afatinib	Giotrif		1	1		
Macitentan	Opsumit		1	1		
Aflibercept	Eylea		1	1		
Teriflunomide	Aubagio		1	1		
Simeprevir	Galexos		1		1	
Alogliptin	Nesina		1	1		
Linaclotide	Constella		1	1		
Multicomponent meningococcal B vacine	Bexsero	1		1		
Radium-223 dichlo	Xofigo		1	1		
Sofosbuvir	Sovaldi	1			1	
Umeclidinium and vilanterol	Anoro ellipta		1	1		
Pomalidomide	Pomalyst	1			1	
Lomitapide	Juxtapid		1	1		
Aflibercept	Zaltrap		1	1		
Bosutinibs	Bosulif		1	1		1
Recombinant human coagulation Factor IX, FC fusion	Alprolix		1	1		
Tofacitinib	Xeljanz		1	1		
Tesamorelin	Egrifta		1	1		
Canagliflozin	Invokana		1	1		
Taliglucerase Alfa	Elelyso		1	1		
Eslicarbazepine	Aptiom		1	1		
Antihemophilic factor, FC fusion protein	Eloctate		1	1		
Ledipasvir and sofosbuvir	Harvoni		1		1	
Vortioxetine	Trintellix		1	1		
Simoctocog alfa	Nuwiq		1	1		

Azelastine and fluticasone	Dymista		1	1		
Conjugated estrogens and bazedoxifene acetate	Duavive		1	1		
Apremilast	Otezla		1	1		
Ibrutinib	Imbruvica	1			1	1
Obinutuzumab	Gazyva	1		1		
Siltuximab	Sylvant		1		1	
Dapagliflozin	Forxiga		1	1		
Ritonavir, paritaprevir, ombitasvir, dasabuvir	Holkira Pak		1		1	
Sodium phenylbutyrate	Pheburane		1		1	
Vedolizumab	Entyvio		1	1		
Human papillomavirus 9 valent vaccine, recombinant	Gardasil 9		1	1		
Deferiprone	Ferriprox		1	1		
Secukinumab	Cosentyx		1	1		
Tedizolid	Sivextro		1	1		
Idelalisib	Zydelig		1	1		1
Ceritinib	Zykadia		1	1		1
Ponatinib	Iclusig		1	1		1
Carglumic Acid	Carbaglu	1			1	
Ivermectin	Rosiver		1	1		
Levomilnacipran	Fetzima		1	1		
Pembrolizumab	Keytruda		1	1		1
Naloxegol	Movantik		1	1		
Nintedanib	Ofev		1	1		
Ramucirumab	Cyramza		1	1		
Empagliflozin	Jardiance		1	1		
Mifepristone and Misoprostol	Mifegymiso		1	1		
Daclatasvir	Daklinza		1	1		1

Asfotase Alfa	Strensiq	1	1		1
Teduglutide	Revestive		1	1	
Evolocumab	Repatha		1	1	
Nivolumab	Opdivo	1		1	
Ceftolozane Sulfate and Tazobactam	Zerbaxa		1	1	
Sacubitril, Valsartan	Entresto	1		1	
Dulaglutide	Trulicity		1	1	
Elvitegravir, Cobicistat, Emtricitabine, Tenofovir Alafenamide Hemifumarate	Genvoya		1	1	
Mepolizumab	Nucala		1	1	
Lenvatinib	Lenvima		1	1	
Blinatumomab	Blincyto		1	1	1
Carfilzomib	Kyprolis		1	1	
Elbasvir, Grazoprevir	Zepatier		1	1	
Selexipag	Uptravi		1	1	
Ivacaftor, Lumacaftor	Orkambi		1	1	
Sugammadex	Bridion		1	1	
Cobimetinib	Cotellic		1	1	
Brivaracetam	Brivlera		1	1	
Asunaprevir	Sunvepra		1	1	
Palbociclib	Ibrance		1	1	1
Alirocumab	Praluent		1	1	
Bilastine	Blexten		1	1	
Idarucizumab	Praxbind		1	1	1
Olaparib	Lynparza		1	1	1
Ixekizumab	Taltz		1	1	
Osimertinib	Tagrisso		1	1	1

Sofosbuvir + Velpatasvir	Epclusa		1		1	
Ixazomib	Ninlaro		1		1	
Nitisinone	MDK-Nitisinone	1			1	
Venetoclax	Venclexta		1	1		1
Edoxaban	Lixiana		1	1		
Nitisinone	Nitisinone	1			1	
Daclizumab beta	Zinbryta		1	1		
Nitisinone	Orfadin	1			1	
Ivabradine	Lancora		1	1		
		55	454	379	130	42

***Prescrire evaluations as of February 20, 2018; PMPRB evaluations as of December 31, 2016; Prescrir**

s from Patented Medicine Prices Review Board and/or La

Notice of compliance or notice of compliance with	Small molecule	Biologic	ATC group (second level)
1995-01-24			anti-acne preparation
1995-02-07			all other therapeutic products
1995-02-07			drugs for obstructive airway diseases
1995-03-23			other nervous system
1995-03-29			antibacterials for systemic use
1995-04-24			psycholeptics
1995-04-24			psycholeptics
1995-04-24			psycholeptics
1995-05-12			drugs for acid related disorders
1995-06-02			antibacterials for systemic use
1995-07-19			immunostimulants
1995-07-31			antivirals for systemic use
1995-08-22			antibacterials for systemic use
1995-09-18			anesthetics
1995-09-28			agents acting on the renin-angiotensin system
1995-10-04			contrast media
1995-11-02			endocrine therapy
1995-11-15			drugs used in diabetes
1995-11-15			immunosuppressants
1995-12-06			immunosuppressants
1995-12-08			antivirals for systemic use
1995-12-20			drugs for treatment of bone disease
1996-03-26			antivirals for systemic use
1996-03-29			vaccines
1996-04-25			ophthalmologicals
1996-04-25			all other therapeutic products

1996-05-01	antivirals for systemic use
1996-06-25	other gynecologicals
1996-07-02	antibacterials for systemic use
1996-07-04	antithrombotic agents
1996-08-01	endocrine therapy
1996-08-14	antivirals for systemic use
1996-09-12	antineoplastic agents
1996-09-13	antivirals for systemic use
1996-10-08	drugs used in diabetes
1996-10-28	antibacterials for systemic use
1996-10-28	psycholeptics
1996-11-06	other nervous system
1996-11-20	psycholeptics
1996-12-03	anesthetics
1996-12-23	antineoplastic agents
1996-12-24	anesthetics
1997-02-12	other alimentary tract and metabolism products
1997-02-19	lipid modifying agents
1997-03-06	antiepileptics
1997-03-06	drugs for obstructive airway diseases
1997-03-06	antithrombotic agents
1997-03-21	antihemorrhagics
1997-04-15	antineoplastic agents
1997-05-21	antiemetics and antinauseants
1997-05-21	endocrine therapy
1997-06-11	antihistamines for systemic use
1997-06-16	ophthalmologicals
1997-06-24	pituitary and hypothalamic hormones and analogues
1997-07-02	sex hormones and modulators of the genital system
1997-07-04	antineoplastic agents
1997-08-12	psychoanaleptics
1997-08-19	anti-parkinson drugs

1997-08-27	drugs for treatment of bone disease
1997-09-04	immunostimulants
1997-10-08	anti-parkinson drugs
1997-10-21	drugs for obstructive airway diseases
1997-11-03	agents acting on the renin-angiotensin system
1997-11-14	antibacterials for systemic use
1997-11-24	ophthalmologicals
1997-12-02	psycholeptics
1998-01-29	anti-parkinson drugs
1998-02-05	immunostimulants
1998-02-16	ophthalmologicals
1998-02-18	lipid modifying agents
1998-04-09	antibacterials for systemic use
1998-04-28	analgesics
1998-04-28	psychoanaleptics
1998-06-01	agents acting on the renin-angiotensin system
1998-06-01	urologicals
1998-06-17	drugs for obstructive airway diseases
1998-07-22	antivirals for systemic use
1998-08-11	antivirals for systemic use
1998-08-24	analgesics
1998-08-31	antineoplastic agents
1998-09-04	antivirals for systemic use
1998-10-07	antithrombotic agents
1998-10-23	ophthalmologicals
1998-11-06	sex hormones and modulators of the genital system
1998-11-20	agents acting on the renin-angiotensin system
1998-11-20	urologicals
1998-12-02	vaccines

1998-12-04	antibacterials for systemic use
1998-12-04	antibacterials for systemic use
1998-12-30	preparations for wounds and ulcers
1999-01-25	muscle relaxants
1999-02-02	antivirals for systemic use
1999-02-05	psychoanaleptics
1999-02-12	antihemorrhagics
1999-02-26	psychoanaleptics
1999-03-08	urologicals
1999-03-11	immunostimulants
1999-03-19	antivirals for systemic use
1999-04-06	drugs used in diabetes
1999-04-14	antiinflammaotory and antirheumatic products
1999-05-06	endocrine therapy
1999-05-20	immunostimulants
1999-06-03	antiobesity preparations
1999-06-04	antivirals for systemic use
1999-06-11	antithrombotic agents
1999-07-09	agents acting on the renin-angiotensin system
1999-07-13	antivirals for systemic use
1999-07-16	analgesics
1999-08-13	antineoplastic agents
1999-08-16	agents acting on the renin-angiotensin system
1999-08-18	drugs for treatment of bone disease
1999-08-19	antithrombotic agents
1999-09-17	blood substitutes and perfusion solutions
1999-10-13	vaccines
1999-10-25	antineoplastic agents
1999-10-25	antiinflammaotory and antirheumatic products

1999-11-02			antivirals for systemic use
1999-11-04			immunostimulants
1999-11-08			contrast media
1999-12-10			antibacterials for systemic use
1999-12-23			antivirals for systemic use
2000-01-04		1	antineoplastic agents
2000-03-16	1		immunosuppressants
2000-03-17		1	immunosuppressants
2000-03-21	1		drugs used in diabetes
2000-04-13	1		antiepileptics
2000-04-13	1		psychoanaleptics
2000-05-11	1		psycholeptics
2000-05-31	1		ophthalmologicals
2000-06-30	1		anti-parkinson drugs
2000-08-17	1		endocrine therapy
2000-08-17	1		drugs used in diabetes
2000-08-21	1		drugs for treatment of bone disease
2000-08-30	1		other nervous system
2000-08-31	1		antiinflammaotory and antirheumatic products
2000-09-01		1	immunosuppressants
2000-10-19	1		antibacterials for systemic use
2000-10-20		1	immunostimulants
2000-12-01		1	immunosuppressants
2000-12-11	1		contrast media
2000-12-28	1		antiobesity preparations
2001-01-05	1		immunosuppressants
2001-01-09	1		antibacterials for systemic use
2001-01-11		1	pancreatic hormones
2001-01-17	1		other dermatological preparations
2001-03-01	1		antivirals for systemic use
2001-03-09	1		antivirals for systemic use
2001-04-02	1		antibacterials for systemic use
2001-04-17	1		antianemic preparations

2001-04-30	1		calcium homeostasis
2001-05-07	1		drugs for acid related disorders
2001-05-08	1		anti-parkinson drugs
2001-05-10	1		antiprotozoals
2001-05-18	1		psychoanaleptics
2001-05-29	1		antihistamines for systemic use
2001-06-06		1	immunosuppressants
2001-07-29	1		antimycotics for systemic use
2001-07-31	1		psychoanaleptics
2001-08-17	1		drugs for acid related disorders
2001-09-20	1		antineoplastic agents
2001-10-17		1	antithrombotic agents
2001-11-09	1		ophthalmologicals
2001-11-30	1		antihypertensives
2001-12-18		1	vaccines
2002-01-25	1		drugs used in diabetes
2002-02-13	1		drugs used in diabetes
2002-02-21			urologicals
2002-03-12	1		drugs for constipation
2002-05-01	1		pituitary and hypothalamic hormones and analogues
2002-05-03	1		antivirals for systemic use
2002-05-15		1	immune sera and immunoglobulins
2002-05-24	1		antibiotics and chemotherapeutics for dermatological use
2002-05-24	1		ophthalmologicals
2002-05-24		1	immunosuppressants
2002-05-28		1	antihemorrhagics
2002-05-31		1	immunostimulants
2002-06-13	1		antithrombotic agents
2002-07-08	1		blood substitutes and perfusion solutions
2002-08-02		1	antianemic preparations

2002-08-20	1		sex hormones and modulators of the genital system
2002-10-04	1		antithrombotic agents
2002-10-09	1		antithrombotic agents
2002-11-20	1		drugs for obstructive airway diseases
2002-12-11	1		antiinflammaotory and antirheumatic products
2003-01-31		1	antithrombotic agents
2003-02-18	1		lipid modifying agents
2003-02-21		1	vaccines
2003-03-06	1		antiepileptics
2003-03-18	1		antivirals for systemic use
2003-03-19	1		other dermatological preparations
2003-05-12	1		antibacterials for systemic use
2003-05-12	1		lipid modifying agents
2003-05-28	1		antibacterials for systemic use
2003-07-14	1		antivirals for systemic use
2003-07-22	1		urologicals
2003-08-13		1	immunostimulants
2003-08-13	1		pituitary and hypothalamic hormones and analogues
2003-08-27	1		antivirals for systemic use
2003-09-17	1		urologicals
2003-10-01	1		agents acting on the renin-angiotensin system
2003-10-29		1	all other therapeutic products
2003-12-05	1		antivirals for systemic use
2003-12-17	1		antineoplastic agents
2004-01-23		1	other alimentary tract and metabolism products
2004-02-06		1	other alimentary tract and metabolism products
2004-02-17	1		endocrine therapy

2004-03-09	1		antibacterials for systemic use
2004-03-12		1	immunostimulants
2004-03-17	1		urologicals
2004-03-31	1		contrast media
2004-03-31	1		other alimentary tract and metabolism products
2004-04-16		1	muscle relaxants
2004-05-10		1	immunostimulants
2004-05-11	1		sex hormones and modulators of the genital system
2004-05-21	1		antineoplastic agents
2004-05-31		1	other alimentary tract and metabolism products
2004-06-03		1	calcium homeostasis
2004-08-04	1		calcium homeostasis
2004-08-05	1		analgesics
2004-08-20	1		antimycotics for systemic use
2004-09-03	1		analgesics
2004-09-24		1	immunosuppressants
2004-10-06		1	immunosuppressants
2004-11-18		1	drugs for obstructive airway diseases
2004-12-08	1		psychoanaleptics
2004-12-10	1		antivirals for systemic use
2004-12-10	1		sex hormones and modulators of the genital system
2004-12-24	1		psychoanaleptics
2004-12-24	1		psychoanaleptics
2005-01-27	1		antineoplastic agents
2005-03-31	1		calcium homeostasis
2005-04-22	1		drugs for acid related disorders
2005-05-02	1		ophthalmologicals
2005-05-10		1	therapeutic radiopharmaceuticals
2005-06-03	1		antiepileptics

2005-06-24		1	sex hormones and modulators of the genital system
2005-07-07	1		antineoplastic agents
2005-07-20	1		analgesics
2005-08-05	1		other nervous system
2005-08-23	1		agents acting on the renin-angiotensin system
2005-09-09		1	antineoplastic agents
2005-09-09		1	antineoplastic agents
2005-09-29		1	drugs used in diabetes
2005-10-17		1	pituitary and hypothalamic hormones and analogues
2005-10-24		1	immunosuppressants
2005-11-14	1		urologicals
2005-11-21	1		antivirals for systemic use
2005-11-21	1		antivirals for systemic use
2005-11-30		1	immunosuppressants
2005-12-09		1	all other therapeutic products
2006-01-10	1		urologicals
2006-02-20	1		urologicals
2006-03-10	1		endocrine therapy
2006-04-12		1	drugs used in diabetes
2006-05-26	1		antineoplastic agents
2006-06-16	1		pituitary and hypothalamic hormones and analogues
2006-06-29		1	immunosuppressants
2006-07-10		1	vaccines
2006-07-17	1		antivirals for systemic use
2006-07-28	1		antineoplastic agents
2006-07-28	1		antivirals for systemic use
2006-08-01		1	vaccines
2006-08-14		1	other alimentary tract and metabolism products
2006-08-17	1		anti-parkinson drugs
2006-09-11	1		drugs for obstructive airway diseases

2006-09-14	1		antibacterials for systemic use
2006-09-28		1	immunosuppressants
2006-10-17	1		all other therapeutic products
2006-10-18	1		all other therapeutic products
2006-10-31	1		contrast media
2006-11-28	1		antivirals for systemic use
2007-01-24	1		other nervous system
2007-03-16	1		other nervous system
2007-03-26	1		antineoplastic agents
2007-03-26	1		antimycotics for systemic use
2007-05-22	1		antimycotics for systemic use
2007-05-30	1		antihypertensives
2007-06-13	1		other alimentary tract and metabolism products
2007-06-15	1		antineoplastic agents
2007-06-26		1	ophthalmologicals
2007-08-14	1		drugs for obstructive airway diseases
2007-08-24	1		antiemetics and antinauseants
2007-09-21	1		antivirals for systemic use
2007-09-24	1		antibacterials for systemic use
2007-09-26	1		psycholeptics
2007-11-01	1		psychoanaleptics
2007-11-08		1	cardiac therapy
2007-11-14	1		agents acting on the renin-angiotensin system
2007-11-14	1		antimycotics for systemic use
2007-11-27	1		antivirals for systemic use
2007-11-29	1		psychoanaleptics
2007-12-14	1		drugs used in diabetes
2007-12-21	1		antineoplastic agents
2008-01-17	1		immunosuppressants
2008-03-20	1		antihypertensives
2008-03-27	1		antivirals for systemic use

2008-03-28	1		drugs for constipation
2008-04-03		1	antineoplastic agents
2008-04-17	1		ophthalmologicals
2008-06-10	1		antithrombotic agents
2008-06-26	1		antibacterials for systemic use
2008-07-23	1		psychoanaleptics
2008-09-09	1		antineoplastic agents
2008-09-15	1		antithrombotic agents
2008-10-28	1		agents acting on the renin-angiotensin system
2008-12-11		1	vaccines
2008-12-12		1	immunosuppressants
2008-12-23	1		ophthalmologicals
2009-01-28		1	immunosuppressants
2009-02-04	1		psychoanaleptics
2009-02-19	1		psychoanaleptics
2009-02-19		1	antihemorrhagics
2009-02-26	1		antineoplastic agents
2009-02-26	1		diuretics
2009-04-01	1		antivirals for systemic use
2009-04-07		1	immunosuppressants
2009-05-15	1		antineoplastic agents
2009-06-11	1		antineoplastic agents
2009-07-09	1		psycholeptics
2009-07-16	1		antineoplastic agents
2009-08-11	1		cardiac therapy
2009-08-12		1	immunosuppressants
2009-09-02	1		antibacterials for systemic use
2009-09-11	1		antibacterials for systemic use
2009-09-14	1		drugs used in diabetes
2009-10-23	1		ophthalmologicals
2009-10-23	1		antineoplastic agents
2009-10-29		1	vaccines
2009-11-13	1		antineoplastic agents
2009-11-16	1		endocrine therapy

2009-12-09	1		psycholeptics
2009-12-14	1		antineoplastic agents
2009-12-15		1	antihemorrhagics
2009-12-21		1	vaccines
2010-01-14	1		contrast media
2010-02-03		1	vaccines
2010-02-26		1	immunosuppressants
2010-04-16	1		antithrombotic agents
2010-04-30		1	immunosuppressants
2010-04-30	1		other alimentary tract and metabolism products
2010-05-13	1		antineoplastic agents
2010-05-21		1	drugs used in diabetes
2010-05-21		1	vaccines
2010-05-27	1		antineoplastic agents
2010-06-30	1		psycholeptics
2010-07-07	1		all other therapeutic products
2010-07-22	1		drugs for acid related disorders
2010-08-06		1	drugs for treatment of bone disease
2010-09-22	1		antigout preparations
2010-09-30	1		antiepileptics
2010-10-01		1	other alimentary tract and metabolism products
2010-11-23	1		drugs for obstructive airway diseases
2010-12-02	1		analgesics
2011-01-11	1		urologicals
2011-01-12	1		antihemorrhagics
2011-01-13	1		drugs used in diabetes
2011-03-09	1		immunosuppressants
2011-05-30	1		antithrombotic agents
2011-06-16	1		antineoplastic agents
2011-06-22	1		antiepileptics
2011-07-06		1	immunosuppressants

2011-07-21	1		antivirals for systemic use
2011-07-25	1		diuretics
2011-07-27	1		endocrine therapy
2011-07-28	1		drugs used in diabetes
2011-07-29	1		antivirals for systemic use
2011-08-10	1		immunostimulants
2011-08-16	1		antivirals for systemic use
2011-09-22	1		lipid modifying agents
2011-10-07	1		psycholeptics
2011-10-12	1		sex hormones and modulators of the genital system
2011-12-06	1		drugs for obstructive airway diseases
2011-12-07	1		drugs for constipation
2011-12-08	1		immunostimulants
2011-12-14	1		antineoplastic agents
2011-12-16	1		antithrombotic agents
2012-01-12	1		antineoplastic agents
2012-02-01		1	antineoplastic agents
2012-02-09	1		urologicals
2012-02-10	1		other nervous system
2012-02-15			antineoplastic agents
2012-03-08	1		agents acting on the renin-angiotensin system
2012-03-09		1	antineoplastic agents
2012-03-14	1		antiemetics and antinauseants
2012-04-25	1		antineoplastic agents
2012-06-07	1		antidiarrheals, intestinal antiinflammatory/antiinfective agents
2012-06-13	1		psycholeptics
2012-06-19	1		antineoplastic agents
2012-07-05		1	other drugs for disorders of the musculo-skeletal system
2012-07-12	1		antineoplastic agents
2012-07-19		1	antihemorrhagics
2012-08-24	1		antineoplastic agents
2012-10-01			immunosuppressants

2012-11-26	1		antivirals for systemic use
2012-11-26	1		other respiratory system products
2012-12-21	1		antiepileptics
2012-12-21	1		beta blocking agents
2013-01-30	1		antibiotics and chemotherapeutics for dermatological use
2013-02-01		1	antineoplastic agents
2013-03-05		1	vaccines
2013-03-06	1		urologicals
2013-03-11	1		antineoplastic agents
2013-03-21	1		anti-parkinson drugs
2013-04-03	1		other nervous system
2013-04-04	1		antiepileptics
2013-04-12		1	antineoplastic agents
2013-05-29	1		endocrine therapy
2013-06-24	1		sex hormones and modulators of the genital system
2013-07-12	1		antineoplastic agents
2013-07-16	1		antineoplastic agents
2013-07-18	1		antineoplastic agents
2013-07-23	1		drugs for obstructive airway diseases
2013-07-29	1		drugs for obstructive airway diseases
2013-08-13	1		antidiarrheals, intestinal antiinflammatory/antiinfective agents
2013-08-13		1	ophthalmologicals
2013-09-11		1	antineoplastic agents
2013-09-16		1	other alimentary tract and metabolism products
2013-09-19	1		antihypertensives

2013-09-23	1		pituitary and hypothalamic hormones and analogues
2013-10-02	1		drugs used in diabetes
2013-10-16	1		antineoplastic agents
2013-10-31	1		antivirals for systemic use
2013-11-01	1		antineoplastic agents
2013-11-06	1		antihypertensives
2013-11-08		1	antineoplastic agents
2013-11-14	1		immunosuppressants
2013-11-18	1		antivirals for systemic use
2013-11-27	1		drugs used in diabetes
2013-12-02	1		drugs for constipation
2013-12-06		1	vaccines
2013-12-12		1	therapeutic radiopharmaceuticals
2013-12-13	1		antivirals for systemic use
2013-12-23	1		drugs for obstructive airway diseases
2014-01-20	1		immunosuppressants
2014-02-04	1		lipid modifying agents
2014-02-12		1	antineoplastic agents
2014-03-14	1		antineoplastic agents
2014-03-20		1	antihemmorhagics
2014-04-17	1		immunosuppressants
2014-04-29	1		pituitary and hypothalamic hormones and analogues
2014-05-23	1		drugs used in diabetes
2014-05-29		1	other alimentary tract and metabolism products
2014-07-08	1		antiepileptics
2014-08-22		1	antihemmorhagics
2014-10-15	1		antivirals for systemic use
2014-10-22	1		psychoanaleptics
2014-10-23		1	antihemmorhagics

2014-10-23	1		nasal preparations
2014-10-23	1		sex hormones and modulators of the genital system
2014-11-12	1		immunosuppressants
2014-11-17	1		antineoplastic agents
2014-11-25		1	antineoplastic agents
2014-12-03		1	immunosuppressants
2014-12-12	1		drugs used in diabetes
2014-12-22	1		antivirals for systemic use
2015-01-26	1		other alimentary tract and metabolism products
2015-01-29		1	immunosuppressants
2015-02-05		1	vaccines
2015-02-13	1		all other therapeutic products
2015-02-27		1	immunosuppressants
2015-03-17	1		antibacterials for systemic use
2015-03-27	1		antineoplastic agents
2015-03-27	1		antineoplastic agents
2015-04-02	1		antineoplastic agents
2015-04-10	1		other alimentary tract and metabolism products
2015-04-22	1		antihelmintics
2015-05-08	1		psychoanaleptics
2015-05-19		1	antineoplastic agents
2015-06-02	1		drugs for constipation
2015-06-25	1		antineoplastic agents
2015-07-16		1	antineoplastic agents
2015-07-23	1		drugs used in diabetes
2015-07-29	1		sex hormones and modulators of the genital system
2015-08-13	1		antivirals for systemic use

2015-08-14		1	other alimentary tract and metabolism products
2015-09-04		1	other alimentary tract and metabolism products
2015-09-10		1	lipid modifying agents
2015-09-25		1	antineoplastic agents
2015-09-30	1		antibacterials for systemic use
2015-10-02	1		agents acting on the renin-angiotensin system
2015-11-10		1	drugs used in diabetes
2015-11-27	1		antivirals for systemic use
2015-12-03		1	drugs for obstructive airway diseases
2015-12-22	1		antineoplastic agents
2015-12-22		1	antineoplastic agents
2016-01-15	1		antineoplastic agents
2016-01-19	1		antivirals for systemic use
2016-01-20	1		antithrombotic agents
2016-01-26	1		pther respiratory system products
2016-02-05	1		all other therapeutic products
2016-02-22	1		antineoplastic agents
2016-03-09	1		antiepileptics
2016-03-09	1		antivirals for systemic use
2016-03-16	1		antineoplastic agents
2016-04-11		1	lipid modifying agents
2016-04-21	1		antihistamines for systemic use
2016-04-29		1	all other therapeutic products
2016-04-29	1		antineoplastic agents
2016-05-25		1	immunosuppressants
2016-07-05	1		antineoplastic agents

2016-07-11	1		antivirals for systemic use
2016-08-04	1		antineoplastic agents
2016-09-20	1		other alimentary tract and metabolism products
2016-09-30	1		antineoplastic agents
2016-11-04	1		antithrombotic agents
2016-11-04	1		other alimentary tract and metabolism products
2016-12-08		1	immunosuppressants
2016-12-13	1		other alimentary tract and metabolism products
2016-12-23	1		cardiac therapy
	286	99	

e ratings - offers an advantage, possibly helpful, nothing new,

Supplementary Table 2: All drugs approved between 1995-2016 that did not receive th

Generic name	Brand name	Review status	
		Standard	Priority
Albutrepenonacog Alfa	Idelvion	1	
Antihemophilic Factor (Recombinant) Porcine Sequence	Obizur	1	
Antihemophilic Factor	Adynovate	1	
Bepotastine	Bepreve	1	
Butenafine	Dr. Scholl's athlete's foot cream	1	
Cefdinir	Omnicef	1	
Ceftibuten	Cedax	1	
Doxycycline	Efracea	1	
Ezogabine	Potiga	1	
Ferumoxytol	Feraheme	1	
Fleroxacin	Megalone	1	
Fosfomycin	Monurol	1	
Fosphenytoin	Cerebyx injection	1	
Levobupivacaine	Chirocaine	1	
Lonoctocog Alfa	Afstyla	1	
Lumiracoxib	Prexige	1	
Methoxy Polyethylene glycol-epoetin beta	Mircera	1	
Oxiconazole	Oxizole	1	
Praziquantel	Biltricide	1	
Remifentanil	Ultiva injection	1	
Retapamulin	Altargo	1	
Rupatadine	Rupall	1	
Sevelamer	Renagel	1	
Telavancin	Vibativ	1	
Trandolapril	Odrik	1	
Turoctocog alfa	Zonovate	1	

Fomepizole	Antizol		1
Iron dextran	Dexferrum		1
Tegafur/uracil and leucovorin calcium	Orzel	1	
Aminolevulinic acid	Levulan	1	
Losoxantrone	Bianda	1	
Pegaspargase	Oncaspar	1	
Valrubicin	Valstar		1
Nelarabine	Atriance		
Alectinib	Alecensaro		
Elotuzumab	Empliciti		1
Daratumumab	Darzalex		
Anagrelide as hydrochloride	Agrylin		1
Dexfenfluramine	Redux	1	
Halofantrine	Halfan	1	
Tazarotene	Tazorac Gel	1	
Vorapaxar	Zontivity	1	
Reviparin	Clivarine	1	
Nadroparin	Fraxiparine	1	
Argatroban	Argatroban		1
Saquinavir	Saquinavir		1
Carvedilol	Dilatrend	1	
Carvedilol	Kredex	1	
Clevidipine	Cleviprex	1	
Ibutilide	Corvert injection	1	
Mangafodipir	Teslascan	1	
Sulfur Hexafluoride	Sonovue	1	
Gadoterate Meglumine	Dotarem	1	
Ferumoxsil	Gastromark	1	
Palmitic acid/Galactose	Levovist	1	
Gadolinium (III)	Gadolite	1	
Ioxilan	Oxilan	1	
Rimexolone	Vexol	1	

Difluprednate	Durezol	1	
Thyrotropin	Thyrogen	1	
Methacholine	Methacoline	1	
Sulesomab	Leukoscan	1	
Kit for preparation of indium in 111 imciromab pentetate	Myoscint	1	
Arcitumomab	CEA-Scan	1	
Bicisate	OncoScint	1	
Pantoprazole	Panto-Byk	1	
Lubiprostone	Amitiza	1	
Olodaterol	Striverdi respimat	1	
Reslizumab	Cinqair	1	
Tiludronate	Skelid	1	
Albiglutide	Eperzan	1	
Miglitol	Glyset	1	
Toremifene	Fareston	1	
Botulinium antitoxin	BAT	1	
Cytomegalovirus immune globulin	Cytogam	1	
Peginterferon Beta-1A	Plegridy	1	
F-Fluorodeoxyglucose	Cantrace		1
Rubidium chloride rb 82	Ruby-fill		1
Troglitazone	Rezulin		1
Respiratory syncytial virus immune globulin	Respigam		1
Molgramostim	Leucomax		1
Anti-thymocyte globulin	Thymoglobulin	1	
Infliximab	Remicade		1
Cisatracurium	Nimbex injection	1	
Unoprostone isopropyl	Rescula	1	
Tafluprost	Saflutan	1	
Bromfenac	Prolensa	1	
Olopatadine	Patanol	1	
Human C1 esterase inhibitor	Berinert	1	

Tetrabenazine	Nitoman	1	
Finafloxacin	Xtoro	1	
Sermorelin	Geref	1	
Dextromethylphenidate	Attenade	1	
Vilazodone	Viibryd	1	
Choriogonadotropin Alfa	Ovidrel	1	
Follitropin alpha	Gonal-F	1	
Amlexanox	Apthera	1	
Lexidronam	Quadramet	1	
Zucapsaicin	Civanex (Zuacta)	1	
Rotavirus vaccine	Rotarix	1	
Influenza vaccine	Flumist	1	
Haemagglutinin-Strain A	Arepranrix H5N1	1	
Polidocanol	Varithena	1	
Glycerol	Ravicti		1
Elosulfase Alfa	Vimizim		1
Levocarnitine	Carnitor		1
Alitretinoin	Panretin		1
Nitric oxide	Inomax		1
Yttrium-90	Yttrium-90		1
Tositumomab	Bexxar		1
Remestemcel-L	Prochymal		1
Measles virus	Moru-Viraten		1
Diptheria, tetanus &	Infanrix		1
Lipoprotein-OspA	Lymerix		1

ıerapeutic assessments

Notice of compliance with conditions	Notice of compliance or Notice of compliance with conditions date	Small molecule	Biologic	ATC group (second level)
	1/26/2016		1	antihemorrhagics
	10/14/2015		1	antihemorrhagics
	11/17/2016		1	antihemorrhagics
	7/27/2016	1		antihistamines for systemic use
	4/15/1997			antifungals for dermatological use
	2/5/1999			antibacterials for systemic use
	5/9/1995			antibacterials for systemic use
	11/14/2011	1		antibacterials for systemic use
	10/8/2012	1		antiepileptics
	12/8/2011	1		antianemic preparations
	8/21/1996			antibacterials for systemic use
	4/12/1999			antibacterials for systemic use
	3/20/1997			antiepileptics
	3/20/2002	1		anesthetics
	12/12/2016		1	antihemorrhagics
	11/2/2006	1		antiinflammatory and antirheumatic
	3/31/2008		1	antianemic preparations
	8/8/1997			antifungals for dermatological use
	3/7/1997			anthelminics
	12/24/1996			anesthetics
	3/19/2008	1		antibiotics and chemotherapeutics for dermatological use
	7/20/2016	1		antihistamines for systemic use
	2/24/2000	1		all other therapeutic products
	9/29/2009	1		antibacterials for systemic use
	5/15/1997			agents acting on the renin-angiotensin system
	12/8/2014		1	antihemorrhagics

	11/30/2000	1		all other therapeutic products
	1/9/1996			antianemic preparations
	4/6/2001	1		antineoplastic agents
	6/20/2001	1		antineoplastic agents
	2/19/1995			antineoplastic agents
	11/19/1997			antineoplastic agents
	7/4/2000	1		antineoplastic agents
1	9/22/2007	1		antineoplastic agents
1	9/29/2016	1		antineoplastic agents
	6/21/2016		1	antineoplastic agents
1	6/29/2016		1	antineoplastic agents
	11/19/1997			antineoplastic agents
	7/29/1996			antiobesity preparations
	3/29/1995			antiprotozoals
	2/25/1997			antipsoriatics
	5/13/2016	1		antithrombotic agents
	9/10/1996			antithrombotic agents
	11/27/1997			antithrombotic agents
	6/4/2001	1		antithrombotic agents
	3/22/1996			antivirals for systemic use
	2/27/1995			beta blocking agents
	2/27/1995			beta blocking agents
	4/15/2011	1		calcium channel blockers
	7/14/2000	1		cardiac therapy
	2/9/2000	1		contrast media
	2/12/2004	1		contrast media
	11/25/2016	1		contrast media
	3/15/1996			contrast media
	7/31/1996			contrast media
	4/8/1998			contrast media
	10/5/1999			contrast media
	1/17/1996			corticosteroids for systemic use

11/4/2013	1		corticosteroids, dermatological preparations
5/31/2002		1	diagnostic agents
2/25/1999			diagnostic agents
1/17/2005		1	diagnotic radiopharmaceuticals
7/2/1997			diagnotic radiopharmaceuticals
9/16/1997			diagnotic radiopharmaceuticals
1/16/1998			diagnotic radiopharmaceuticals
7/5/1996			drugs for acid related disorders
10/14/2015	1		drugs for constipation
6/11/2013	1		drugs for obstructive airway diseases
7/20/2016		1	drugs for obstructive airway diseases
2/6/1997			drugs for treatment of bone diseases
7/15/2015		1	drugs used in diabetes
7/22/1998			drugs used in diabetes
12/14/1998			endocrine therapy
12/8/2016		1	immune sera and immunoglobulins
8/1/1997			immune sera and immunoglobulins
8/10/2015		1	immunostimulants
7/27/2006		1	diagnotic radiopharmaceuticals
9/20/2011		1	diagnotic radiopharmaceuticals
5/9/1997			drugs used in diabetes
8/20/1997			immune sera and immunoglobulins
3/10/1997			immunostimulants
11/20/2002		1	immunosuppressants
9/27/2001		1	immunosuppressants
12/18/1996			muscle relaxants
4/3/2002	1		ophthalmologicals
5/26/2014	1		ophthalmologicals
3/26/2015	1		ophthalmologicals
9/16/1997			ophthalmologicals
5/31/2010		1	other hematological agents

12/29/1995			other nervous system drugs
3/11/2016	1		otologicals
6/8/1995			pituitary and hypothalamic hormones and analogues
8/12/2003	1		psychoanaleptics
7/16/2015	1		psychoanaleptics
12/16/2004		1	sex hormones and modulators of the genital system
6/6/1997			sex hormones and modulators of the
12/11/2000	1		stomatological preparations
6/22/1998			therapeutic radiopharmaceuticals
7/15/2010	1		topical products for joint and muscular pain
10/9/2007		1	vaccines
6/22/2010		1	vaccines
2/13/2013		1	vaccines
8/4/2015	1		vasoprotectives
3/16/2016	1		other alimentary tract and
7/2/2014		1	other alimentary tract and
1/19/1995			other alimentary tract and metabolism products
6/11/1999			other dermatological preparations
9/23/2005	1		other respiratory system products
12/2/2004		1	therapeutic radiopharmaceuticals
8/18/2005		1	therapeutic radiopharmaceuticals
5/17/2012		1	unassigned
2/26/1996			vaccines
12/17/1996			vaccines
12/2/1998			vaccines

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Location in study
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Ttile, page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Structured summary, pages 2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Introduction, page 5
Objectives	3	State specific objectives, including any prespecified hypotheses	Introduction, page 6
Methods			
Study design	4	Present key elements of study design early in the paper	Methods, pages 6-8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Methods, pages 6-8, 10
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	Methods, pages 6, 7
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Methods, pages 8-10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Methods, pages 7-10
Bias	9	Describe any efforts to address potential sources of bias	Not relevant
Study size	10	Explain how the study size was arrived at	Not relevant
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Not relevant
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Methods, page 10
		(*b*) Describe any methods used to examine subgroups and interactions	Methods, pages 9, 10

		(*c*) Explain how missing data were addressed	Not relevant
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	Not relevant
		(*e*) Describe any sensitivity analyses	Not relevant
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Results, pages 10-12
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	Not relevant
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Not relevant
		(b) Indicate number of participants with missing data for each variable of interest	Results, page 13
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	Not relevant
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	Results, pages 11-15
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	Not relevant
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not relevant
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Not relevant
Discussion			
Key results	18	Summarise key results with reference to study objectives	Discussion, page 16
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Limitations, page 19
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Conclusion, page 19

Generalisability	21	Discuss the generalisability (external validity) of the study results	Not relevant
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 20

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Health Canada's use of expedited review pathways and therapeutic innovation, 1995-2016: cross sectional analysis

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Health Canada's use of expedited review pathways and therapeutic innovation, 1995-2016: cross sectional analysis

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Word count:

3030

Structured summary

Objectives

This study examines the use of expedited approval pathways by Health Canada over the period 1995 to 2016 inclusive and the relationship between the use of these pathways and the therapeutic gain offered by new products.

Design

Cross sectional study.

Data sources

Therapeutic Products Directorate, Biologics and Genetic Therapies Directorate, Notice of Compliance database, Notice of Compliance with conditions web site, Patented Medicine Prices Review Board, La revue Prescrire, World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) classification system.

Interventions

None

Primary and secondary outcomes

Percent of new drugs evaluated by Health Canada that went through an expedited pathway between 1995 and 2016 inclusive. Kappa values comparing the review status to assessments of therapeutic value for individual drugs.

Results

Of 623 drugs approved by Health Canada between 1995 and 2016, 438 (70.3%) drugs went through the standard pathway, 185 (29.7%) an expedited pathway. Therapeutic evaluations were available for 509 drugs. Health Canada used an expedited approval pathway for 159 of the 509 drugs whereas only 55 were judged to be therapeutically innovative. Forty-two of the 55 therapeutically innovative drugs received an expedited review and 13 received a standard review. The Kappa value for the entire period for all 509 drugs was 0.276 (95% CI 0.194, 0.359) indicating "fair" agreement between Health Canada's use of expedited pathways and independent evaluations of therapeutic innovation.

Conclusion

Health Canada's use of expedited approvals was stable over the entire time period. Its ability to predict which drugs will offer a major therapeutic gain is poor. The findings in this study should provoke a discussion about whether Health Canada should continue to use these pathways and if so how their use can be improved.

Article Summary

Strengths and limitations of this study

- Cross sectional analysis of the use of expedited approval pathways by Health Canada over an extended period of time.
- Comparison of use of expedited approval pathways to independent assessment of therapeutic evaluation.
- Analysis of approvals and therapeutic value of therapeutic subgroups.
- Twenty percent of new drugs approved did not have therapeutic evaluations.

- **Acknowledgements**
- None

- **Competing Interests**
- In 2015-2017, Joel Lexchin received payment from two non-profit organizations for being a consultant on a project looking at indication-based prescribing and a second looking at which drugs should be distributed free of charge by general practitioners. In 2015, he received payment from a for-profit organization for being on a panel that discussed expanding drug insurance in Canada. He is on the Foundation Board of Health Action International.

- **Funding**
- This research received no specific grant from any funding agency in the public, commercial or not-for profit sectors.

- **Data sharing statement**
- Full data that was extracted is available from the online data repository Dryad http://datadryad.org with the DOI: doi:10.5061/dryad.0bf6000.

- **Contributorship statement**
- JL came up with the idea for this study, gathered and analyzed the data and wrote the manuscript.

Introduction

In order to obtain authorization to market a new active substance (NAS - a molecule never marketed before in Canada in any form) in Canada, companies typically file a New Drug Submission (NDS) which includes preclinical and clinical scientific information about the product's safety, efficacy and quality and information about its claimed therapeutic value, conditions for use and side effects [1]. Health Canada then has a 300-day period to evaluate this information and make a decision about whether to allow the product to be sold, i.e., whether to issue a Notice of Compliance (NOC).

In an effort to ensure that promising therapies for serious, life-threatening or debilitating illnesses reach Canadians in a timely manner, Health Canada has developed two other pathways for approving NAS. These are described in detail elsewhere [2], but briefly, the first of these is a priority review that involves the company submitting a complete NDS but with a review period of 180 days [3]. The second is the Notice of Compliance with conditions (NOC/c) [4] whereby Health Canada will give a conditional approval based on limited evidence – Phase II clinical trials or trials with only surrogate markers. In return for NOC/c status, companies commit to further studies that definitively establish efficacy and submit the results of these to Health Canada. A failure to complete these studies or negative results from them could lead to the marketing authorization being cancelled.

Lexchin has examined how closely Health Canada's use of the two pathways (priority review and NOC/c, hereafter collectively termed expedited review pathways) corresponds to independent assessments of the therapeutic innovation of drugs at the level of individual drugs. For the period 1997-2012, the Kappa value was 0.334 (95% CI 0.220, 0.447) or fair [5].

This current study is a further and more detailed look at how Health Canada uses its expedited review pathways, by extending previous work in a number of ways. First it covers a wider time period – 1995 to 2016, inclusive. Second, it looks at the use of both of the expedited review pathways over this entire time period for the entire sample of drugs as well as subgroups – small molecule drugs, biologics, and therapies for serious diseases. Third, it calculates the Kappa values for the entire sample of drugs as well as the subgroups listed above. These subgroups were chosen because small molecules and biologics have fundamentally different characteristics and these may influence a decision to use an expedited review pathway and how accurately Health Canada can predict their therapeutic value. Similarly, when the treatment is for serious medical conditions, Health Canada may be more willing to use an expedited review pathway and may be more likely to believe that the new product will provide a significant therapeutic benefit.

Methods

Data sources

All NAS approved from 1995 to 2016 inclusive were documented using the annual reports from the Therapeutic Products and the Biologics and Genetic Therapies Directorates that are in charge of reviewing applications for new small molecule drugs and biologics and vaccines, respectively. (Reports are available by directly contacting the directorates at publications@hc-sc.gc.ca.) A starting year of 1995 was selected as there are no annual reports from Health Canada prior to that year. Generic and brand names along with the specific approval pathway – standard, priority, NOC/c (only from 1998 onwards) – and whether the product was a small molecule drug or biologic (information available only from 2000 onwards) were manually extracted from the annual reports by the author.

Not all of the drugs with a NOC/c are documented in the annual reports and they were supplemented using four additional sources: articles by Lexchin [6] and Law [7], the Notice of Compliance database (http://webprod5.hc-sc.gc.ca/noc-ac/index-eng.jsp) and the Notice of Compliance with conditions web site (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/conditions/index-eng.php). Only NAS approved for the first time under a NOC/c were considered. Drugs can receive both a priority and NOC/c review and in this case they were only counted as receiving a priority review.

Assessment of therapeutic innovation

The therapeutic value of drugs was assessed using the ratings from the annual reports of the Canadian Patented Medicine Prices Review Board (PMPRB) (http://www.pmprb-cepmb.gc.ca/english/View.asp?x=91) and Prescrire International, the English language translation of the French drug bulletin La revue Prescrire [8]. The processes that these two organizations use in arriving at their decisions about therapeutic innovation have been previously described [5]. For the purpose of this study, products that the PMPRB deemed breakthrough and substantial improvement were termed "innovative" and products in other categories were termed "not innovative" (category 3 = moderate, little or no improvement over existing medicines prior to 2010; slight or no improvement, moderate improvement – primary and moderate improvement – secondary from 2010 onward). Prescrire uses seven categories to rate therapeutic innovation. The first two, bravo (major therapeutic innovation in an area where previously no treatment was available); a real advance (important therapeutic innovation but has limitations) were defined as a significant therapeutic innovation and the other Prescrire categories (except judgment reserved) were defined as no therapeutic advance.

If both the PMPRB and Prescrire evaluated the drug and the ratings were discordant, i.e., one said it was not innovative and one said it was, the drug was still considered innovative. Table 1 shows that there is substantial agreement among the definitions used by Health Canada, the PMPRB and Prescrire in assessing therapeutic innovation. Ratings were current for PMPRB as of December 31, 2016 (the annual report for 2017 was not available at the time of writing) and for Prescrire as of February 20, 2018.

Table 1: Criteria used by Health Canada in determination of priority review or Notice of Compliance with conditions pathway and by Human Drug Advisory Panel and Prescrire in determining innovation status

Health Canada – criteria for priority review and NOC/c* pathway	**Human Drug Advisory Panel of Patented Medicine Prices Review Board – criteria for breakthrough and substantial improvement**	**Prescrire – criteria for bravo and a real advance**
Priority review: A serious, life-threatening or severely debilitating illness or condition for which there is substantial evidence of clinical effectiveness that the drug provides: effective treatment, prevention or diagnosis of a disease or condition for which no drug is presently marketed in Canada	Breakthrough = first drug product to treat effectively a particular illness	Bravo = major therapeutic innovation in an area where previously no treatment was available
Priority review: A serious, life-threatening or severely debilitating illness or condition for which there is substantial evidence of clinical effectiveness that the drug provides: significant increase in efficacy and/or significant decrease in risk such that the overall benefit/risk profile is improved over existing therapies	Substantial improvement = provides a substantial improvement over existing drug products	A real advance = product is an important therapeutic innovation but has certain limitations

NOC/c pathway: Provides patients suffering from serious, life threatening or severely debilitating diseases or conditions with earlier access to promising new drugs		

Adapted from: [9]
*Notice of Compliance with conditions

Data analysis

The number and percent of drugs approved through the standard, priority and NOC/c pathways were calculated for each year and for the 22-year period.

Kappa values were used to compare the review status from Health Canada to the assessments for the same drug from the PMPRB and/or Prescrire for each year and for the 22-year period. Drugs approved through the priority review and NOC/c pathways were analyzed together as a single group. Kappa scores measure whether there is more or less agreement between different evaluations than would be expected by chance. Levels of agreement were graded in accordance with the recommendations of Landis and Koch where < 0 indicates no agreement, 0 – 0.20 slight agreement, 0.21 – 0.40 fair agreement, 0.41 – 0.60 moderate agreement, 0.61 – 0.80 substantial agreement, and 0.81–1.0 almost perfect agreement [10].

Subgroup analyses

The number and percent of small molecule drugs and biologics approved through the standard, priority and NOC/c pathways were calculate and compared using the Chi-square statistic. Similarly, the Kappa values were calculated separately for small molecule drugs and biologics.

All drugs were categorized using the second level of the World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) classification system [11]. Drugs in three therapeutic groups – antineoplastic agents (L01), antivirals for systemic use (J05) and immunosuppressants (L04) – were chosen for subgroup analyses because they are primarily used for serious life-threatening diseases and because there are sufficient numbers in each group to allow for statistical analyses. The number and percent of each subgroup that received an expedited review was calculated as were the Kappa values on a drug-by-drug basis and for drugs in the "all other therapeutic groups". Distribution of approval pathways in the subgroups individually and for the three subgroups combined versus all other therapeutic groups was compared using the Chi-square statistic. Calculations were done using Excel 2016 for Macintosh (Microsoft) and Prism 7.0 (GraphPad Software).

Patient and public involvement

No patients were involved in any aspect of this study.

Ethics

No patients were involved in this study and only publicly available data was gathered. Therefore, ethics approval was not required.

Results

Review status

From January 1, 1995 to December 31, 2016 Health Canada approved a total of 623 NAS. Of these, 438 (70.3%) went through the standard pathway, 152 (24.4%) the priority pathway and 33 (5.3%) received a NOC/c. Almost 30 percent (29.7%) went through the expedited review pathways over the entire period, varying from a low of 9.1% in 2010 to a high of 47.8% in 2006 (Table 2). (Health Canada used both a priority and NOC/c approval for 11 drugs, data

not shown.) Figure 1 shows that there is no trend to using expedited review pathways more liberally or more conservatively over the time period. (Supplementary Tables 1 & 2, drugs with and without therapeutic evaluations, respectively, give all of the data extracted for the 623 drugs in question.)

Table 2: Review status of new active substances approved 1995-2016

Year	Number of new active substances approved	Number (%) with standard review	Number (%) with priority review	Number (%) with NOC/c* review	Number (%) with any expedited pathway review
1995	30	26 (86.7)	4 (13.3)	--	4 (13.3)
1996	33	24 (72.7)	9 (27.3)	--	9 (27.3)
1997	42	34 (81.0)	8 (19.0)	--	8 (19.0)
1998	30	26 (86.7)	2 (6.7)	2 (6.7)	4 (13.3)
1999	36	24 (66.7)	12 (33.3)	0 (0)	12 (33.3)
2000	26	15 (57.7)	11 (42.3)	0 (0)	11 (42.3)
2001	27	17 (63.0)	9 (33.3)	1 (3.7)	10 (37.0)
2002	24	20 (83.3)	4 (16.7)	0 (0)	4 (16.7)
2003	20	12 (60.0)	8 (40.0)	0 (0)	8 (40.0)
2004	29	19 (65.5)	9 (31.0)	1 (3.4)	10 (34.5)
2005	24	13 (54.2)	10 (41.7)	1 (4.2)	11 (45.8)
2006	23	12 (52.2)	9 (39.1)	2 (8.7)	11 (47.8)
2007	24	14 (58.3)	7 (29.2)	3 (12.5)	10 (41.7)
2008	17	11 (64.7)	2 (11.8)	4 (23.5)	6 (35.3)
2009	27	21 (77.8)	6 (22.2)	0 (0)	6 (22.2)
2010	22	20 (90.9)	2 (9.1)	0 (0)	2 (9.1)
2011	27	21 (77.8)	6 (22.2)	0 (0)	6 (22.2)
2012	23	16 (69.6)	5 (21.7)	2 (8.7)	7 (30.4)
2013	39	28 (71.8)	9 (23.1)	2 (5.1)	11 (28.2)
2014	25	18 (72.0)	6 (24.0)	1 (4.0)	7 (28.0)
2015	37	25 (67.6)	5 (13.5)	7 (18.9)	12 (32.4)
2016	38	21 (55.3)	10 (26.3)	7 (18.4)	17 (44.7)
Total	623	438 (70.3)	152 (24.4)	33 (5.3)	185 (29.7)

*Notice of Compliance with conditions
†Patented Medicine Prices Review Board

There were 126 biologics approved versus 323 small molecules (data only available from 2000 onward). There was no difference in the distribution of the approval pathways (p = 0.4867) (Table 3). There were 81 approvals for antineoplastic agents, 47 for antivirals for systemic use, 36 for immunosuppressants and 365 for drugs in the "all other 68 therapeutic groups" (Supplementary Table 1). The distribution of approval pathways was significantly different for the three subgroups (p = 0.0018) and for the three subgroups combined versus "all other therapeutic groups" (p < 0.00001) (Table 3).

Table 3: Subgroup comparison of review pathways

Subgroup	Standard	Priority	Notice of compliance with conditions	Total
Small molecules	129	72	22	323
Biologics	73	45	8	126
Antineoplastic agents	34	26	21	81
Antivirals for systemic use	16	26	5	47
Immunosuppressants	22	13	1	36
All other 68 therapeutic groups	365	89	5	459

Small molecules vs. biologics: chi-square = 1.4402 (p = 0.4867)
Antineoplastics vs. antivirals vs. immunosuppressants: chi-square = 17.1978 (p = 0.0018)
Antineoplastics + antivirals + immunosuppressants vs. all other therapeutic groups: chi-square = 97.4874 (p < 0.00001)

Therapeutic value

Out of the 623 NAS, 509 (81.7%) were evaluated for their therapeutic innovation either by the PMPRB and/or Prescrire. Health Canada used an expedited review pathway for 159 of the 509 drugs whereas only 55 were judged to be therapeutically innovative by one or both of the independent reviews. Forty-two of the 55 drugs that were therapeutic innovations received an expedited review, 13 received a standard review and 117 (159 – 42) that were not therapeutic innovations also received an expedited review (Table 4). The Kappa value for the entire

period for all 509 drugs was 0.276 (95% CI 0.194, 0.359) or fair. Figure 2 presents the Kappa values for each year which generally ranged from 0 (slight) to 0.4 (fair).

Table 4: Number of new active substances with an expedited review and therapeutically innovative rating

Year	Number (%) of NAS* with a therapeutic assessment from Patented Medicine Prices Review Board and/or Prescrire	Number of NAS with an expedited review	Number of NAS rated as therapeutic innovation by either Patented Medicine Prices Review Board and/or Prescrire	Number of therapeutically innovative NAS with an expedited review
1995	22 (73.3)	3	1	0
1996	20 (60.6)	5	4	3
1997	24 (57.1)	4	4	2
1998	24 (80.0)	4	1	0
1999	31 (86.1)	10	1	0
2000	20 (76.9)	9	4	4
2001	23 (85.2)	8	1	1
2002	20 (83.3)	4	0	0
2003	19 (95.0)	8	2	2
2004	26 (89.7)	9	3	3
2005	21 (87.5)	9	3	2
2006	21 (91.3)	9	3	2
2007	22 (91.7)	9	3	3
2008	15 (88.2)	6	2	2
2009	26 (96.3)	7	0	0
2010	19 (86.4)	2	2	2
2011	23 (85.3)	5	2	2
2012	21 (91.3)	6	3	2
2013	36 (92.3)	11	6	3
2014	22 (88.0)	6	3	2
2015	30 (81.1)	12	4	4
2016	24 (63.2)	13	3	3
1995-2016	509 (81.7)	159	55	42

*New active substance

†Number of drugs rated as innovative as a percent of all drugs given an expedited approval review by Health Canada

‡Number of drugs rated as not therapeutically innovative as a percent of all drugs given a standard review by Health Canada

There were 286 and 99 small molecule drugs and biologics, respectively, with therapeutic ratings. The Kappa values were 0.313 (95% CI 0.205, 0.420) (fair) and 0.233 (95% CI 0.061, 0.405) (fair), respectively. The overlapping 95% CIs indicate no difference in the Kappa values between the two groups (Table 5).

Table 5: Subgroup analyses: Kappa values

Subgroup	Number (%)	Kappa value (95% CI)
Small molecule drugs	286	0.313 (0.205, 0.420)
Biologics	99	0.233 (0.061, 0.405)
Antineoplastic agents	71	0.091 (0.017, 0.200)
Antivirals for systemic use	46	0.122 (0.011, 0.233)
Immunosuppressants	35	0.376 (0.075, 0.675)
All other therapeutic groups	357	0.385 (0.263, 0.506)

The 509 drugs were in 58 different second level ATC groups (drugs in 13 ATC groups did not have therapeutic evaluations): antineoplastic agents (71), antivirals for systemic use (46), immunosuppressants (35) and "all other therapeutic groups" (357) (Supplementary Table 1). Kappa values for the four groups were: 0.091 (95% CI 0.017, 0.200) (slight), 0.200), 0.122 (95% CI 0.011, 0.233) (slight)), 0.376 (95% CI 0.075, 0.675) (fair) and (95% CI 0.263, 0.506)0.385 (fair), respectively. The 95% CIs for the Kappa values for the antineoplastic agents, antivirals for systemic use and immunosuppressants overlapped indicating no difference among the groups but there was no overlap of any of these with the 95% CI for "all other therapeutic groups". Drugs in the three therapeutic subgroups were much less likely to receive a standard review than were drugs in "all other therapeutic groups", 43.7% versus 79.3% (data not shown).

Discussion

Almost 30% of the 623 new active substances that Health Canada reviewed between 1995 and 2016 went through at least one of two expedited review pathways – priority review or NOC/c, primarily a priority review. There is no difference between small molecule drugs and biologics in the approval pathways used indicating that for these two groups Health Canada does not see one or the other being more likely to offer significant new therapeutic benefits. However, the same is not true for the therapeutic subgroups. Drugs in the three specifically examined – antineoplastics, antivirals and immunosuppressants – were collectively more likely to be assigned to an expedited review pathway (56%) compared to drugs in "all other therapeutic groups" (20.5%), possibly because of the nature of the diseases that they treat.

Just over 80% of the NAS approved had been assessed by the PMPRB and/or Prescrire for their therapeutic benefit. The Kappa value for the 509 drugs was 0.276 meaning that Health Canada's ability to predict major therapeutic gain from these drugs was only fair. Furthermore, almost 25% (13/55) of the drugs that were therapeutic innovations did not receive an expedited review underscoring that Health Canada is not reliably able to predict which drugs will offer major therapeutic gains. The relatively low Kappa value may relate to when Health Canada makes its decision about what type of approval pathway to use. This assignment is at the start of the review process when all of the data will not have been fully assessed. In contrast, the PMPRB and Prescrire make their assessments after the drug has been marketed when more information about efficacy and safety is available.

As was the case with the assignment of an expedited review pathway, there is no difference in how accurately Health Canada predicts the therapeutic value of small molecule drugs and biologics as measured by Kappa values. The Kappa value for drugs in "all other therapeutic

groups" is higher than the value for drugs in the antineoplastic, antiviral and immunosuppressant groups. This difference may because Health Canada is better able to predict these drugs are less likely to be therapeutic innovations than drugs in the antineoplastic, antiviral and immunosuppressant groups. Out of the 357 drugs that had therapeutic evaluations in the "all other therapeutic groups," 79.3% received a standard review compared to 43.7% of the 151 drugs in the three therapeutic subgroups.

How Health Canada uses its expedited review pathways is important for a number of reasons. First, their use may explicitly create an impression among clinicians and patients that these drugs are likely to deliver major new therapeutic benefits despite the fact that the likelihood that they will is only "fair" as measured by the Kappa value. Second, the NOC/c pathway requires companies to commit to conducting post-market studies to validate the efficacy of the product, but many of these studies are delayed [6, 7], leaving clinicians and patients uncertain about the value of these products. In at least one case, Health Canada did not suspend the sale of a drug and allowed it to stay on the market despite not fulfilling the conditions required under its NOC/c. In December 2003, Iressa (gefitinib) was approved as a third-line treatment for non-small cell lung cancer on the condition that the company submit a study showing that it improved survival [12]. When the study results were submitted to Health Canada they showed no survival benefit for gefitinib compared to placebo [13]. Health Canada recognized that the conditions had not been fulfilled, but rather than removing gefitinib from the market, in February 2005 it elected to allow it to continue to be sold [12]. In 2009, the drug was deemed to have met its conditions after a new study showed non-inferiority, i.e., survival after taking it was no worse compared to another chemotherapeutic agent [14]. Third, although the priority and standard approval pathways are equivalent in terms of the amount of data reviewed, the former is done in 180 days compared to 300 days

for the latter, meaning that the priority pathway is more resource intensive possibly drawing resources from other Health Canada activities. Finally, drugs reviewed through both expedited review pathways are more likely to receive safety warnings once they are on the market compared to drugs with a standard approval [2, 15].

As Figure 1 indicates, Health Canada is not using the expedited review pathways more liberally (or more conservatively) over time, but as Figure 2 shows it has not improved its ability to predict therapeutic innovation over the 22 years evaluated in this study. The Introduction describes the criteria that Health Canada uses to assign a drug to either a priority review or a NOC/c review but how those criteria are applied and whether Health Canada periodically reviews its performance are not known.

Contrary to the situation in the United States (US) where the Food and Drug Administration (FDA) has been using an increasing number of expedited development or review programs, Health Canada's use of its programs has been relatively stable since 1995. Between 1987 and 2014, 43% received a priority review from the FDA and 19% were approved through the fast track program which approximately corresponds to a NOC/c [16]. (Drugs could be associated with both programs.) However, when it comes to approving oncology drugs through an expedited pathway, Health Canada is only marginally better than the FDA. In the US, only 1 of 15 (6.7%) oncology drugs approved through an expedited program from January 1, 2008, through December 31, 2012 had a proven survival benefit compared to the other 6 and 8 that either had no overall survival benefit or an unknown benefit, respectively [17]. In this current study, out of 42 antineoplastic agents that Health Canada gave an expedited review, only 6 (14.3%) were rated as therapeutically innovative. The European Medicines Agency (EMA) does not have the equivalent of a priority review but its exceptional conditions (EC) and

conditional approvals (CA) pathways are roughly equivalent to a NOC/c. These were used for 12.5% (70/558) new drugs it approved from 1995 to 2009 [18], while Health Canada used a NOC/c for 5.3% (33/623) approvals between 1995 and 2016.

Limitations

Almost 20% of new drugs approved by Health Canada were not evaluated for their therapeutic innovation by either the PMPRB or La revue Prescrire. The absence of these evaluations may have skewed the Kappa values in either a more positive or more negative direction. The lack of the availability of reports from Health Canada reviewers means that the reasons why drugs were assigned to a specific review pathway cannot be evaluated.

Conclusion

Health Canada continues to use expedited review pathways for about 30% of new drugs. Other regulatory authorities such as the Australian Therapeutic Goods Administration and the EMA are in the process of either implementing or expanding expedited review pathways [19-21] and should study the example of what has happened in Canada. The rationale for using expedited review pathways is to get important therapeutic advances to patients in a timely manner, but Health Canada's ability to predict which of these drugs will fulfill this expectation has not improved over a 22-year period and remains relatively low. Moreover, use of these pathways comes with both health related and resource costs. The findings in this study should provoke a discussion about whether Health Canada should continue to use these pathways and if so how their use can be improved.

Figure 1 legend

Grey – Percent with Notice of Compliance with conditions

Orange – Percent with priority

Blue – Percent with standard

Figure 2 legend

Kappa values:

< 0 = no agreement

0 – 0.20 = slight agreement

0.21 – 0.40 = fair agreement

0.41 – 0.60 = moderate agreement

0.61 – 0.80 = substantial agreement

0.81 – 1.0 = almost perfect agreement

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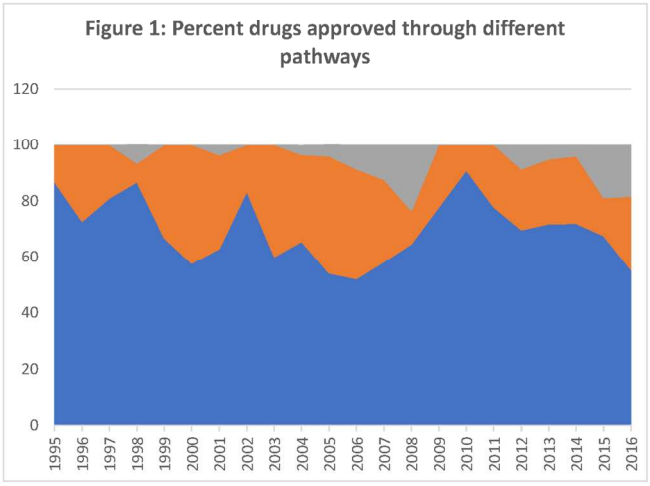

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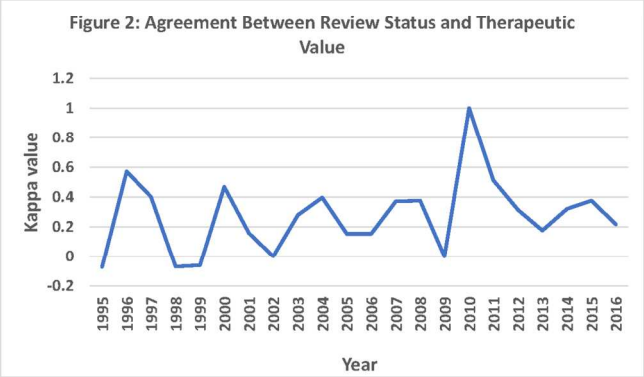

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Supplementary Table 1: All drugs approved between 1995-2016 that received therapeutic assessments from Patented Medicine Prices Review Board and/or La revue Prescrire*

Generic name	Brand name	PMPRB breakthrough, substantial improvement and/or Prescrire bravo, a real advance	PMPRB and/or Prescrire no significant therapeutic innovation†	Review status			Notice of compliance or notice of compliance with conditions date	Small molecule	Biologic	ATC group (second level)
				Standard	Priority	Notice of compliance with conditions				
Adapalene	Differin		1	1			1995-01-24			anti-acne preparation
Dexrazoxane	Zinecard	1		1			1995-02-07			all other therapeutic products
Bambuterol	Bambec		1	1			1995-02-07			drugs for obstructive airway diseases
Naltrexone	Revia		1	1			1995-03-23			other nervous system drugs
Cefprozil	Cefzil		1	1			1995-03-29			antibacterials for
Zuclopenthixol	Clopixol		1	1			1995-04-24			psycholeptics
Zuclopenthixol	Clopixol acuphase		1	1			1995-04-24			psycholeptics
Zuclopenthixol	Clopixol depot		1	1			1995-04-24			psycholeptics
Lansoprazole	Prevacid		1	1			1995-05-12			drugs for acid related disorders
Cefepime	Maxipime		1	1			1995-06-02			antibacterials for systemic use
Interferon Beta-	Betaseron		1		1		1995-07-19			immunostimulants
Famciclovir	Famvir		1	1			1995-07-31			antivirals for systemic use
Cefpodoxime	Orelox		1	1			1995-08-22			antibacterials for
Sevoflurane	Sevorane		1	1			1995-09-18			systemic use anesthetics

Losartan	Cozaar		1	1		1995-09-28	agents acting on the renin-angiotensin system
Iotrolan	Osmovist 280		1	1		1995-10-04	contrast media
Bicalutamide	Casodex		1	1		1995-11-02	endocrine therapy
Acarbose	Prandase		1	1		1995-11-15	drugs used in diabetes
Mycophenolate	Cellcept		1	1		1995-11-15	immunosuppressants
Tacrolimus	Prograf		1		1	1995-12-06	immunosuppressants
Lamivudine	3TC		1		1	1995-12-08	antivirals for systemic use
Alendronate	Fosamax		1	1		1995-12-20	drugs for treatment of bone disease
Stavudine	Zerit		1	1		1996-03-26	antivirals for systemic use
Acellular pertussis vaccine adsorbed	Acel-P		1		1	1996-03-29	vaccines
Dorzolamide	Trusopt		1	1		1996-04-25	ophthalmologicals
Amifostine	Ethyol	1			1	1996-04-25	all other therapeutic products
Valacyclovir	Valtrex		1	1		1996-05-01	antivirals for systemic use
Quinagolide	Norprolac		1	1		1996-06-25	other gynecologicals
Meropenem	Merrem		1	1		1996-07-02	antibacterials for systemic use
Abciximab	Reopro	1		1		1996-07-04	antithrombotic agents
Anastrozole	Arimidex		1	1		1996-08-01	endocrine therapy
Ritonavir	Norvir	1			1	1996-08-14	antivirals for systemic use
Raltitrexed	Tomudex		1		1	1996-09-12	antineoplastic agents
Indinavir	Crixivan	1			1	1996-09-13	antivirals for systemic use
Insulin lispro	Humalog		1	1		1996-10-08	drugs used in diabetes

Dirithromycin	Dynabac		1	1	1996-10-28	antibacterials for systemic use
Olanzapine	Zyprexa		1	1	1996-10-28	psycholeptics
Nalmefene	Revex		1	1	1996-11-06	other nervous system
Zolpidem	Ambien		1	1	1996-11-20	psycholeptics
Desflurane	Suprane		1	1	1996-12-03	anesthetics
Gemcitabine	Gemzar		1	1	1996-12-23	antineoplastic agents
Ropivacaine	Naropin injections		1	1	1996-12-24	anesthetics
Imiglucerase	Cerezyme	1		1	1997-02-12	other alimentary tract and metabolism products
Atorvastatin	Lipitor		1	1	1997-02-19	lipid modifying agents
Topiramate	Topamax		1	1	1997-03-06	antiepileptics
Formoterol	Foradil dry powder capsules		1	1	1997-03-06	drugs for obstructive airway diseases
Epoprostenol	Flolan		1	1	1997-03-06	antithrombotic agents
Coagulation factor IX	Benefix	1		1	1997-03-21	antihemorrhagics
Topotecan	Hycamtin		1	1	1997-04-15	antineoplastic agents
Dolasetron	Anzemet		1	1	1997-05-21	antiemetics and antinauseants
Letrozole	Femara		1	1	1997-05-21	endocrine therapy
Fexofenadine	Allegra		1	1	1997-06-11	antihistamines for systemic use
Latanoprost	Xalatan		1	1	1997-06-16	ophthalmologicals
Carbetocin	Duratocin		1	1	1997-06-24	pituitary and hypothalamic hormones and analogues
Follitropin beta	Puregon		1	1	1997-07-02	sex hormones and modulators of the genital system

Irinotecan	Camptosar	1		1	1997-07-04	antineoplastic agents
Donepezil	Aricept	1		1	1997-08-12	psychoanaleptics
Ropinirole	Requip		1	1	1997-08-19	anti-parkinson drugs
Ibandronate	Bondronat		1	1	1997-08-27	drugs for treatment of bone disease
Glatiramer	Copaxone for injection		1	1	1997-09-04	immunostimulants
Tolcapone	Tasmar		1	1	1997-10-08	anti-parkinson drugs
Zafirlukast	Accolate		1	1	1997-10-21	drugs for obstructive airway diseases
Valsartan	Diovan		1	1	1997-11-03	agents acting on the renin-angiotensin system
Levofloxacin	Levaquin		1	1	1997-11-14	antibacterials for systemic use
Brimonidine	Alphagan opthalmic		1	1	1997-11-24	ophthalmologicals
Quetiapine	Seroquel		1	1	1997-12-02	psycholeptics
Pramipexole	Mirapex		1	1	1998-01-29	anti-parkinson drugs
Interferon Beta-	Rebif		1	1	1998-02-05	immunostimulants
Emedastine	Emadine ophthalmic		1	1	1998-02-16	ophthalmologicals
Cerivastatin	Baycol		1	1	1998-02-18	lipid modifying agents
Grepafloxacin	Raxar		1	1	1998-04-09	antibacterials for systemic use
Naratriptan	Amerge		1	1	1998-04-28	analgesics
Bupropion	Wellbutrin SR		1	1	1998-04-28	psychoanaleptics
Irbesartan	Avapro		1	1	1998-06-01	agents acting on the renin-angiotensin system
Tamsulosin	Flomax		1	1	1998-06-01	urologicals
Montelukast	Singulair		1	1	1998-06-17	drugs for obstructive airway diseases

Delavirdine	Rescriptor		1	1		1	1998-07-22	antivirals for systemic use
Nelfinavir	Viracept		1		1		1998-08-11	antivirals for systemic use
Zolmitriptan	Zomig		1	1			1998-08-24	analgesics
Capecitabine	Xeloda		1		1		1998-08-31	antineoplastic agents
Nevirapine	Viramune		1	1		1	1998-09-04	antivirals for systemic use
Clopidogrel	Plavix		1	1			1998-10-07	antithrombotic agents
Brinzolamide	Azopt ophthalmic suspension		1	1			1998-10-23	ophthalmologicals
Raloxifene	Evista		1	1			1998-11-06	sex hormones and modulators of the genital system
Candesartan	Atacand		1	1			1998-11-20	agents acting on the renin-angiotensin system
Tolterodine	Detrol		1	1			1998-11-20	urologicals
Varicella vaccine	Varivax	1		1			1998-12-02	vaccines
Alatrofloxacin	Trovan (IV)		1	1			1998-12-04	antibacterials for systemic use
Trovafloxacin	Trovan (tablets)		1	1			1998-12-04	antibacterials for systemic use
Becaplermin gel	Regranex		1	1			1998-12-30	preparations for wounds and ulcers
Tizanidine	Zanaflex		1	1			1999-01-25	muscle relaxants
Penciclovir	Denavir		1	1			1999-02-02	antivirals for systemic use
Citalopram	Celexa		1	1			1999-02-05	psychoanaleptics
Recombinant factor VIIa	Niastase		1		1	1	1999-02-12	antihemorrhagics
Modafinil	Alertec		1	1			1999-02-26	psychoanaleptics

Sildenafil	Viagra	1		1		1999-03-08	urologicals
Recombinant-methionyl interferon consensus 1	Infergen		1		1	1999-03-11	immunostimulants
Efavirenz	Sustiva		1		1	1999-03-19	antivirals for systemic use
Repaglinide	Gluconorm		1	1		1999-04-06	drugs used in diabetes
Celecoxib	Celebrex		1		1	1999-04-14	antiinflammaotory and antirheumatic products
Triptorelin	Trelstar		1	1		1999-05-06	endocrine therapy
Ancestim	Stemgen		1	1		1999-05-20	immunostimulants
Orlistat	Xenical		1	1		1999-06-03	antiobesity preparations
Abacavir	Ziagen		1	1	1	1999-06-04	antivirals for systemic use
Eptifibatide	Integrilin		1	1		1999-06-11	antithrombotic agents
Eprosartan	Teveten		1	1		1999-07-09	agents acting on the renin-angiotensin system
Cidofovir	Vistide		1	1		1999-07-13	antivirals for systemic use
Rizatriptan	Maxalt		1	1		1999-07-16	analgesics
Trastuzumab	Herceptin		1		1	1999-08-13	antineoplastic agents
Telmisartan	Micardis		1	1		1999-08-16	agents acting on the renin-angiotensin system
Risedronate	Actonel		1	1		1999-08-18	drugs for treatment of bone disease
Tirofiban	Aggrastat		1	1		1999-08-19	antithrombotic agents
Icodextrin	Extraneal		1	1		1999-09-17	blood substitutes and perfusion solutions
Varicella zoster vaccine	Varilrix		1		1	1999-10-13	vaccines
Temozolomide	Temodal		1	1		1999-10-25	antineoplastic agents

Rofecoxib	Vioxx		1		1		1999-10-25			antiinflammaotory and antirheumatic products
Zanamivir	Relenza		1		1	1	1999-11-02			antivirals for systemic use
Melanoma theracine	Melacine		1		1		1999-11-04			immunostimulants
Gadobutrol	Gadovist		1	1			1999-11-08			contrast media
Dalfopristin	Synercid		1	1			1999-12-10			antibacterials for systemic use
Oseltamivir	Tamiflu		1	1			1999-12-23			antivirals for systemic use
Daclizumab	Zenaprax		1		1		2000-01-04		1	antineoplastic agents
Leflunomide	Arava		1	1			2000-03-16	1		immunosuppressants
Rituximab	Rituxan	1			1		2000-03-17		1	immunosuppressants
Rosiglitazone	Avandia		1		1		2000-03-21	1		drugs used in diabetes
Oxcarbazepine	Trileptal		1	1			2000-04-13	1		antiepileptics
Rivastigmine	Exelon		1	1			2000-04-13	1		psychoanaleptics
Zaleplon	Starnoc		1	1			2000-05-11	1		psycholeptics
Verteporfin	Visudyne	1			1		2000-05-31	1		ophthalmologicals
Cabergoline	Dostinex		1	1			2000-06-30	1		anti-parkinson drugs
Exemestane	Aromasin		1	1			2000-08-17	1		endocrine therapy
Pioglitazone	Actos		1		1		2000-08-17	1		drugs used in diabetes
Zoledronic acid	Zometa		1		1		2000-08-21	1		drugs for treatment of bone disease
Riluzole	Rilutek	1			1	1	2000-08-30	1		other nervous system
Meloxicam	Mobic		1	1			2000-08-31	1		antiinflammaotory and antirheumatic products
Basiliximab	Simulect		1		1		2000-09-01		1	immunosuppressants
Moxifloxacin	Avelox		1	1			2000-10-19	1		antibacterials for systemic use
Peginterferon Alfa-2b	Peg-intron		1	1			2000-10-20		1	immunostimulants
Etanercept	Enbrel	1			1		2000-12-01		1	immunosuppressants

Gadoversetamide	Optimark		1	1			2000-12-11	1		contrast media
Sibutramine	Meridia		1	1			2000-12-28	1		antiobesity preparations
Sirolimus	Rapamune		1	1			2001-01-05	1		immunosuppressants
Gatifloxacin	Tequin		1	1			2001-01-09	1		antibacterials for systemic use
Glucagon, rDNA origin	Glucagon		1		1		2001-01-11		1	pancreatic hormones
Mequinol/tretinoin	Solage		1	1			2001-01-17	1		other dermatological preparations
Amprenavir	Agenerase		1	1		1	2001-03-01	1		antivirals for systemic use
Lopinavir/ritonavir	Kaletra		1		1		2001-03-09	1		antivirals for systemic use
Linezolid	Zyvoxam		1	1			2001-04-02	1		antibacterials for systemic use
Iron	Venofer		1		1		2001-04-17	1		antianemic preparations
Doxercalciferol	Hectorol		1	1			2001-04-30	1		calcium homeostasis
Rabeprazole	Pariet		1	1			2001-05-07	1		drugs for acid related disorders
Entacapone	Comtan		1	1			2001-05-08	1		anti-parkinson drugs
Eflornithine	Vaniqa		1	1			2001-05-10	1		antiprotozoals
Mirtazapine	Remeron		1	1			2001-05-18	1		psychoanaleptics
Desloratadine	Aerius		1	1			2001-05-29	1		antihistamines for systemic use
Infliximab	Remicade		1	1			2001-06-06		1	immunosuppressants
Caspofungin	Cancidas		1		1		2001-07-29	1		antimycotics for systemic use
Galantamine	Reminyl		1	1			2001-07-31	1		psychoanaleptics
Esomeprazole	Nexium		1	1			2001-08-17	1		drugs for acid related disorders
Imatinib	Gleevec	1			1	1	2001-09-20	1		antineoplastic agents
Tenecteplase	Tnkase		1	1			2001-10-17		1	antithrombotic agents
Travoprost	Travatan		1	1			2001-11-09	1		ophthalmologicals

Bosentan	Tracleer	1		1	2001-11-30	1	antihypertensives
Meningococcal group C polysaccharide, tetanus toxoid	Neisvac-C	1		1	2001-12-18		1 vaccines
Glimepiride	Amaryl	1	1		2002-01-25	1	drugs used in diabetes
Nateglinide	Starlix	1	1		2002-02-13	1	drugs used in diabetes
Alfuzosin	Xatral	1	1		2002-02-21		urologicals
Tegaserod	Zelnorm	1	1		2002-03-12	1	drugs for constipation
Ganirelix	Orgalutran	1	1		2002-05-01	1	pituitary and hypothalamic hormones
Valganciclovir	Valcyte	1	1		2002-05-03	1	antivirals for systemic use
Palivizumab	Synagis	1	1		2002-05-15		1 immune sera and immunoglobulins
Docosanol	Abreva	1	1		2002-05-24	1	antibiotics and chemotherapeutics for dermatological use
Bimatoprost	Lumigan	1	1		2002-05-24	1	ophthalmologicals
Anakinra	Kineret	1		1	2002-05-24		1 immunosuppressants
Moroctocog alpha	Refacto	1		1	2002-05-28		1 antihemorrhagics
Peginterferon Alfa-2b ribavirin	Pegetron	1	1		2002-05-31		1 immunostimulants
Fondaparinux	Arixtra	1		1	2002-06-13	1	antithrombotic agents
Hetastarch	Hextend	1	1		2002-07-08	1	blood substitutes and perfusion solutions
Darbepoetin alpha	Aranesp	1	1		2002-08-02		1 antianemic preparations
Norelgestromin/ ethinyl estradiol	Evra	1	1		2002-08-20	1	sex hormones and modulators of the genital system
Treprostinil	Remodulin	1		1	2002-10-04	1	antithrombotic agents
Bivalirudin	Angiomax	1	1		2002-10-09	1	antithrombotic agents

Tiotropium	Spiriva		1	1			2002-11-20	1		drugs for obstructive airway diseases
Valdecoxib	Betra		1	1			2002-12-11	1		antiinflammaotory and antirheumatic products
Drotrecogin Alfa	Xigris	1			1		2003-01-31		1	antithrombotic agents
Rosuvastatin	Crestor		1	1			2003-02-18	1		lipid modifying agents
Recombinant cholera toxin B subunit	Dukoral		1		1		2003-02-21		1	vaccines
Levetiracetam	Keppra		1	1			2003-03-06	1		antiepileptics
Tenofovir	Viread		1		1	1	2003-03-18	1		antivirals for systemic use
Pimecrolimus	Elidel		1	1			2003-03-19	1		other dermatological preparations
Ertapenem	Invanz		1	1			2003-05-12	1		antibacterials for systemic use
Ezetimibe	Ezetrol		1	1			2003-05-12	1		lipid modifying agents
Telithromycin	Ketek		1	1			2003-05-28	1		antibacterials for systemic use
Enfuvirtide	Fuzeon	1			1		2003-07-14	1		antivirals for systemic use
Dutasteride	Avodart		1	1			2003-07-22	1		urologicals
Peginterferon Alfa-2a	Pegasys		1	1			2003-08-13		1	immunostimulants
Cetrorelix	Cetrotide		1	1			2003-08-13	1		pituitary and hypothalamic hormones
Adefovir	Hepsera		1		1		2003-08-27	1		antivirals for systemic use
Tadalafil	Cialis		1	1			2003-09-17	1		urologicals
Almotriptan	Axert		1	1			2003-10-01	1		agents acting on the renin-angiotensin system
Rasburicase	Fasturtec		1		1		2003-10-29		1	all other therapeutic products

Atazanavir	Reyataz		1		1		2003-12-05	1		antivirals for systemic use
Gefitinib	Iressa		1		1	1	2003-12-17	1		antineoplastic agents
Agalsidase Beta	Fabrazyme		1		1		2004-01-23		1	other alimentary tract and metabolism products
Agalsidase	Replagal	1			1	1	2004-02-06		1	other alimentary tract and metabolism products
Fulvestrant	Faslodex		1	1			2004-02-17	1		endocrine therapy
Gemifloxacin	Factive		1	1			2004-03-09	1		antibacterials for systemic use
Pegfilgrastim	Neulasta		1	1			2004-03-12		1	immunostimulants
Vardenafil	Levitra		1	1			2004-03-17	1		urologicals
Gadobenate	Multihance		1	1			2004-03-31	1		contrast media
Miglustat	Zavesca		1		1		2004-03-31	1		other alimentary tract and metabolism products
Botulinum Toxin Type B	Myobloc		1	1			2004-04-16		1	muscle relaxants
Peginterferon Alfa-2A Ribavirin	Pegasys RBV		1		1		2004-05-10		1	immunostimulants
Ethinyl estradiol/etonogestrel	Nuvaring		1	1			2004-05-11	1		sex hormones and modulators of the genital system
Pemetrexed	Alimta		1		1		2004-05-21	1		antineoplastic agents
Laronidase	Adlurazyme	1			1		2004-05-31		1	other alimentary tract and metabolism products
Teriparatide	Forteo		1		1		2004-06-03		1	calcium homeostasis
Cinacalcet	Sensipar	1			1		2004-08-04	1		calcium homeostasis
Eletriptan	Relpax		1	1			2004-08-05	1		analgesics

Voriconazole	Vfend		1	1			2004-08-20	1		antimycotics for systemic use
Frovatriptan	Frova		1	1			2004-09-03	1		analgesics
Adalimumab	Humira		1	1			2004-09-24		1	immunosuppressants
Alefacept	Amevive		1	1			2004-10-06		1	immunosuppressants
Omalizumab	Xolair		1	1			2004-11-18		1	drugs for obstructive airway diseases
Memantine	Ebixa		1	1		1	2004-12-08	1		psychoanaleptics
Fosamprenavir	Telzir		1	1			2004-12-10	1		antivirals for systemic use
Drospirenone/ethinyl estradiol	Yasmin 21/28		1	1			2004-12-10	1		sex hormones and modulators of the genital system
Atomoxetine	Strattera		1	1			2004-12-24	1		psychoanaleptics
Escitalopram	Cipralex		1	1			2004-12-24	1		psychoanaleptics
Bortezomib	Velcade		1	1		1	2005-01-27	1		antineoplastic agents
Paricalcitol	Zemplar		1	1			2005-03-31	1		calcium homeostasis
Pantoprazole	Pantaloc M		1	1			2005-04-22	1		drugs for acid related disorders
Pegaptanib	Macugen	1			1		2005-05-02	1		ophthalmologicals
Ibritumomab	Zevalin		1		1		2005-05-10		1	therapeutic radiopharmaceuticals
Pregabalin	Lyrica		1	1			2005-06-03	1		antiepileptics
Lutropin Alfa	Luveris		1	1			2005-06-24		1	sex hormones and modulators of the genital system
Erlotinib	Tarceva		1		1		2005-07-07	1		antineoplastic agents
Tramadol	Tramacet		1	1			2005-07-20	1		analgesics
Sodium oxybate	Xyrem		1	1			2005-08-05	1		other nervous system
Perindopril	Coversyl		1	1			2005-08-23	1		agents acting on the renin-angiotensin system
Bevacizumab	Avastin		1		1		2005-09-09		1	antineoplastic agents

Cetuximab	Erbitux		1		1		2005-09-09		1	antineoplastic agents
Insulin detemir	Levemir		1	1			2005-09-29		1	drugs used in diabetes
Pegvisomant	Somavert		1		1		2005-10-17		1	pituitary and hypothalamic hormones
Efalizumab	Raptiva		1	1			2005-10-24		1	immunosuppressants
Darifenacin	Enablex		1	1			2005-11-14	1		urologicals
Emtricitabine	Emtriva		1	1			2005-11-21	1		antivirals for systemic use
Tipranavir	Aptivus		1		1		2005-11-21	1		antivirals for systemic use
Alemtuzumab	Mabcampath	1		1			2005-11-30		1	immunosuppressants
Palifermin	Kepivance	1			1		2005-12-09		1	all other therapeutic products
Trospium	Trosec		1	1			2006-01-10	1		urologicals
Solifenacin	Vesicare		1	1			2006-02-20	1		urologicals
Histrelin	Vantas		1	1			2006-03-10	1		endocrine therapy
Insulin glulisine	Apidra		1	1			2006-04-12		1	drugs used in diabetes
Sunitinib	Sutent		1		1	1	2006-05-26	1		antineoplastic agents
Entecavir	Baraclude		1		1		2006-06-16	1		pituitary and hypothalamic hormones and analogues
Abatacept	Orencia		1		1		2006-06-29		1	immunosuppressants
Recombinant human papillomavirus	Gardasil	1			1		2006-07-10		1	vaccines
Lanreotide	Somatuline autogel		1	1			2006-07-17	1		antivirals for systemic use
Sorafenib	Nexavar		1	1			2006-07-28	1		antineoplastic agents
Darunavir	Prezista		1	1		1	2006-07-28	1		antivirals for systemic use
Rotaviruses	Rotateq	1		1			2006-08-01		1	vaccines

Alglucosidase Alfa	Myozyme	1			1		2006-08-14		1	other alimentary tract and metabolism products
Rasagiline	Azilect		1	1			2006-08-17	1		anti-parkinson drugs
Ciclesonide	Alvesco		1	1			2006-09-11	1		drugs for obstructive airway diseases
Tigecycline	Tygacil		1	1			2006-09-14	1		antibacterials for systemic use
Natalizumab	Tysabri		1		1		2006-09-28		1	immunosuppressants
Lanthanum	Fosrenol		1	1			2006-10-17	1		all other therapeutic products
Deferasirox	Exjade		1		1	1	2006-10-18	1		all other therapeutic products
Gadofosveset	Vasovist		1	1			2006-10-31	1		contrast media
Telbivudine	Sebivo		1		1		2006-11-28	1		antivirals for systemic use
Varenicline	Champix		1	1			2007-01-24	1		other nervous system
Acamprosate	Campral		1	1			2007-03-16	1		other nervous system
Dasatinib	Sprycell	1		1		1	2007-03-26	1		antineoplastic agents
Posaconazole	Spriafil (Posanol)	1			1		2007-03-26	1		antimycotics for systemic use
Micafungin	Mycamine		1	1			2007-05-22	1		antimycotics for systemic use
Sitaxentan	Thelin		1	1			2007-05-30	1		antihypertensives
Idursulfase	Elaprase		1		1		2007-06-13	1		other alimentary tract and metabolism products
Oxaliplatin	Eloxatin		1		1		2007-06-15	1		antineoplastic agents
Ranibizumab	Lucentis	1			1		2007-06-26		1	ophthalmologicals
Fluticasone	Avamys		1	1			2007-08-14	1		drugs for obstructive airway diseases
Aprepitant	Emend		1	1			2007-08-24	1		antiemetics and antinauseants

Maraviroc	Celsentri		1		1		2007-09-21	1		antivirals for systemic use
Daptomycin	Cubicin		1	1			2007-09-24	1		antibacterials for systemic use
Paliperidone	Invega		1	1			2007-09-26	1		psycholeptics
Duloxetine	Cymbalta		1	1			2007-11-01	1		psychoanaleptics
Nesiritide	Natrecor		1	1		1	2007-11-08		1	cardiac therapy
Aliskiren	Rasilez		1	1			2007-11-14	1		agents acting on the renin-angiotensin system
Anidulafungin	Eraxis		1	1			2007-11-14	1		antimycotics for systemic use
Raltegravir	Isentress		1		1	1	2007-11-27	1		antivirals for systemic use
Rivastigmine	Exelon patch		1	1			2007-11-29	1		psychoanaleptics
Sitagliptin	Januvia		1	1			2007-12-14	1		drugs used in diabetes
Temsirolimus	Torisel		1		1		2007-12-21	1		antineoplastic agents
Lenalidomide	Revlimid	1		1		1	2008-01-17	1		immunosuppressants
Ambrisentan	Volibris		1	1			2008-03-20	1		antihypertensives
Etravirine	Intelence		1		1		2008-03-27	1		antivirals for systemic use
Methylnaltrexone	Relistor	1			1		2008-03-28	1		drugs for constipation
Panitumumab	Vectibix		1	1		1	2008-04-03		1	antineoplastic agents
Nepafenac	Nevanac		1	1			2008-04-17	1		ophthalmologicals
Dabigatran	Pradaxa		1	1			2008-06-10	1		antithrombotic agents
Ceftobiprole	Zeftera		1	1			2008-06-26	1		antibacterials for systemic use
Idebenone	Catena		1	1		1	2008-07-23	1		psychoanaleptics
Nilotinib	Tasigna		1	1		1	2008-09-09	1		antineoplastic agents
Rivaroxaban	Xarelto		1	1			2008-09-15	1		antithrombotic agents

Olmesartan	Olmetec	1	1			2008-10-28	1	agents acting on the renin-angiotensin system
Capsular polysaccharide	Synflorix	1	1			2008-12-11	1	vaccines
Ustekinumab	Stelara	1	1			2008-12-12	1	immunosuppressants
Loteprednol	Alrex	1	1			2008-12-23	1	ophthalmologicals
Eculizumab	Soliris	1		1		2009-01-28	1	immunosuppressants
Desvenlafaxine	Pristiq	1	1			2009-02-04	1	psychoanaleptics
Lisdexamfetamine	Vyvanse	1	1			2009-02-19	1	psychoanaleptics
Romiplostim	Nplate	1		1		2009-02-19	1	antihemorrhagics
Methyl aminolevulinate	Metvix	1	1			2009-02-26	1	antineoplastic agents
Eplerenone	Inspra	1	1			2009-02-26	1	diuretics
Fosaprepitant	Emend IV	1	1			2009-04-01	1	antivirals for systemic use
Golimumab	Simponi	1	1			2009-04-07	1	immunosuppressants
Lapatinib	Tykerb	1	1			2009-05-15	1	antineoplastic agents
Vorinostat	Zolinza	1	1			2009-06-11	1	antineoplastic agents
Aripiprazole	Abilify	1	1			2009-07-09	1	psycholeptics
Clofarabine	Clolar	1	1			2009-07-16	1	antineoplastic agents
Dronedarone	Multaq	1		1		2009-08-11	1	cardiac therapy
Certolizumab	Cimzia	1	1			2009-08-12	1	immunosuppressants
Doripenem	Doribax	1	1			2009-09-02	1	antibacterials for systemic use
Aztreonam	Cayston	1		1	1	2009-09-11	1	antibacterials for systemic use
Saxagliptin	Onglyza	1	1			2009-09-14	1	drugs used in diabetes
Besifloxacin	Besivance	1	1			2009-10-23	1	ophthalmologicals
Azacitidine	Vidaza	1		1		2009-10-23	1	antineoplastic agents

Japanese encephalitis vaccine	Ixiaro		1	1			2009-10-29		1	vaccines
Alitretinoin	Toctino		1	1			2009-11-13	1		antineoplastic agents
Degarelix	Firmagon		1	1			2009-11-16	1		endocrine therapy
Dexmedetomidine	Precedex		1	1			2009-12-09	1		psycholeptics
Everolimus	Afinitor		1	1		1	2009-12-14	1		antineoplastic agents
Thrombin alfa	Recothrom		1	1			2009-12-15		1	antihemorrhagics
Pneumococcal conjugate	Prevnar		1		1		2009-12-21		1	vaccines
Gadoxetate	Primovist		1	1			2010-01-14	1		contrast media
Recombinant human papillomavirus	Cervarix		1	1			2010-02-03		1	vaccines
Canakinumab	Ilaris	1			1		2010-02-26		1	immunosuppressants
Prasugrel	Effient		1	1			2010-04-16	1		antithrombotic agents
Tocilizumab	Actemra		1	1			2010-04-30		1	immunosuppressants
Sapropterin	Kuvan	1			1		2010-04-30	1		other alimentary tract and metabolism products
Trabectedin	Yondelis		1	1			2010-05-13	1		antineoplastic agents
Liraglutide	Victoza - 1.2 mg pen-injector		1	1			2010-05-21		1	drugs used in diabetes
Meningococcal oligosaccharides conjugated	Menveo		1	1			2010-05-21		1	vaccines
Pazopanib	Votrient		1	1			2010-05-27	1		antineoplastic agents
Paliperidone	Invega sustenna		1	1			2010-06-30	1		psycholeptics
Sevelamer	Renvela		1	1			2010-07-07	1		all other therapeutic products
Dexlansoprazole	Dexilant		1	1			2010-07-22	1		drugs for acid related disorders

Denosumab	Prolia		1	1		2010-08-06		1	drugs for treatment of bone disease
Febuxostat	Uloric		1	1		2010-09-22	1		antigout preparations
Lacosamide	Vimpat		1	1		2010-09-30	1		antiepileptics
Velaglucerase alf	VPRIV		1	1		2010-10-01		1	other alimentary tract and metabolism products
Roflumilast	Daxas		1	1		2010-11-23	1		drugs for obstructive airway diseases
Tapentadol	Nucynta CR		1	1		2010-12-02	1		analgesics
Silodosin	Rapaflo		1	1		2011-01-11	1		urologicals
Eltrombopag	Revolade		1	1		2011-01-12	1		antihemorrhagics
Exenatide	Byetta		1	1		2011-01-13	1		drugs used in diabetes
Fingolimod	Gilenya		1	1		2011-03-09	1		immunosuppressants
Ticagrelor	Brilinta		1		1	2011-05-30	1		antithrombotic agents
Cabazitaxel	Jevtana		1	1		2011-06-16	1		antineoplastic agents
Rufinamide	Banzel		1	1		2011-06-22	1		antiepileptics
Belimumab	Benlysta		1	1		2011-07-06		1	immunosuppressants
Rilpivirine	Edurant		1	1		2011-07-21	1		antivirals for systemic use
Tolvaptan	Samsca		1	1		2011-07-25	1		diuretics
Abiraterone	Zytiga		1		1	2011-07-27	1		endocrine therapy
Linagliptin	Trajenta		1	1		2011-07-28	1		drugs used in diabetes
Boceprevir	Victrelis	1			1	2011-07-29	1		antivirals for systemic use
Boceprevir, peginterferon alfa-2b, ribavirin	Victrelis Triple	1			1	2011-08-10	1		immunostimulants
Telaprevir	Incivek		1		1	2011-08-16	1		antivirals for systemic use
Colesevelam	Lodalis		1	1		2011-09-22	1		lipid modifying agents
Senapine	Saphris		1	1		2011-10-07	1		psycholeptics

Dienogest	Visanne		1	1		2011-10-12	1		sex hormones and modulators of the genital system
Indacaterol	Onbrez breezhaler		1	1		2011-12-06	1		drugs for obstructive airway diseases
Prucalopride	Resotran		1	1		2011-12-07	1		drugs for constipation
Plerixafor	Mozobil		1	1		2011-12-08	1		immunostimulants
Eribulin	Halaven		1	1		2011-12-14	1		antineoplastic agents
Apixaban	Eliquis		1	1		2011-12-16	1		antithrombotic agents
Vandetanib	Caprelsa		1	1		2012-01-12	1		antineoplastic agents
Ipilimumab	Yervoy		1	1		2012-02-01		1	antineoplastic agents
Fesoterodine	Toviaz		1	1		2012-02-09	1		urologicals
Fampridine	Fampyra		1	1		2012-02-10	1		other nervous system
Vemurafenib	Zelboraf	1			1	2012-02-15			antineoplastic agents
Azilsartan	Edarbi		1	1		2012-03-08	1		agents acting on the renin-angiotensin system
Ofatumumab	Arzerra		1	1		2012-03-09		1	antineoplastic agents
Palonosetron	Aloxi		1	1		2012-03-14	1		antiemetics and antinauseants
Crizotinib	Xalkori		1	1	1	2012-04-25	1		antineoplastic agents
Fidaxomicin	Dificid		1	1		2012-06-07	1		antidiarrheals, intestinal antiinflammatory/antiinfective agents
Lurasidone	Latuda		1	1		2012-06-13	1		psycholeptics
Ruxolitinib	Jakavi		1		1	2012-06-19	1		antineoplastic agents
Collagenase clostridium histolyticum	Xiaflex	1		1		2012-07-05		1	other drugs for disorders of the musculo-skeletal system
Axitinib	Inlyta		1	1		2012-07-12	1		antineoplastic agents
Catridecacog	Tretten		1		1	2012-07-19		1	antihemorrhagics
Bendamustine	Treanda		1	1		2012-08-24	1		antineoplastic agents
Pirfenidone	Esbriet		1		1	2012-10-01			immunosuppressants

Elvitegravir, emtricitabine, tenofovir, cobicistat	Stribild		1	1		2012-11-26	1		antivirals for systemic use
Ivacaftor	Kalydeco	1			1	2012-11-26	1		other respiratory system products
Stiripentol	Diacomit		1	1		2012-12-21	1		antiepileptics
Nebivolol	Bystolic		1	1		2012-12-21	1		beta blocking agents
Ingenol	Picato		1	1		2013-01-30	1		antibiotics and chemotherapeutics for dermatological use
Brentuximab	Adcetris		1	1	1	2013-02-01		1	antineoplastic agents
Meningococcal polysaccharide groups A,C,W-135 & Y conjugate vaccine, Tetanus toxoid	Nimenrix		1	1		2013-03-05		1	vaccines
Mirabegron	Myrbetriq		1	1		2013-03-06	1		urologicals
Regorafenib	Stivarga		1		1	2013-03-11	1		antineoplastic agents
Rotigotine	Neupro		1	1		2013-03-21	1		anti-parkinson drugs
Dimethyl	Tecfidera		1	1		2013-04-03	1		other nervous system
Perampanel	Fycompa		1	1		2013-04-04	1		antiepileptics
Pertuzumab	Perjeta	1			1	2013-04-12		1	antineoplastic agents
Enzalutamide	Xtandi		1		1	2013-05-29	1		endocrine therapy
Ulipristal	Fibristal		1	1		2013-06-24	1		sex hormones and modulators of the genital system
Vismodegib	Erivedge		1	1		2013-07-12	1		antineoplastic agents
Dabrafenib	Tafinlar		1	1		2013-07-16	1		antineoplastic agents
Trametinib	Mekinist		1	1		2013-07-18	1		antineoplastic agents

Fluticasone and vilatnerol	Breo ellipta		1	1		2013-07-23	1		drugs for obstructive airway diseases
Aclidinium	Tudorza genuair		1	1		2013-07-29	1		drugs for obstructive airway diseases
Rifaximin	Zaxine		1		1	2013-08-13	1		antidiarrheals, intestinal antiinflammatory/antiinfective agents
Ocriplasmin	Jetrea	1			1	2013-08-13		1	ophthalmologicals
Trastuzumab emtansine	Kadcyla		1		1	2013-09-11		1	antineoplastic agents
Galsulfase	Naglazyme	1		1		2013-09-16		1	other alimentary tract and metabolism products
Riociguat	Adempas		1		1	2013-09-19	1		antihypertensives
Pasireotide	Signifor	1		1		2013-09-23	1		pituitary and hypothalamic hormones
Efinaconazole	Jublia		1	1		2013-10-02	1		drugs used in diabetes
Romidepsin	Istodax		1	1		2013-10-16	1		antineoplastic agents
Dolutegravir	Tivicay		1	1		2013-10-31	1		antivirals for systemic use
Afatinib	Giotrif		1	1		2013-11-01	1		antineoplastic agents
Macitentan	Opsumit		1	1		2013-11-06	1		antihypertensives
Aflibercept	Eylea		1	1		2013-11-08		1	antineoplastic agents
Teriflunomide	Aubagio		1	1		2013-11-14	1		immunosuppressants
Simeprevir	Galexos		1		1	2013-11-18	1		antivirals for systemic use
Alogliptin	Nesina		1	1		2013-11-27	1		drugs used in diabetes
Linaclotide	Constella		1	1		2013-12-02	1		drugs for constipation
Multicomponent meningococcal B vacine	Bexsero	1		1		2013-12-06		1	vaccines
Radium-223 dichl	Xofigo		1	1		2013-12-12		1	therapeutic radiopharmaceuticals

Sofosbuvir	Sovaldi	1			1		2013-12-13	1		antivirals for systemic use
Umeclidinium and vilanterol	Anoro ellipta		1	1			2013-12-23	1		drugs for obstructive airway diseases
Pomalidomide	Pomalyst	1			1		2014-01-20	1		immunosuppressants
Lomitapide	Juxtapid		1	1			2014-02-04	1		lipid modifying agents
Aflibercept	Zaltrap		1	1			2014-02-12		1	antineoplastic agents
Bosutinibs	Bosulif		1	1		1	2014-03-14	1		antineoplastic agents
Recombinant human coagulation Factor IX, FC fusion protein	Alprolix		1	1			2014-03-20		1	antihemmorhagics
Tofacitinib	Xeljanz		1	1			2014-04-17	1		immunosuppressants
Tesamorelin	Egrifta		1	1			2014-04-29	1		pituitary and hypothalamic hormones
Canagliflozin	Invokana		1	1			2014-05-23	1		drugs used in diabetes
Taliglucerase Alfa	Elelyso		1	1			2014-05-29		1	other alimentary tract and metabolism products
Eslicarbazepine	Aptiom		1	1			2014-07-08	1		antiepileptics
Antihemophilic factor, FC fusion protein	Eloctate		1	1			2014-08-22		1	antihemmorhagics
Ledipasvir and sofosbuvir	Harvoni		1		1		2014-10-15	1		antivirals for systemic use
Vortioxetine	Trintellix		1	1			2014-10-22	1		psychoanaleptics
Simoctocog alfa	Nuwiq		1	1			2014-10-23		1	antihemmorhagics
Azelastine and fluticasone	Dymista		1	1			2014-10-23	1		nasal preparations
Conjugated estrogens and bazedoxifene acetate	Duavive		1	1			2014-10-23	1		sex hormones and modulators of the genital system

Apremilast	Otezla		1	1			2014-11-12	1		immunosuppressants
Ibrutinib	Imbruvica	1			1	1	2014-11-17	1		antineoplastic agents
Obinutuzumab	Gazyva	1		1			2014-11-25		1	antineoplastic agents
Siltuximab	Sylvant		1		1		2014-12-03		1	immunosuppressants
Dapagliflozin	Forxiga		1	1			2014-12-12	1		drugs used in diabetes
Ritonavir, paritaprevir, ombitasvir, dasabuvir	Holkira Pak		1		1		2014-12-22	1		antivirals for systemic use
Sodium phenylbutyrate	Pheburane		1		1		2015-01-26	1		other alimentary tract and metabolism products
Vedolizumab	Entyvio		1	1			2015-01-29		1	immunosuppressants
Human papillomavirus 9 valent vaccine, recombinant	Gardasil 9		1	1			2015-02-05		1	vaccines
Deferiprone	Ferriprox		1	1			2015-02-13	1		all other therapeutic products
Secukinumab	Cosentyx		1	1			2015-02-27		1	immunosuppressants
Tedizolid	Sivextro		1	1			2015-03-17	1		antibacterials for systemic use
Idelalisib	Zydelig		1	1		1	2015-03-27	1		antineoplastic agents
Ceritinib	Zykadia		1	1		1	2015-03-27	1		antineoplastic agents
Ponatinib	Iclusig		1	1		1	2015-04-02	1		antineoplastic agents
Carglumic Acid	Carbaglu	1			1		2015-04-10	1		other alimentary tract and metabolism products
Ivermectin	Rosiver		1	1			2015-04-22	1		anthelmintics
Levomilnacipran	Fetzima		1	1			2015-05-08	1		psychoanaleptics
Pembrolizumab	Keytruda		1	1		1	2015-05-19		1	antineoplastic agents
Naloxegol	Movantik		1	1			2015-06-02	1		drugs for constipation
Nintedanib	Ofev		1	1			2015-06-25	1		antineoplastic agents

Ramucirumab	Cyramza		1	1			2015-07-16		1	antineoplastic agents
Empagliflozin	Jardiance		1	1			2015-07-23	1		drugs used in diabetes
Mifepristone and Misoprostol	Mifegymiso		1	1			2015-07-29	1		sex hormones and modulators of the genital system
Daclatasvir	Daklinza		1	1		1	2015-08-13	1		antivirals for systemic use
Asfotase Alfa	Strensiq	1		1		1	2015-08-14		1	other alimentary tract and metabolism products
Teduglutide	Revestive		1		1		2015-09-04		1	other alimentary tract and metabolism products
Evolocumab	Repatha		1	1			2015-09-10		1	lipid modifying agents
Nivolumab	Opdivo	1			1		2015-09-25		1	antineoplastic agents
Ceftolozane Sulfate and Tazobactam Sodium	Zerbaxa		1	1			2015-09-30	1		antibacterials for systemic use
Sacubitril, Valsartan	Entresto	1			1		2015-10-02	1		agents acting on the renin-angiotensin system
Dulaglutide	Trulicity		1	1			2015-11-10		1	drugs used in diabetes
Elvitegravir, Cobicistat, Emtricitabine, Tenofovir Alafenamide Hemifumarate	Genvoya		1	1			2015-11-27	1		antivirals for systemic use
Mepolizumab	Nucala		1	1			2015-12-03		1	drugs for obstructive airway diseases
Lenvatinib	Lenvima		1	1			2015-12-22	1		antineoplastic agents
Blinatumomab	Blincyto		1	1		1	2015-12-22		1	antineoplastic agents
Carfilzomib	Kyprolis		1		1		2016-01-15	1		antineoplastic agents

Elbasvir, Grazoprevir	Zepatier		1		1		2016-01-19	1		antivirals for systemic use
Selexipag	Uptravi		1	1			2016-01-20	1		antithrombotic agents
Ivacaftor, Lumacaftor	Orkambi		1		1		2016-01-26	1		other respiratory system products
Sugammadex	Bridion		1	1			2016-02-05	1		all other therapeutic products
Cobimetinib	Cotellic		1	1			2016-02-22	1		antineoplastic agents
Brivaracetam	Brivlera		1	1			2016-03-09	1		antiepileptics
Asunaprevir	Sunvepra		1	1			2016-03-09	1		antivirals for systemic use
Palbociclib	Ibrance		1	1		1	2016-03-16	1		antineoplastic agents
Alirocumab	Praluent		1	1			2016-04-11		1	lipid modifying agents
Bilastine	Blexten		1	1			2016-04-21	1		antihistamines for systemic use
Idarucizumab	Praxbind		1	1		1	2016-04-29		1	all other therapeutic products
Olaparib	Lynparza		1	1		1	2016-04-29	1		antineoplastic agents
Ixekizumab	Taltz		1	1			2016-05-25		1	immunosuppressants
Osimertinib	Tagrisso		1	1		1	2016-07-05	1		antineoplastic agents
Sofosbuvir + Velpatasvir	Epclusa		1		1		2016-07-11	1		antivirals for systemic use
Ixazomib	Ninlaro		1		1		2016-08-04	1		antineoplastic agents
Nitisinone	MDK-Nitisinone	1			1		2016-09-20	1		other alimentary tract and metabolism products
Venetoclax	Venclexta		1	1		1	2016-09-30	1		antineoplastic agents
Edoxaban	Lixiana		1	1			2016-11-04	1		antithrombotic agents
Nitisinone	Nitisinone	1			1		2016-11-04	1		other alimentary tract and metabolism products
Daclizumab beta	Zinbryta		1	1			2016-12-08		1	immunosuppressants

Nitisinone	Orfadin	1				1		2016-12-13	1		other alimentary tract and metabolism products
Ivabradine	Lancora		1	1				2016-12-23	1		cardiac therapy
		55	454	379	130	42			286	99	

***Prescrire evaluations as of February 20, 2018; PMPRB evaluations as of December 31, 2016; Prescrire ratings - offers an advantage, possibly helpful, nothing new, not acceptable; PMPRB ratings - category 3 = moderate, little or no improvement (prior to 2010), slight or no improvement, moderate improvement - primary, moderate improvement - secondary (2010 onwards)**

Supplementary Table 2: All drugs approved between 1995-2016 that did not receive therapeutic assessments

Generic name	Brand name	Review status			Notice of compliance or Notice of compliance with conditions date	Small molecule	Biologic	ATC group (second level)
		Standard	Priority	Notice of compliance with conditions				
Levocarnitine	Carnitor		1		1995-01-19			other alimentary tract and metabolism products
Losoxantrone	Bianda	1			1995-02-19			antineoplastic agents
Carvedilol	Dilatrend	1			1995-02-27			beta blocking agents
Carvedilol	Kredex	1			1995-02-27			beta blocking agents
Halofantrine	Halfan	1			1995-03-29			antiprotozoals
Ceftibuten	Cedax	1			1995-05-09			antibacterials for systemic use
Sermorelin	Geref	1			1995-06-08			pituitary and hypothalamic hormones and analogues
Tetrabenazine	Nitoman	1			1995-12-29			other nervous system drugs
Iron dextran	Dexferrum		1		1996-01-09			antianemic preparations
Rimexolone	Vexol	1			1996-01-17			corticosteroids for systemic use
Measles virus vaccine/Rubella virus vaccine	Moru-Viraten		1		1996-02-26			vaccines
Ferumoxsil	Gastromark	1			1996-03-15			contrast media
Saquinavir	Saquinavir		1		1996-03-22			antivirals for systemic use
Pantoprazole	Panto-Byk	1			1996-07-05			drugs for acid related disorders
Dexfenfluramine	Redux	1			1996-07-29			antiobesity preparations
Palmitic acid/Galactose	Levovist	1			1996-07-31			contrast media
Fleroxacin	Megalone	1			1996-08-21			antibacterials for systemic use

Reviparin	Clivarine	1		1996-09-10	antithrombotic agents
Diptheria, tetanus & acellular pertussis vaccine	Infanrix		1	1996-12-17	vaccines
Cisatracurium	Nimbex injectior	1		1996-12-18	muscle relaxants
Remifentanil	Ultiva injection	1		1996-12-24	anesthetics
Tiludronate	Skelid	1		1997-02-06	drugs for treatment of bone disease
Tazarotene	Tazorac Gel	1		1997-02-25	antipsoriatics
Praziquantel	Biltricide	1		1997-03-07	anthelmintics
Molgramostim	Leucomax		1	1997-03-10	immunostimulants
Fosphenytoin	Cerebyx injectio	1		1997-03-20	antiepileptics
Butenafine	Dr. Scholl's athle	1		1997-04-15	antifungals for dermatological use
Troglitazone	Rezulin		1	1997-05-09	drugs used in diabetes
Trandolapril	Odrik	1		1997-05-15	agents acting on the renin-angiotensin system
Follitropin alpha	Gonal-F	1		1997-06-06	sex hormones and modulators of the genital system
Kit for preparation of indium in 111 imciromab pentetate	Myoscint	1		1997-07-02	diagnotic radiopharmaceuticals
Cytomegalovirus immune globulin	Cytogam	1		1997-08-01	immune sera and immunoglobulins
Oxiconazole	Oxizole	1		1997-08-08	antifungals for dermatological use
Respiratory syncytial virus immune globulin	Respigam		1	1997-08-20	immune sera and immunoglobulins
Arcitumomab	CEA-Scan	1		1997-09-16	diagnotic radiopharmaceuticals

Olopatadine	Patanol	1		1997-09-16		ophthalmologicals
Pegaspargase	Oncaspar	1		1997-11-19		antineoplastic agents
Anagrelide as hydrochloride	Agrylin		1	1997-11-19		antineoplastic agents
Nadroparin	Fraxiparine	1		1997-11-27		antithrombotic agents
Bicisate	OncoScint	1		1998-01-16		diagnotic radiopharmaceuticals
Gadolinium (III)	Gadolite	1		1998-04-08		contrast media
Lexidronam	Quadramet	1		1998-06-22		therapeutic radiopharmaceuticals
Miglitol	Glyset	1		1998-07-22		drugs used in diabetes
Lipoprotein-OspA antigen recombinant	Lymerix		1	1998-12-02		vaccines
Toremifene	Fareston	1		1998-12-14		endocrine therapy
Cefdinir	Omnicef	1		1999-02-05		antibacterials for systemic use
Methacholine	Methacoline	1		1999-02-25		diagnostic agents
Fosfomycin	Monurol	1		1999-04-12		antibacterials for systemic use
Alitretinoin	Panretin		1	1999-06-11		other dermatological preparations
Ioxilan	Oxilan	1		1999-10-05		contrast media
Mangafodipir	Teslascan	1		2000-02-09	1	contrast media
Sevelamer	Renagel	1		2000-02-24	1	all other therapeutic products
Valrubicin	Valstar		1	2000-07-04	1	antineoplastic agents
Ibutilide	Corvert injection	1		2000-07-14	1	cardiac therapy
Fomepizole	Antizol		1	2000-11-30	1	all other therapeutic products
Amlexanox	Apthera	1		2000-12-11	1	stomatological preparations
Tegafur/uracil and leucovorin calcium	Orzel	1		2001-04-06	1	antineoplastic agents
Argatroban	Argatroban		1	2001-06-04	1	antithrombotic agents

Aminolevulinic acid	Levulan	1			2001-06-20	1		antineoplastic agents
Infliximab	Remicade		1		2001-09-27		1	immunosuppressants
Levobupivacaine	Chirocaine	1			2002-03-20	1		anesthetics
Unoprostone isopropyl	Rescula	1			2002-04-03	1		ophthalmologicals
Thyrotropin	Thyrogen	1			2002-05-31		1	diagnostic agents
Anti-thymocyte globulin	Thymoglobulin	1			2002-11-20		1	immunosuppressants
Dextromethylpheni date	Attenade	1			2003-08-12	1		psychoanaleptics
Sulfur Hexafluoride	Sonovue	1			2004-02-12	1		contrast media
Yttrium-90	Yttrium-90		1		2004-12-02		1	therapeutic radiopharmaceuticals
Choriogonadotropin Alfa	Ovidrel	1			2004-12-16		1	sex hormones and modulators of the genital system
Sulesomab	Leukoscan	1			2005-01-17		1	diagnotic radiopharmaceuticals
Tositumomab	Bexxar		1		2005-08-18		1	therapeutic radiopharmaceuticals
Nitric oxide	Inomax		1		2005-09-23	1		other respiratory system products
F-Fluorodeoxyglucose	Cantrace		1		2006-07-27		1	diagnotic radiopharmaceuticals
Lumiracoxib	Prexige	1			2006-11-02	1		antiinflammatory and antirheumatic products
Nelarabine	Atriance			1	2007-09-22	1		antineoplastic agents
Rotavirus vaccine	Rotarix	1			2007-10-09		1	vaccines
Retapamulin	Altargo	1			2008-03-19	1		antibiotics and chemotherapeutics for dermatological use

Methoxy Polyethylene glycol-epoetin beta	Mircera	1		2008-03-31		1	antianemic preparations
Telavancin	Vibativ	1		2009-09-29	1		antibacterials for systemic use
Human C1 esterase inhibitor	Berinert	1		2010-05-31		1	other hematological agents
Influenza vaccine	Flumist	1		2010-06-22		1	vaccines
Zucapsaicin	Civanex (Zuacta	1		2010-07-15	1		topical products for joint and muscular pain
Clevidipine	Cleviprex	1		2011-04-15	1		calcium channel blockers
Rubidium chloride rb 82	Ruby-fill		1	2011-09-20		1	diagnotic radiopharmaceuticals
Doxycycline	Efracea	1		2011-11-14	1		antibacterials for systemic use
Ferumoxytol	Feraheme	1		2011-12-08	1		antianemic preparations
Remestemcel-L	Prochymal		1	2012-05-17		1	unassigned
Ezogabine	Potiga	1		2012-10-08	1		antiepileptics
Haemagglutinin-Strain A	Arepranrix H5N1	1		2013-02-13		1	vaccines
Olodaterol	Striverdi respima	1		2013-06-11	1		drugs for obstructive airway diseases
Difluprednate	Durezol	1		2013-11-04	1		corticosteroids, dermatological preparations
Tafluprost	Saflutan	1		2014-05-26	1		ophthalmologicals
Elosulfase Alfa	Vimizim		1	2014-07-02		1	other alimentary tract and metabolism products
Turoctocog alfa	Zonovate	1		2014-12-08		1	antihemorrhagics
Bromfenac	Prolensa	1		2015-03-26	1		ophthalmologicals
Albiglutide	Eperzan	1		2015-07-15		1	drugs used in diabetes
Vilazodone	Viibryd	1		2015-07-16	1		psychoanaleptics
Polidocanol	Varithena	1		2015-08-04	1		vasoprotectives
Peginterferon Beta-1A	Plegridy	1		2015-08-10		1	immunostimulants

Antihemophilic Factor (Recombinant) Porcine Sequence	Obizur	1			2015-10-14		1	antihemorrhagics
Lubiprostone	Amitiza	1			2015-10-14	1		drugs for constipation
Albutrepenonacog Alfa	Idelvion	1			2016-01-26		1	antihemorrhagics
Finafloxacin	Xtoro	1			2016-03-11	1		otologicals
Glycerol Phenylbutyrate	Ravicti		1		2016-03-16	1		other alimentary tract and metabolism products
Vorapaxar	Zontivity	1			2016-05-13	1		antithrombotic agents
Elotuzumab	Empliciti		1		2016-06-21		1	antineoplastic agents
Daratumumab	Darzalex			1	2016-06-29		1	antineoplastic agents
Rupatadine	Rupall	1			2016-07-20	1		antihistamines for systemic use
Reslizumab	Cinqair	1			2016-07-20		1	drugs for obstructive airway diseases
Bepotastine	Bepreve	1			2016-07-27	1		antihistamines for systemic use
Alectinib	Alecensaro			1	2016-09-29	1		antineoplastic agents
Antihemophilic Factor (Recombinant), PEGylated	Adynovate	1			2016-11-17		1	antihemorrhagics
Gadoterate Meglumine	Dotarem	1			2016-11-25	1		contrast media
Botulinium antitoxin serotypes A, B,C, D, E, F and G	BAT	1			2016-12-08		1	immune sera and immunoglobulins
Lonoctocog Alfa	Afstyla	1			2016-12-12		1	antihemorrhagics

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Location in study
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Ttile, page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Structured summary, pages 2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Introduction, page 5
Objectives	3	State specific objectives, including any prespecified hypotheses	Introduction, page 6
Methods			
Study design	4	Present key elements of study design early in the paper	Methods, pages 6-8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Methods, pages 6-8, 10
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	Methods, pages 6, 7
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Methods, pages 8-10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Methods, pages 7-10
Bias	9	Describe any efforts to address potential sources of bias	Not relevant
Study size	10	Explain how the study size was arrived at	Not relevant
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Not relevant
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Methods, page 10
		(*b*) Describe any methods used to examine subgroups and interactions	Methods, pages 9, 10

		(*c*) Explain how missing data were addressed	Not relevant
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	Not relevant
		(*e*) Describe any sensitivity analyses	Not relevant
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Results, pages 10-12
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	Not relevant
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Not relevant
		(b) Indicate number of participants with missing data for each variable of interest	Results, page 13
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	Not relevant
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	Results, pages 11-15
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	Not relevant
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not relevant
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Not relevant
Discussion			
Key results	18	Summarise key results with reference to study objectives	Discussion, page 16
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Limitations, page 19
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Conclusion, page 19

Generalisability	21	Discuss the generalisability (external validity) of the study results	Not relevant
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 20

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Health Canada's use of expedited review pathways and therapeutic innovation, 1995-2016: cross sectional analysis

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Health Canada's use of expedited review pathways and therapeutic innovation, 1995-2016: cross sectional analysis

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Structured summary

Objectives

This study examines the use of expedited approval pathways by Health Canada over the period 1995 to 2016 inclusive and the relationship between the use of these pathways and the therapeutic gain offered by new products.

Design

Cross sectional study.

Data sources

Therapeutic Products Directorate, Biologics and Genetic Therapies Directorate, Notice of Compliance database, Notice of Compliance with conditions web site, Patented Medicine Prices Review Board, La revue Prescrire, World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) classification system.

Interventions

None

Primary and secondary outcomes

Percent of new drugs evaluated by Health Canada that went through an expedited pathway between 1995 and 2016 inclusive. Kappa values comparing the review status to assessments of therapeutic value for individual drugs.

Results

Of 623 drugs approved by Health Canada between 1995 and 2016, 438 (70.3%) drugs went through the standard pathway, 185 (29.7%) an expedited pathway. Therapeutic evaluations were available for 509 drugs. Health Canada used an expedited approval pathway for 159 of the 509 drugs whereas only 55 were judged to be therapeutically innovative. Forty-two of the 55 therapeutically innovative drugs received an expedited review and 13 received a standard review. The Kappa value for the entire period for all 509 drugs was 0.276 (95% CI 0.194, 0.359) indicating "fair" agreement between Health Canada's use of expedited pathways and independent evaluations of therapeutic innovation.

Conclusion

Health Canada's use of expedited approvals was stable over the entire time period. It was unable to reliably predict which drugs will offer major therapeutic gains. The findings in this study should provoke a discussion about whether Health Canada should continue to use these pathways and if so how their use can be improved.

Article Summary

Strengths and limitations of this study

- Cross sectional analysis of the use of expedited approval pathways by Health Canada over an extended period of time.
- Comparison of use of expedited approval pathways to independent assessment of therapeutic evaluation.
- Analysis of approvals and therapeutic value of therapeutic subgroups.
- Twenty percent of new drugs approved did not have therapeutic evaluations.

- **Acknowledgements**
- None

- **Competing Interests**
- In 2015-2017, Joel Lexchin received payment from two non-profit organizations for being a consultant on a project looking at indication-based prescribing and a second looking at which drugs should be distributed free of charge by general practitioners. In 2015, he received payment from a for-profit organization for being on a panel that discussed expanding drug insurance in Canada. He is on the Foundation Board of Health Action International.

- **Funding**
- This research received no specific grant from any funding agency in the public, commercial or not-for profit sectors.

- **Data sharing statement**
- Extra data can be accessed via the Dryad data repository at http://datadryad.org/ with the doi: 10.5061/dryad.0bf6000

- **Contributorship statement**
- JL came up with the idea for this study, gathered and analyzed the data and wrote the manuscript.

Introduction

In order to obtain authorization to market a new active substance (NAS - a molecule never marketed before in Canada in any form) in Canada, companies typically file a New Drug Submission (NDS) which includes preclinical and clinical scientific information about the product's safety, efficacy and quality and information about its claimed therapeutic value, conditions for use and side effects [1]. Health Canada then has a 300-day period to evaluate this information and make a decision about whether to allow the product to be sold, i.e., whether to issue a Notice of Compliance (NOC).

In an effort to ensure that promising therapies for serious, life-threatening or debilitating illnesses reach Canadians in a timely manner, Health Canada has developed two other pathways for approving NAS. These are described in detail elsewhere [2], but briefly, the first of these is a priority review that involves the company submitting a complete NDS but with a review period of 180 days [3]. The second is the Notice of Compliance with conditions (NOC/c) [4] whereby Health Canada will give a conditional approval based on limited evidence – Phase II clinical trials or trials with only surrogate markers. In return for NOC/c status, companies commit to further studies that definitively establish efficacy and submit the results of these to Health Canada. A failure to complete these studies or negative results from them could lead to the marketing authorization being cancelled.

Lexchin has examined how closely Health Canada's use of the two pathways (priority review and NOC/c, hereafter collectively termed expedited review pathways) corresponds to independent assessments of the therapeutic innovation of drugs at the level of individual drugs. For the period 1997-2012, the Kappa value was 0.334 (95% CI 0.220, 0.447) or fair [5].

This current study is a further and more detailed look at how Health Canada uses its expedited review pathways, by extending previous work in a number of ways. First it covers a wider time period – 1995 to 2016, inclusive. Second, it looks at the use of both of the expedited review pathways over this entire time period for the entire sample of drugs as well as subgroups – small molecule drugs, biologics, and therapies for serious diseases. Third, it calculates the Kappa values for the entire sample of drugs as well as the subgroups listed above. These subgroups were chosen because small molecules and biologics have fundamentally different characteristics and these may influence a decision to use an expedited review pathway and how accurately Health Canada can predict their therapeutic value. Similarly, when the treatment is for serious medical conditions, Health Canada may be more willing to use an expedited review pathway and may be more likely to believe that the new product will provide a significant therapeutic benefit.

Methods

Data sources

All NAS approved from 1995 to 2016 inclusive were documented using the annual reports from the Therapeutic Products and the Biologics and Genetic Therapies Directorates that are in charge of reviewing applications for new small molecule drugs and biologics and vaccines, respectively. (Reports are available by directly contacting the directorates at publications@hc-sc.gc.ca.) A starting year of 1995 was selected as there are no annual reports from Health Canada prior to that year. Generic and brand names along with the specific approval pathway – standard, priority, NOC/c (only from 1998 onwards) – and whether the product was a small molecule drug or biologic (information available only from 2000 onwards) were manually extracted from the annual reports by the author.

Not all of the drugs with a NOC/c are documented in the annual reports and they were supplemented using four additional sources: articles by Lexchin [6] and Law [7], the Notice of Compliance database (http://webprod5.hc-sc.gc.ca/noc-ac/index-eng.jsp) and the Notice of Compliance with conditions web site (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/conditions/index-eng.php). Only NAS approved under a NOC/c were considered. Drugs can receive both a priority and NOC/c review and in this case they were only counted as receiving a priority review.

Assessment of therapeutic innovation

The therapeutic value of drugs was assessed using the ratings from the annual reports of the Canadian Patented Medicine Prices Review Board (PMPRB) (http://www.pmprb-cepmb.gc.ca/english/View.asp?x=91) and Prescrire International, the English language translation of the French drug bulletin La revue Prescrire [8]. The processes that these two organizations use in arriving at their decisions about therapeutic innovation have been previously described [5]. For the purpose of this study, products that the PMPRB deemed breakthrough and substantial improvement were termed "innovative" and products in other categories were termed "not innovative" (category 3 = moderate, little or no improvement over existing medicines prior to 2010; slight or no improvement, moderate improvement – primary and moderate improvement – secondary from 2010 onward). Prescrire uses seven categories to rate therapeutic innovation. The first two, bravo (major therapeutic innovation in an area where previously no treatment was available); a real advance (important therapeutic innovation but has limitations) were defined as a significant therapeutic innovation and the other Prescrire categories (except judgment reserved) were defined as no therapeutic advance.

If both the PMPRB and Prescrire evaluated the drug and the ratings were discordant, i.e., one said it was not innovative and one said it was, the drug was still considered innovative. Table 1 shows that there is substantial agreement among the definitions used by Health Canada, the PMPRB and Prescrire in assessing therapeutic innovation. Ratings were current for PMPRB as of December 31, 2016 (the annual report for 2017 was not available at the time of writing) and for Prescrire as of February 20, 2018.

Table 1: Criteria used by Health Canada in determination of priority review or Notice of Compliance with conditions pathway and by Human Drug Advisory Panel and Prescrire in determining innovation status

Health Canada – criteria for priority review and NOC/c* pathway	**Human Drug Advisory Panel of Patented Medicine Prices Review Board – criteria for breakthrough and substantial improvement**	**Prescrire – criteria for bravo and a real advance**
Priority review: A serious, life-threatening or severely debilitating illness or condition for which there is substantial evidence of clinical effectiveness that the drug provides: effective treatment, prevention or diagnosis of a disease or condition for which no drug is presently marketed in Canada	Breakthrough = first drug product to treat effectively a particular illness	Bravo = major therapeutic innovation in an area where previously no treatment was available
NOC/c pathway: Provides patients suffering from serious, life threatening or severely debilitating diseases or conditions with earlier access to promising new drugs	Substantial improvement = provides a substantial improvement over existing drug products	A real advance = product is an important therapeutic innovation but has certain limitations

Adapted from: [9]
*Notice of Compliance with conditions

Data analysis

The number and percent of drugs approved through the standard, priority and NOC/c

pathways were calculated for each year and for the 22-year period.

Kappa values were used to compare the review status from Health Canada to the assessments for the same drug from the PMPRB and/or Prescrire for each year and for the 22-year period. Drugs approved through the priority review and NOC/c pathways were analyzed together as a single group. Kappa scores measure whether there is more or less agreement between different evaluations than would be expected by chance. Levels of agreement were graded in accordance with the recommendations of Landis and Koch where < 0 indicates no agreement, 0 – 0.20 slight agreement, 0.21 – 0.40 fair agreement, 0.41 – 0.60 moderate agreement, 0.61 – 0.80 substantial agreement, and 0.81–1.0 almost perfect agreement [10].

Subgroup analyses

The number and percent of small molecule drugs and biologics approved through the standard, priority and NOC/c pathways were calculated and compared using the Chi-square statistic. Similarly, the Kappa values were calculated separately for small molecule drugs and biologics.

All drugs were categorized using the second level of the World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) classification system [11]. Drugs in three therapeutic groups – antineoplastic agents (L01), antivirals for systemic use (J05) and immunosuppressants (L04) – were chosen for subgroup analyses because they are primarily used for serious, life-threatening diseases and because there are sufficient numbers in each group to allow for statistical analyses. The number and percent of each subgroup that received an expedited review was calculated and the review status and therapeutic ratings were compared for each drug in each of the subgroups including "all other therapeutic groups" and Kappa values were calculated for each subgroup. Distribution of approval pathways in the subgroups individually

and for the three subgroups combined versus all other therapeutic groups was compared using the Chi-square statistic. Calculations were done using Excel 2016 for Macintosh (Microsoft) and Prism 7.0 (GraphPad Software).

Patient and public involvement

No patients were involved in any aspect of this study.

Ethics

No patients were involved in this study and only publicly available data was gathered. Therefore, ethics approval was not required.

Results

Review status

From January 1, 1995 to December 31, 2016 Health Canada approved a total of 623 NAS. Of these, 438 (70.3%) went through the standard pathway, 152 (24.4%) the priority pathway and 33 (5.3%) received a NOC/c. Almost 30 percent (29.7%) went through the expedited review pathways over the entire period, varying from a low of 9.1% in 2010 to a high of 47.8% in 2006 (Table 2). (Health Canada used both a priority and NOC/c approval for 11 drugs, data not shown.) Visual inspection of Figure 1 shows that there is no trend to using expedited review pathways more liberally or more conservatively over the time period. (Supplementary Tables 1 & 2, drugs with and without therapeutic evaluations, respectively, give all of the data extracted for the 623 drugs in question.)

Table 2: Review status of new active substances approved 1995-2016

Year	Number of new active	Number (%) with standard	Number (%) with	Number (%) with NOC/c*	Number (%) with any

	substances approved	review	priority review	review	expedited pathway review
1995	30	26 (86.7)	4 (13.3)	--	4 (13.3)
1996	33	24 (72.7)	9 (27.3)	--	9 (27.3)
1997	42	34 (81.0)	8 (19.0)	--	8 (19.0)
1998	30	26 (86.7)	2 (6.7)	2 (6.7)	4 (13.3)
1999	36	24 (66.7)	12 (33.3)	0 (0)	12 (33.3)
2000	26	15 (57.7)	11 (42.3)	0 (0)	11 (42.3)
2001	27	17 (63.0)	9 (33.3)	1 (3.7)	10 (37.0)
2002	24	20 (83.3)	4 (16.7)	0 (0)	4 (16.7)
2003	20	12 (60.0)	8 (40.0)	0 (0)	8 (40.0)
2004	29	19 (65.5)	9 (31.0)	1 (3.4)	10 (34.5)
2005	24	13 (54.2)	10 (41.7)	1 (4.2)	11 (45.8)
2006	23	12 (52.2)	9 (39.1)	2 (8.7)	11 (47.8)
2007	24	14 (58.3)	7 (29.2)	3 (12.5)	10 (41.7)
2008	17	11 (64.7)	2 (11.8)	4 (23.5)	6 (35.3)
2009	27	21 (77.8)	6 (22.2)	0 (0)	6 (22.2)
2010	22	20 (90.9)	2 (9.1)	0 (0)	2 (9.1)
2011	27	21 (77.8)	6 (22.2)	0 (0)	6 (22.2)
2012	23	16 (69.6)	5 (21.7)	2 (8.7)	7 (30.4)
2013	39	28 (71.8)	9 (23.1)	2 (5.1)	11 (28.2)
2014	25	18 (72.0)	6 (24.0)	1 (4.0)	7 (28.0)
2015	37	25 (67.6)	5 (13.5)	7 (18.9)	12 (32.4)
2016	38	21 (55.3)	10 (26.3)	7 (18.4)	17 (44.7)
Total	623	438 (70.3)	152 (24.4)	33 (5.3)	185 (29.7)

*Notice of Compliance with conditions
†Patented Medicine Prices Review Board

There were 126 biologics approved versus 323 small molecules (data only available from 2000 onward). There was no difference in the distribution of the approval pathways (p = 0.4867) (Table 3). There were 81 approvals for antineoplastic agents, 47 for antivirals for systemic use, 36 for immunosuppressants and 365 for drugs in the remaining 68 categories ("all other 68 therapeutic groups") (Supplementary Table 1). The distribution of approval pathways was significantly different for the three subgroups (p = 0.0018) and for the three subgroups combined versus "all other therapeutic groups" (p < 0.00001) (Table 3).

Table 3: Subgroup comparison of review pathways

Subgroup	Standard	Priority	Notice of compliance with conditions	Total
Small molecules	129	72	22	323
Biologics	73	45	8	126
Antineoplastic agents	34	26	21	81
Antivirals for systemic use	16	26	5	47
Immunosuppressants	22	13	1	36
All other 68 therapeutic groups	365	89	5	459

Small molecules vs. biologics: chi-square = 1.4402 (p = 0.4867)
Antineoplastics vs. antivirals vs. immunosuppressants: chi-square = 17.1978 (p = 0.0018)
Antineoplastics + antivirals + immunosuppressants vs. all other therapeutic groups: chi-square = 97.4874 (p < 0.00001)

Therapeutic value

Out of the 623 NAS, 509 (81.7%) were evaluated for their therapeutic innovation either by the PMPRB and/or Prescrire. Health Canada used an expedited review pathway for 159 of the 509 drugs whereas only 55 were judged to be therapeutically innovative by one or both of the independent reviews. Forty-two of the 55 drugs that were therapeutic innovations received an expedited review, 13 received a standard review and 117 (159 – 42) that were not therapeutic innovations also received an expedited review (Table 4). The Kappa value for the entire period for all 509 drugs was 0.276 (95% CI 0.194, 0.359) or fair. Figure 2 presents the Kappa values for each year which generally ranged from 0 (slight) to 0.4 (fair).

Table 4: Number of new active substances with an expedited review and therapeutically innovative rating

Year	Number (%) of NAS* with a therapeutic assessment from	Number of NAS with an expedited review	Number of NAS rated as therapeutic innovation by	Number of therapeutically innovative NAS with an

	Patented Medicine Prices Review Board and/or Prescrire		either Patented Medicine Prices Review Board and/or Prescrire	expedited review
1995	22 (73.3)	3	1	0
1996	20 (60.6)	5	4	3
1997	24 (57.1)	4	4	2
1998	24 (80.0)	4	1	0
1999	31 (86.1)	10	1	0
2000	20 (76.9)	9	4	4
2001	23 (85.2)	8	1	1
2002	20 (83.3)	4	0	0
2003	19 (95.0)	8	2	2
2004	26 (89.7)	9	3	3
2005	21 (87.5)	9	3	2
2006	21 (91.3)	9	3	2
2007	22 (91.7)	9	3	3
2008	15 (88.2)	6	2	2
2009	26 (96.3)	7	0	0
2010	19 (86.4)	2	2	2
2011	23 (85.3)	5	2	2
2012	21 (91.3)	6	3	2
2013	36 (92.3)	11	6	3
2014	22 (88.0)	6	3	2
2015	30 (81.1)	12	4	4
2016	24 (63.2)	13	3	3
1995-2016	509 (81.7)	159	55	42

*New active substance

†Number of drugs rated as innovative as a percent of all drugs given an expedited approval review by Health Canada

‡Number of drugs rated as not therapeutically innovative as a percent of all drugs given a standard review by Health Canada

There were 286 and 99 small molecule drugs and biologics, respectively, with therapeutic ratings. The Kappa values were 0.313 (95% CI 0.205, 0.420) (fair) and 0.233 (95% CI 0.061, 0.405) (fair), respectively. The overlapping 95% CIs indicate no difference in the Kappa values between the two groups (Table 5).

Table 5: Subgroup analyses: Kappa values

Subgroup	Number (%)	Kappa value (95% CI)
Small molecule	286	0.313 (0.205,

drugs		0.420)
Biologics	99	0.233 (0.061, 0.405)
Antineoplastic agents	71	0.091 (0.017, 0.200)
Antivirals for systemic use	46	0.122 (0.011, 0.233)
Immunosuppressants	35	0.376 (0.075, 0.675)
All other therapeutic groups	357	0.385 (0.263, 0.506)

The 509 drugs were in 58 different second level ATC groups (drugs in 13 ATC groups did not have therapeutic evaluations): antineoplastic agents (71), antivirals for systemic use (46), immunosuppressants (35) and "all other therapeutic groups" (357) (Supplementary Table 1). Kappa values for the four groups were: 0.091 (95% CI 0.017, 0.200) (slight), 0.200), 0.122 (95% CI 0.011, 0.233) (slight)), 0.376 (95% CI 0.075, 0.675) (fair) and 0.385 (95% CI 0.263, 0.506) (fair), respectively. The 95% CIs for the Kappa values for the antineoplastic agents, antivirals for systemic use and immunosuppressants overlapped indicating no difference among the groups and the 95% CI for the immunosuppressants overlapped with the 95% CI for "all other therapeutic groups". Drugs in the three therapeutic subgroups were much less likely to receive a standard review than were drugs in "all other therapeutic groups", 43.7% versus 79.1% (data not shown).

Discussion

Almost 30% of the 623 new active substances that Health Canada reviewed between 1995 and 2016 went through at least one of two expedited review pathways – priority review or NOC/c, primarily a priority review. There is no difference between small molecule drugs and biologics in the approval pathways used indicating that for these two groups Health Canada does not see one or the other being more likely to offer significant new therapeutic benefits. However, the same is not true for the therapeutic subgroups. Drugs in the three specifically

examined – antineoplastics, antivirals and immunosuppressants – were collectively more likely to be assigned to an expedited review pathway (56%) compared to drugs in "all other therapeutic groups" (20.9%), possibly because of the nature of the diseases that they treat.

Just over 80% of the NAS approved had been assessed by the PMPRB and/or Prescrire for their therapeutic benefit. The Kappa value for the 509 drugs was 0.276 meaning that Health Canada's ability to predict major therapeutic gain from these drugs was only fair. Furthermore, almost 25% (13/55) of the drugs that were therapeutic innovations did not receive an expedited review underscoring that Health Canada is not reliably able to predict which drugs will offer major therapeutic gains. The relatively low Kappa value may relate to when Health Canada makes its decision about what type of approval pathway to use. This assignment is at the start of the review process when all of the data will not have been fully assessed. In contrast, the PMPRB and Prescrire make their assessments after the drug has been marketed when more information about efficacy and safety is available.

As was the case with the assignment of an expedited review pathway, there is no difference in how accurately Health Canada predicts the therapeutic value of small molecule drugs and biologics as measured by Kappa values. The Kappa value for drugs in "all other therapeutic groups" is higher than the value for drugs in the antineoplastic, antiviral and immunosuppressant groups. This difference may be because Health Canada is better able to predict that these drugs are less likely to be therapeutic innovations than drugs in the antineoplastic, antiviral and immunosuppressant groups. Out of the 357 drugs that had therapeutic evaluations in the "all other therapeutic groups," 79.3% received a standard review compared to 43.7% of the 151 drugs in the three therapeutic subgroups.

How Health Canada uses its expedited review pathways is important for a number of reasons. First, their use may explicitly create an impression among clinicians and patients that these drugs are likely to deliver major new therapeutic benefits despite the fact that the likelihood that they will is only "fair" as measured by the Kappa value. Second, the NOC/c pathway requires companies to commit to conducting post-market studies to validate the efficacy of the product, but many of these studies are delayed [6 7], leaving clinicians and patients uncertain about the value of these products. In at least one case, Health Canada did not suspend the sale of a drug and allowed it to stay on the market despite not fulfilling the conditions required under its NOC/c. In December 2003, Iressa (gefitinib) was approved as a third-line treatment for non-small cell lung cancer on the condition that the company submit a study showing that it improved survival [12]. When the study results were submitted to Health Canada they showed no survival benefit for gefitinib compared to placebo [13]. Health Canada recognized that the conditions had not been fulfilled, but rather than removing gefitinib from the market, in February 2005 it elected to allow it to continue to be sold [12]. In 2009, the drug was deemed to have met its conditions after a new study showed non-inferiority, i.e., survival after taking it was no worse compared to another chemotherapeutic agent [14]. Third, although the priority and standard approval pathways are equivalent in terms of the amount of data reviewed, the former is done in 180 days compared to 300 days for the latter, meaning that the priority pathway is more resource intensive possibly drawing resources from other Health Canada activities. Finally, drugs reviewed through both expedited review pathways are more likely to receive safety warnings once they are on the market compared to drugs with a standard approval [2 15].

As Figure 1 indicates, Health Canada is not using the expedited review pathways more liberally (or more conservatively) over time, but as Figure 2 shows it has not improved its

ability to predict therapeutic innovation over the 22 years evaluated in this study. The Introduction describes the criteria that Health Canada uses to assign a drug to either a priority review or a NOC/c review but how those criteria are applied and whether Health Canada periodically reviews its performance are not known.

Contrary to the situation in the United States (US) where the Food and Drug Administration (FDA) has been using an increasing number of expedited development or review programs, Health Canada's use of its programs has been relatively stable since 1995. Between 1987 and 2014, 43% received a priority review from the FDA and 19% were approved through the fast track program which approximately corresponds to a NOC/c [16]. (Drugs could be associated with both programs.) However, when it comes to approving oncology drugs through an expedited pathway, Health Canada is only marginally better than the FDA. In the US, only 1 of 15 (6.7%) oncology drugs approved through an expedited program from January 1, 2008, through December 31, 2012 had a proven survival benefit compared to the other 6 and 8 that either had no overall survival benefit or an unknown benefit, respectively [17]. In this current study, out of 42 antineoplastic agents that Health Canada gave an expedited review, only 6 (14.3%) were rated as therapeutically innovative. The accelerated assessment (AA) process and the conditional approvals pathway used by the European Medicines Agency (EMA) are roughly the equivalent of Health Canada's priority review and NOC/c pathway [18]. The EMA used the former for 15.5% (23/148) of new drugs between 2012 and 2016 [19 20], while the latter was used for 10.1% (30/296) of new drugs between 2006 and 2016 [20 21]. In the same time periods, Health Canada used a priority approval 21.6% (35/162) of the time time and its NOC/c pathway 9.1% (28/308) of the time.

Limitations

Almost 20% of new drugs approved by Health Canada were not evaluated for their therapeutic innovation by either the PMPRB or La revue Prescrire. The absence of these evaluations may have skewed the Kappa values in either a more positive or more negative direction. The lack of the availability of reports from Health Canada reviewers means that the reasons why drugs were assigned to a specific review pathway cannot be evaluated.

Conclusion

Health Canada continues to use expedited review pathways for about 30% of new drugs. Other regulatory authorities such as the Australian Therapeutic Goods Administration and the EMA are in the process of either implementing or expanding expedited review pathways [22-24] and should study the example of what has happened in Canada. The rationale for using expedited review pathways is to get important therapeutic advances to patients in a timely manner, but Health Canada's ability to predict which of these drugs will fulfill this expectation has not improved over a 22-year period and remains relatively low. Moreover, use of these pathways comes with both health related and resource costs. The findings in this study should provoke a discussion about whether Health Canada should continue to use these pathways and if so how their use can be improved.

Figure 1 legend

Grey – Percent with Notice of Compliance with conditions

Orange – Percent with priority

Blue – Percent with standard

Figure 2 legend

Kappa values:

< 0 = no agreement

0 – 0.20 = slight agreement

0.21 – 0.40 = fair agreement

0.41 – 0.60 = moderate agreement

0.61 – 0.80 = substantial agreement

0.81 – 1.0 = almost perfect agreement

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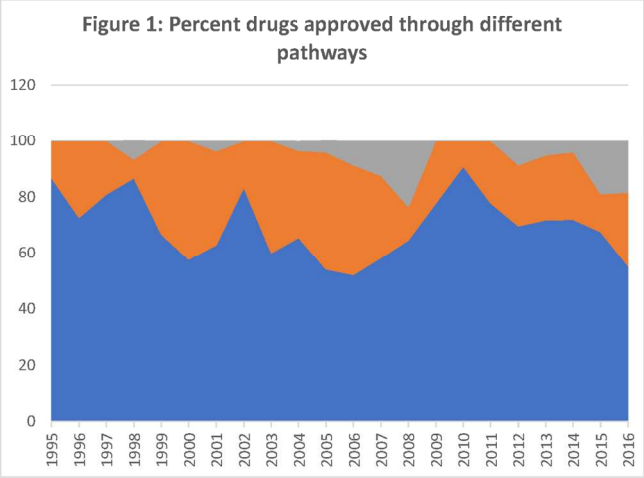

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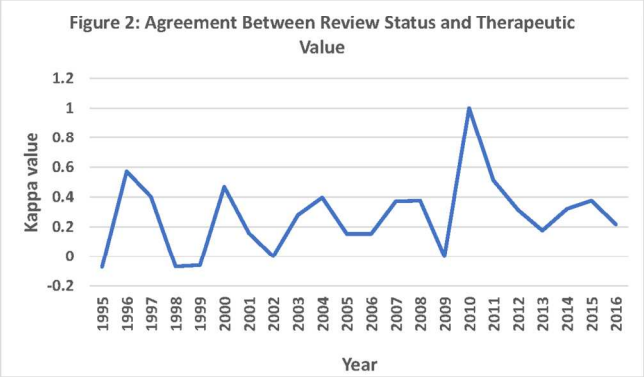

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Supplementary Table 1: All drugs approved between 1995-2016 that received therapeutic assessments from Patented Medicine Prices Review Board and/or La revue Prescrire*

Generic name	Brand name	PMPRB breakthrough, substantial improvement and/or Prescrire bravo, a real advance	PMPRB and/or Prescrire no significant therapeutic innovation†	Review status			Notice of compliance or notice of compliance with conditions date	Small molecule	Biologic	ATC group (second level)
				Standard	Priority	Notice of compliance with conditions				
Adapalene	Differin		1	1			1995-01-24			anti-acne preparation
Dexrazoxane	Zinecard	1		1			1995-02-07			all other therapeutic products
Bambuterol	Bambec		1	1			1995-02-07			drugs for obstructive airway diseases
Naltrexone	Revia		1	1			1995-03-23			other nervous system drugs
Cefprozil	Cefzil		1	1			1995-03-29			antibacterials for
Zuclopenthixol	Clopixol		1	1			1995-04-24			psycholeptics
Zuclopenthixol	Clopixol acuphase		1	1			1995-04-24			psycholeptics
Zuclopenthixol	Clopixol depot		1	1			1995-04-24			psycholeptics
Lansoprazole	Prevacid		1	1			1995-05-12			drugs for acid related disorders
Cefepime	Maxipime		1	1			1995-06-02			antibacterials for systemic use
Interferon Beta-	Betaseron		1		1		1995-07-19			immunostimulants
Famciclovir	Famvir		1	1			1995-07-31			antivirals for systemic use
Cefpodoxime	Orelox		1	1			1995-08-22			antibacterials for
Sevoflurane	Sevorane		1	1			1995-09-18			systemic use anesthetics

Losartan	Cozaar		1	1		1995-09-28	agents acting on the renin-angiotensin system
Iotrolan	Osmovist 280		1	1		1995-10-04	contrast media
Bicalutamide	Casodex		1	1		1995-11-02	endocrine therapy
Acarbose	Prandase		1	1		1995-11-15	drugs used in diabetes
Mycophenolate	Cellcept		1	1		1995-11-15	immunosuppressants
Tacrolimus	Prograf		1		1	1995-12-06	immunosuppressants
Lamivudine	3TC		1		1	1995-12-08	antivirals for systemic use
Alendronate	Fosamax		1	1		1995-12-20	drugs for treatment of bone disease
Stavudine	Zerit		1	1		1996-03-26	antivirals for systemic use
Acellular pertussis vaccine adsorbed	Acel-P		1		1	1996-03-29	vaccines
Dorzolamide	Trusopt		1	1		1996-04-25	ophthalmologicals
Amifostine	Ethyol	1			1	1996-04-25	all other therapeutic products
Valacyclovir	Valtrex		1	1		1996-05-01	antivirals for systemic use
Quinagolide	Norprolac		1	1		1996-06-25	other gynecologicals
Meropenem	Merrem		1	1		1996-07-02	antibacterials for systemic use
Abciximab	Reopro	1		1		1996-07-04	antithrombotic agents
Anastrozole	Arimidex		1	1		1996-08-01	endocrine therapy
Ritonavir	Norvir	1			1	1996-08-14	antivirals for systemic use
Raltitrexed	Tomudex		1		1	1996-09-12	antineoplastic agents
Indinavir	Crixivan	1			1	1996-09-13	antivirals for systemic use
Insulin lispro	Humalog		1	1		1996-10-08	drugs used in diabetes

Dirithromycin	Dynabac		1	1	1996-10-28	antibacterials for systemic use
Olanzapine	Zyprexa		1	1	1996-10-28	psycholeptics
Nalmefene	Revex		1	1	1996-11-06	other nervous system
Zolpidem	Ambien		1	1	1996-11-20	psycholeptics
Desflurane	Suprane		1	1	1996-12-03	anesthetics
Gemcitabine	Gemzar		1	1	1996-12-23	antineoplastic agents
Ropivacaine	Naropin injections		1	1	1996-12-24	anesthetics
Imiglucerase	Cerezyme	1		1	1997-02-12	other alimentary tract and metabolism products
Atorvastatin	Lipitor		1	1	1997-02-19	lipid modifying agents
Topiramate	Topamax		1	1	1997-03-06	antiepileptics
Formoterol	Foradil dry powder capsules		1	1	1997-03-06	drugs for obstructive airway diseases
Epoprostenol	Flolan		1	1	1997-03-06	antithrombotic agents
Coagulation factor IX	Benefix	1		1	1997-03-21	antihemorrhagics
Topotecan	Hycamtin		1	1	1997-04-15	antineoplastic agents
Dolasetron	Anzemet		1	1	1997-05-21	antiemetics and antinauseants
Letrozole	Femara		1	1	1997-05-21	endocrine therapy
Fexofenadine	Allegra		1	1	1997-06-11	antihistamines for systemic use
Latanoprost	Xalatan		1	1	1997-06-16	ophthalmologicals
Carbetocin	Duratocin		1	1	1997-06-24	pituitary and hypothalamic hormones and analogues
Follitropin beta	Puregon		1	1	1997-07-02	sex hormones and modulators of the genital system

Irinotecan	Camptosar	1		1	1997-07-04	antineoplastic agents
Donepezil	Aricept	1		1	1997-08-12	psychoanaleptics
Ropinirole	Requip		1	1	1997-08-19	anti-parkinson drugs
Ibandronate	Bondronat		1	1	1997-08-27	drugs for treatment of bone disease
Glatiramer	Copaxone for injection		1	1	1997-09-04	immunostimulants
Tolcapone	Tasmar		1	1	1997-10-08	anti-parkinson drugs
Zafirlukast	Accolate		1	1	1997-10-21	drugs for obstructive airway diseases
Valsartan	Diovan		1	1	1997-11-03	agents acting on the renin-angiotensin system
Levofloxacin	Levaquin		1	1	1997-11-14	antibacterials for systemic use
Brimonidine	Alphagan opthalmic		1	1	1997-11-24	ophthalmologicals
Quetiapine	Seroquel		1	1	1997-12-02	psycholeptics
Pramipexole	Mirapex		1	1	1998-01-29	anti-parkinson drugs
Interferon Beta-	Rebif		1	1	1998-02-05	immunostimulants
Emedastine	Emadine ophthalmic		1	1	1998-02-16	ophthalmologicals
Cerivastatin	Baycol		1	1	1998-02-18	lipid modifying agents
Grepafloxacin	Raxar		1	1	1998-04-09	antibacterials for systemic use
Naratriptan	Amerge		1	1	1998-04-28	analgesics
Bupropion	Wellbutrin SR		1	1	1998-04-28	psychoanaleptics
Irbesartan	Avapro		1	1	1998-06-01	agents acting on the renin-angiotensin system
Tamsulosin	Flomax		1	1	1998-06-01	urologicals
Montelukast	Singulair		1	1	1998-06-17	drugs for obstructive airway diseases

Delavirdine	Rescriptor		1	1		1	1998-07-22	antivirals for systemic use
Nelfinavir	Viracept		1		1		1998-08-11	antivirals for systemic use
Zolmitriptan	Zomig		1	1			1998-08-24	analgesics
Capecitabine	Xeloda		1		1		1998-08-31	antineoplastic agents
Nevirapine	Viramune		1	1		1	1998-09-04	antivirals for systemic use
Clopidogrel	Plavix		1	1			1998-10-07	antithrombotic agents
Brinzolamide	Azopt ophthalmic suspension		1	1			1998-10-23	ophthalmologicals
Raloxifene	Evista		1	1			1998-11-06	sex hormones and modulators of the genital system
Candesartan	Atacand		1	1			1998-11-20	agents acting on the renin-angiotensin system
Tolterodine	Detrol		1	1			1998-11-20	urologicals
Varicella vaccine	Varivax	1		1			1998-12-02	vaccines
Alatrofloxacin	Trovan (IV)		1	1			1998-12-04	antibacterials for systemic use
Trovafloxacin	Trovan (tablets)		1	1			1998-12-04	antibacterials for systemic use
Becaplermin gel	Regranex		1	1			1998-12-30	preparations for wounds and ulcers
Tizanidine	Zanaflex		1	1			1999-01-25	muscle relaxants
Penciclovir	Denavir		1	1			1999-02-02	antivirals for systemic use
Citalopram	Celexa		1	1			1999-02-05	psychoanaleptics
Recombinant factor VIIa	Niastase		1		1	1	1999-02-12	antihemorrhagics
Modafinil	Alertec		1	1			1999-02-26	psychoanaleptics

Sildenafil	Viagra	1		1			1999-03-08	urologicals
Recombinant-methionyl interferon consensus 1	Infergen		1		1		1999-03-11	immunostimulants
Efavirenz	Sustiva		1		1		1999-03-19	antivirals for systemic use
Repaglinide	Gluconorm		1	1			1999-04-06	drugs used in diabetes
Celecoxib	Celebrex		1		1		1999-04-14	antiinflammaotory and antirheumatic products
Triptorelin	Trelstar		1	1			1999-05-06	endocrine therapy
Ancestim	Stemgen		1	1			1999-05-20	immunostimulants
Orlistat	Xenical		1	1			1999-06-03	antiobesity preparations
Abacavir	Ziagen		1		1	1	1999-06-04	antivirals for systemic use
Eptifibatide	Integrilin		1	1			1999-06-11	antithrombotic agents
Eprosartan	Teveten		1	1			1999-07-09	agents acting on the renin-angiotensin system
Cidofovir	Vistide		1	1			1999-07-13	antivirals for systemic use
Rizatriptan	Maxalt		1	1			1999-07-16	analgesics
Trastuzumab	Herceptin		1		1		1999-08-13	antineoplastic agents
Telmisartan	Micardis		1	1			1999-08-16	agents acting on the renin-angiotensin system
Risedronate	Actonel		1	1			1999-08-18	drugs for treatment of bone disease
Tirofiban	Aggrastat		1	1			1999-08-19	antithrombotic agents
Icodextrin	Extraneal		1	1			1999-09-17	blood substitutes and perfusion solutions
Varicella zoster vaccine	Varilrix		1		1		1999-10-13	vaccines
Temozolomide	Temodal		1	1			1999-10-25	antineoplastic agents

Rofecoxib	Vioxx		1		1		1999-10-25			antiinflammaotory and antirheumatic products
Zanamivir	Relenza		1		1	1	1999-11-02			antivirals for systemic use
Melanoma theracine	Melacine		1		1		1999-11-04			immunostimulants
Gadobutrol	Gadovist		1	1			1999-11-08			contrast media
Dalfopristin	Synercid		1	1			1999-12-10			antibacterials for systemic use
Oseltamivir	Tamiflu		1	1			1999-12-23			antivirals for systemic use
Daclizumab	Zenaprax		1		1		2000-01-04		1	antineoplastic agents
Leflunomide	Arava		1	1			2000-03-16	1		immunosuppressants
Rituximab	Rituxan	1			1		2000-03-17		1	immunosuppressants
Rosiglitazone	Avandia		1		1		2000-03-21	1		drugs used in diabetes
Oxcarbazepine	Trileptal		1	1			2000-04-13	1		antiepileptics
Rivastigmine	Exelon		1	1			2000-04-13	1		psychoanaleptics
Zaleplon	Starnoc		1	1			2000-05-11	1		psycholeptics
Verteporfin	Visudyne	1			1		2000-05-31	1		ophthalmologicals
Cabergoline	Dostinex		1	1			2000-06-30	1		anti-parkinson drugs
Exemestane	Aromasin		1	1			2000-08-17	1		endocrine therapy
Pioglitazone	Actos		1		1		2000-08-17	1		drugs used in diabetes
Zoledronic acid	Zometa		1		1		2000-08-21	1		drugs for treatment of bone disease
Riluzole	Rilutek	1			1	1	2000-08-30	1		other nervous system
Meloxicam	Mobic		1	1			2000-08-31	1		antiinflammaotory and antirheumatic products
Basiliximab	Simulect		1		1		2000-09-01		1	immunosuppressants
Moxifloxacin	Avelox		1	1			2000-10-19	1		antibacterials for systemic use
Peginterferon Alfa-2b	Peg-intron		1	1			2000-10-20		1	immunostimulants
Etanercept	Enbrel	1			1		2000-12-01		1	immunosuppressants

Gadoversetamide	Optimark		1	1			2000-12-11	1		contrast media
Sibutramine	Meridia		1	1			2000-12-28	1		antiobesity preparations
Sirolimus	Rapamune		1	1			2001-01-05	1		immunosuppressants
Gatifloxacin	Tequin		1	1			2001-01-09	1		antibacterials for systemic use
Glucagon, rDNA origin	Glucagon		1		1		2001-01-11		1	pancreatic hormones
Mequinol/tretinoin	Solage		1	1			2001-01-17	1		other dermatological preparations
Amprenavir	Agenerase		1	1		1	2001-03-01	1		antivirals for systemic use
Lopinavir/ritonavir	Kaletra		1		1		2001-03-09	1		antivirals for systemic use
Linezolid	Zyvoxam		1	1			2001-04-02	1		antibacterials for systemic use
Iron	Venofer		1		1		2001-04-17	1		antianemic preparations
Doxercalciferol	Hectorol		1	1			2001-04-30	1		calcium homeostasis
Rabeprazole	Pariet		1	1			2001-05-07	1		drugs for acid related disorders
Entacapone	Comtan		1	1			2001-05-08	1		anti-parkinson drugs
Eflornithine	Vaniqa		1	1			2001-05-10	1		antiprotozoals
Mirtazapine	Remeron		1	1			2001-05-18	1		psychoanaleptics
Desloratadine	Aerius		1	1			2001-05-29	1		antihistamines for systemic use
Infliximab	Remicade		1	1			2001-06-06		1	immunosuppressants
Caspofungin	Cancidas		1		1		2001-07-29	1		antimycotics for systemic use
Galantamine	Reminyl		1	1			2001-07-31	1		psychoanaleptics
Esomeprazole	Nexium		1	1			2001-08-17	1		drugs for acid related disorders
Imatinib	Gleevec	1			1	1	2001-09-20	1		antineoplastic agents
Tenecteplase	Tnkase		1	1			2001-10-17		1	antithrombotic agents
Travoprost	Travatan		1	1			2001-11-09	1		ophthalmologicals

Bosentan	Tracleer	1		1	2001-11-30	1	antihypertensives
Meningococcal group C polysaccharide, tetanus toxoid	Neisvac-C	1		1	2001-12-18		1 vaccines
Glimepiride	Amaryl	1	1		2002-01-25	1	drugs used in diabetes
Nateglinide	Starlix	1	1		2002-02-13	1	drugs used in diabetes
Alfuzosin	Xatral	1	1		2002-02-21		urologicals
Tegaserod	Zelnorm	1	1		2002-03-12	1	drugs for constipation
Ganirelix	Orgalutran	1	1		2002-05-01	1	pituitary and hypothalamic hormones
Valganciclovir	Valcyte	1	1		2002-05-03	1	antivirals for systemic use
Palivizumab	Synagis	1	1		2002-05-15		1 immune sera and immunoglobulins
Docosanol	Abreva	1	1		2002-05-24	1	antibiotics and chemotherapeutics for dermatological use
Bimatoprost	Lumigan	1	1		2002-05-24	1	ophthalmologicals
Anakinra	Kineret	1		1	2002-05-24		1 immunosuppressants
Moroctocog alpha	Refacto	1		1	2002-05-28		1 antihemorrhagics
Peginterferon Alfa-2b ribavirin	Pegetron	1	1		2002-05-31		1 immunostimulants
Fondaparinux	Arixtra	1		1	2002-06-13	1	antithrombotic agents
Hetastarch	Hextend	1	1		2002-07-08	1	blood substitutes and perfusion solutions
Darbepoetin alpha	Aranesp	1	1		2002-08-02		1 antianemic preparations
Norelgestromin/ ethinyl estradiol	Evra	1	1		2002-08-20	1	sex hormones and modulators of the genital system
Treprostinil	Remodulin	1		1	2002-10-04	1	antithrombotic agents
Bivalirudin	Angiomax	1	1		2002-10-09	1	antithrombotic agents

Tiotropium	Spiriva		1	1			2002-11-20	1		drugs for obstructive airway diseases
Valdecoxib	Betra		1	1			2002-12-11	1		antiinflammaotory and antirheumatic products
Drotrecogin Alfa	Xigris	1			1		2003-01-31		1	antithrombotic agents
Rosuvastatin	Crestor		1	1			2003-02-18	1		lipid modifying agents
Recombinant cholera toxin B subunit	Dukoral		1		1		2003-02-21		1	vaccines
Levetiracetam	Keppra		1	1			2003-03-06	1		antiepileptics
Tenofovir	Viread		1		1	1	2003-03-18	1		antivirals for systemic use
Pimecrolimus	Elidel		1	1			2003-03-19	1		other dermatological preparations
Ertapenem	Invanz		1	1			2003-05-12	1		antibacterials for systemic use
Ezetimibe	Ezetrol		1	1			2003-05-12	1		lipid modifying agents
Telithromycin	Ketek		1	1			2003-05-28	1		antibacterials for systemic use
Enfuvirtide	Fuzeon	1			1		2003-07-14	1		antivirals for systemic use
Dutasteride	Avodart		1	1			2003-07-22	1		urologicals
Peginterferon Alfa-2a	Pegasys		1	1			2003-08-13		1	immunostimulants
Cetrorelix	Cetrotide		1	1			2003-08-13	1		pituitary and hypothalamic hormones
Adefovir	Hepsera		1		1		2003-08-27	1		antivirals for systemic use
Tadalafil	Cialis		1	1			2003-09-17	1		urologicals
Almotriptan	Axert		1	1			2003-10-01	1		agents acting on the renin-angiotensin system
Rasburicase	Fasturtec		1		1		2003-10-29		1	all other therapeutic products

Atazanavir	Reyataz		1		1		2003-12-05	1		antivirals for systemic use
Gefitinib	Iressa		1		1	1	2003-12-17	1		antineoplastic agents
Agalsidase Beta	Fabrazyme		1		1		2004-01-23		1	other alimentary tract and metabolism products
Agalsidase	Replagal	1			1	1	2004-02-06		1	other alimentary tract and metabolism products
Fulvestrant	Faslodex		1	1			2004-02-17	1		endocrine therapy
Gemifloxacin	Factive		1	1			2004-03-09	1		antibacterials for systemic use
Pegfilgrastim	Neulasta		1	1			2004-03-12		1	immunostimulants
Vardenafil	Levitra		1	1			2004-03-17	1		urologicals
Gadobenate	Multihance		1	1			2004-03-31	1		contrast media
Miglustat	Zavesca		1		1		2004-03-31	1		other alimentary tract and metabolism products
Botulinum Toxin Type B	Myobloc		1	1			2004-04-16		1	muscle relaxants
Peginterferon Alfa-2A Ribavirin	Pegasys RBV		1		1		2004-05-10		1	immunostimulants
Ethinyl estradiol/etonogestrel	Nuvaring		1	1			2004-05-11	1		sex hormones and modulators of the genital system
Pemetrexed	Alimta		1		1		2004-05-21	1		antineoplastic agents
Laronidase	Adlurazyme	1			1		2004-05-31		1	other alimentary tract and metabolism products
Teriparatide	Forteo		1		1		2004-06-03		1	calcium homeostasis
Cinacalcet	Sensipar	1			1		2004-08-04	1		calcium homeostasis
Eletriptan	Relpax		1	1			2004-08-05	1		analgesics

Voriconazole	Vfend		1	1			2004-08-20	1		antimycotics for systemic use
Frovatriptan	Frova		1	1			2004-09-03	1		analgesics
Adalimumab	Humira		1	1			2004-09-24		1	immunosuppressants
Alefacept	Amevive		1	1			2004-10-06		1	immunosuppressants
Omalizumab	Xolair		1	1			2004-11-18		1	drugs for obstructive airway diseases
Memantine	Ebixa		1	1		1	2004-12-08	1		psychoanaleptics
Fosamprenavir	Telzir		1	1			2004-12-10	1		antivirals for systemic use
Drospirenone/ethinyl estradiol	Yasmin 21/28		1	1			2004-12-10	1		sex hormones and modulators of the genital system
Atomoxetine	Strattera		1	1			2004-12-24	1		psychoanaleptics
Escitalopram	Cipralex		1	1			2004-12-24	1		psychoanaleptics
Bortezomib	Velcade		1	1		1	2005-01-27	1		antineoplastic agents
Paricalcitol	Zemplar		1	1			2005-03-31	1		calcium homeostasis
Pantoprazole	Pantaloc M		1	1			2005-04-22	1		drugs for acid related disorders
Pegaptanib	Macugen	1			1		2005-05-02	1		ophthalmologicals
Ibritumomab	Zevalin		1		1		2005-05-10		1	therapeutic radiopharmaceuticals
Pregabalin	Lyrica		1	1			2005-06-03	1		antiepileptics
Lutropin Alfa	Luveris		1	1			2005-06-24		1	sex hormones and modulators of the genital system
Erlotinib	Tarceva		1		1		2005-07-07	1		antineoplastic agents
Tramadol	Tramacet		1	1			2005-07-20	1		analgesics
Sodium oxybate	Xyrem		1	1			2005-08-05	1		other nervous system
Perindopril	Coversyl		1	1			2005-08-23	1		agents acting on the renin-angiotensin system
Bevacizumab	Avastin		1		1		2005-09-09		1	antineoplastic agents

Cetuximab	Erbitux		1		1		2005-09-09		1	antineoplastic agents
Insulin detemir	Levemir		1	1			2005-09-29		1	drugs used in diabetes
Pegvisomant	Somavert		1		1		2005-10-17		1	pituitary and hypothalamic hormones
Efalizumab	Raptiva		1	1			2005-10-24		1	immunosuppressants
Darifenacin	Enablex		1	1			2005-11-14	1		urologicals
Emtricitabine	Emtriva		1	1			2005-11-21	1		antivirals for systemic use
Tipranavir	Aptivus		1		1		2005-11-21	1		antivirals for systemic use
Alemtuzumab	Mabcampath	1		1			2005-11-30		1	immunosuppressants
Palifermin	Kepivance	1			1		2005-12-09		1	all other therapeutic products
Trospium	Trosec		1	1			2006-01-10	1		urologicals
Solifenacin	Vesicare		1	1			2006-02-20	1		urologicals
Histrelin	Vantas		1	1			2006-03-10	1		endocrine therapy
Insulin glulisine	Apidra		1	1			2006-04-12		1	drugs used in diabetes
Sunitinib	Sutent		1		1	1	2006-05-26	1		antineoplastic agents
Entecavir	Baraclude		1		1		2006-06-16	1		pituitary and hypothalamic hormones and analogues
Abatacept	Orencia		1		1		2006-06-29		1	immunosuppressants
Recombinant human papillomavirus	Gardasil	1			1		2006-07-10		1	vaccines
Lanreotide	Somatuline autogel		1	1			2006-07-17	1		antivirals for systemic use
Sorafenib	Nexavar		1	1			2006-07-28	1		antineoplastic agents
Darunavir	Prezista		1	1		1	2006-07-28	1		antivirals for systemic use
Rotaviruses	Rotateq	1		1			2006-08-01		1	vaccines

Alglucosidase Alfa	Myozyme	1			1		2006-08-14		1	other alimentary tract and metabolism products
Rasagiline	Azilect		1	1			2006-08-17	1		anti-parkinson drugs
Ciclesonide	Alvesco		1	1			2006-09-11	1		drugs for obstructive airway diseases
Tigecycline	Tygacil		1	1			2006-09-14	1		antibacterials for systemic use
Natalizumab	Tysabri		1		1		2006-09-28		1	immunosuppressants
Lanthanum	Fosrenol		1	1			2006-10-17	1		all other therapeutic products
Deferasirox	Exjade		1		1	1	2006-10-18	1		all other therapeutic products
Gadofosveset	Vasovist		1	1			2006-10-31	1		contrast media
Telbivudine	Sebivo		1		1		2006-11-28	1		antivirals for systemic use
Varenicline	Champix		1	1			2007-01-24	1		other nervous system
Acamprosate	Campral		1	1			2007-03-16	1		other nervous system
Dasatinib	Sprycell	1		1		1	2007-03-26	1		antineoplastic agents
Posaconazole	Spriafil (Posanol)	1			1		2007-03-26	1		antimycotics for systemic use
Micafungin	Mycamine		1	1			2007-05-22	1		antimycotics for systemic use
Sitaxentan	Thelin		1	1			2007-05-30	1		antihypertensives
Idursulfase	Elaprase		1		1		2007-06-13	1		other alimentary tract and metabolism products
Oxaliplatin	Eloxatin		1		1		2007-06-15	1		antineoplastic agents
Ranibizumab	Lucentis	1			1		2007-06-26		1	ophthalmologicals
Fluticasone	Avamys		1	1			2007-08-14	1		drugs for obstructive airway diseases
Aprepitant	Emend		1	1			2007-08-24	1		antiemetics and antinauseants

Maraviroc	Celsentri		1		1		2007-09-21	1		antivirals for systemic use
Daptomycin	Cubicin		1	1			2007-09-24	1		antibacterials for systemic use
Paliperidone	Invega		1	1			2007-09-26	1		psycholeptics
Duloxetine	Cymbalta		1	1			2007-11-01	1		psychoanaleptics
Nesiritide	Natrecor		1	1		1	2007-11-08		1	cardiac therapy
Aliskiren	Rasilez		1	1			2007-11-14	1		agents acting on the renin-angiotensin system
Anidulafungin	Eraxis		1	1			2007-11-14	1		antimycotics for systemic use
Raltegravir	Isentress		1		1	1	2007-11-27	1		antivirals for systemic use
Rivastigmine	Exelon patch		1	1			2007-11-29	1		psychoanaleptics
Sitagliptin	Januvia		1	1			2007-12-14	1		drugs used in diabetes
Temsirolimus	Torisel		1		1		2007-12-21	1		antineoplastic agents
Lenalidomide	Revlimid	1		1		1	2008-01-17	1		immunosuppressants
Ambrisentan	Volibris		1	1			2008-03-20	1		antihypertensives
Etravirine	Intelence		1		1		2008-03-27	1		antivirals for systemic use
Methylnaltrexone	Relistor	1			1		2008-03-28	1		drugs for constipation
Panitumumab	Vectibix		1	1		1	2008-04-03		1	antineoplastic agents
Nepafenac	Nevanac		1	1			2008-04-17	1		ophthalmologicals
Dabigatran	Pradaxa		1	1			2008-06-10	1		antithrombotic agents
Ceftobiprole	Zeftera		1	1			2008-06-26	1		antibacterials for systemic use
Idebenone	Catena		1	1		1	2008-07-23	1		psychoanaleptics
Nilotinib	Tasigna		1	1		1	2008-09-09	1		antineoplastic agents
Rivaroxaban	Xarelto		1	1			2008-09-15	1		antithrombotic agents

Olmesartan	Olmetec	1	1			2008-10-28	1		agents acting on the renin-angiotensin system
Capsular polysaccharide	Synflorix	1	1			2008-12-11		1	vaccines
Ustekinumab	Stelara	1	1			2008-12-12		1	immunosuppressants
Loteprednol	Alrex	1	1			2008-12-23	1		ophthalmologicals
Eculizumab	Soliris	1		1		2009-01-28		1	immunosuppressants
Desvenlafaxine	Pristiq	1	1			2009-02-04	1		psychoanaleptics
Lisdexamfetamine	Vyvanse	1	1			2009-02-19	1		psychoanaleptics
Romiplostim	Nplate	1		1		2009-02-19		1	antihemorrhagics
Methyl aminolevulinate	Metvix	1	1			2009-02-26	1		antineoplastic agents
Eplerenone	Inspra	1	1			2009-02-26	1		diuretics
Fosaprepitant	Emend IV	1	1			2009-04-01	1		antivirals for systemic use
Golimumab	Simponi	1	1			2009-04-07		1	immunosuppressants
Lapatinib	Tykerb	1	1			2009-05-15	1		antineoplastic agents
Vorinostat	Zolinza	1	1			2009-06-11	1		antineoplastic agents
Aripiprazole	Abilify	1	1			2009-07-09	1		psycholeptics
Clofarabine	Clolar	1	1			2009-07-16	1		antineoplastic agents
Dronedarone	Multaq	1		1		2009-08-11	1		cardiac therapy
Certolizumab	Cimzia	1	1			2009-08-12		1	immunosuppressants
Doripenem	Doribax	1	1			2009-09-02	1		antibacterials for systemic use
Aztreonam	Cayston	1		1	1	2009-09-11	1		antibacterials for systemic use
Saxagliptin	Onglyza	1	1			2009-09-14	1		drugs used in diabetes
Besifloxacin	Besivance	1	1			2009-10-23	1		ophthalmologicals
Azacitidine	Vidaza	1		1		2009-10-23	1		antineoplastic agents

Japanese encephalitis vaccine	Ixiaro		1	1			2009-10-29		1	vaccines
Alitretinoin	Toctino		1	1			2009-11-13	1		antineoplastic agents
Degarelix	Firmagon		1	1			2009-11-16	1		endocrine therapy
Dexmedetomidine	Precedex		1	1			2009-12-09	1		psycholeptics
Everolimus	Afinitor		1	1		1	2009-12-14	1		antineoplastic agents
Thrombin alfa	Recothrom		1	1			2009-12-15		1	antihemorrhagics
Pneumococcal conjugate	Prevnar		1		1		2009-12-21		1	vaccines
Gadoxetate	Primovist		1	1			2010-01-14	1		contrast media
Recombinant human papillomavirus	Cervarix		1	1			2010-02-03		1	vaccines
Canakinumab	Ilaris	1			1		2010-02-26		1	immunosuppressants
Prasugrel	Effient		1	1			2010-04-16	1		antithrombotic agents
Tocilizumab	Actemra		1	1			2010-04-30		1	immunosuppressants
Sapropterin	Kuvan	1			1		2010-04-30	1		other alimentary tract and metabolism products
Trabectedin	Yondelis		1	1			2010-05-13	1		antineoplastic agents
Liraglutide	Victoza - 1.2 mg pen-injector		1	1			2010-05-21		1	drugs used in diabetes
Meningococcal oligosaccharides conjugated	Menveo		1	1			2010-05-21		1	vaccines
Pazopanib	Votrient		1	1			2010-05-27	1		antineoplastic agents
Paliperidone	Invega sustenna		1	1			2010-06-30	1		psycholeptics
Sevelamer	Renvela		1	1			2010-07-07	1		all other therapeutic products
Dexlansoprazole	Dexilant		1	1			2010-07-22	1		drugs for acid related disorders

Denosumab	Prolia		1	1		2010-08-06	1	drugs for treatment of bone disease
Febuxostat	Uloric		1	1		2010-09-22	1	antigout preparations
Lacosamide	Vimpat		1	1		2010-09-30	1	antiepileptics
Velaglucerase alf	VPRIV		1	1		2010-10-01	1	other alimentary tract and metabolism products
Roflumilast	Daxas		1	1		2010-11-23	1	drugs for obstructive airway diseases
Tapentadol	Nucynta CR		1	1		2010-12-02	1	analgesics
Silodosin	Rapaflo		1	1		2011-01-11	1	urologicals
Eltrombopag	Revolade		1	1		2011-01-12	1	antihemorrhagics
Exenatide	Byetta		1	1		2011-01-13	1	drugs used in diabetes
Fingolimod	Gilenya		1	1		2011-03-09	1	immunosuppressants
Ticagrelor	Brilinta		1		1	2011-05-30	1	antithrombotic agents
Cabazitaxel	Jevtana		1	1		2011-06-16	1	antineoplastic agents
Rufinamide	Banzel		1	1		2011-06-22	1	antiepileptics
Belimumab	Benlysta		1	1		2011-07-06	1	immunosuppressants
Rilpivirine	Edurant		1	1		2011-07-21	1	antivirals for systemic use
Tolvaptan	Samsca		1	1		2011-07-25	1	diuretics
Abiraterone	Zytiga		1		1	2011-07-27	1	endocrine therapy
Linagliptin	Trajenta		1	1		2011-07-28	1	drugs used in diabetes
Boceprevir	Victrelis	1			1	2011-07-29	1	antivirals for systemic use
Boceprevir, peginterferon alfa-2b, ribavirin	Victrelis Triple	1			1	2011-08-10	1	immunostimulants
Telaprevir	Incivek		1		1	2011-08-16	1	antivirals for systemic use
Colesevelam	Lodalis		1	1		2011-09-22	1	lipid modifying agents
Senapine	Saphris		1	1		2011-10-07	1	psycholeptics

Dienogest	Visanne		1	1		2011-10-12	1		sex hormones and modulators of the genital system
Indacaterol	Onbrez breezhaler		1	1		2011-12-06	1		drugs for obstructive airway diseases
Prucalopride	Resotran		1	1		2011-12-07	1		drugs for constipation
Plerixafor	Mozobil		1	1		2011-12-08	1		immunostimulants
Eribulin	Halaven		1	1		2011-12-14	1		antineoplastic agents
Apixaban	Eliquis		1	1		2011-12-16	1		antithrombotic agents
Vandetanib	Caprelsa		1	1		2012-01-12	1		antineoplastic agents
Ipilimumab	Yervoy		1	1		2012-02-01		1	antineoplastic agents
Fesoterodine	Toviaz		1	1		2012-02-09	1		urologicals
Fampridine	Fampyra		1	1		2012-02-10	1		other nervous system
Vemurafenib	Zelboraf	1			1	2012-02-15			antineoplastic agents
Azilsartan	Edarbi		1	1		2012-03-08	1		agents acting on the renin-angiotensin system
Ofatumumab	Arzerra		1	1		2012-03-09		1	antineoplastic agents
Palonosetron	Aloxi		1	1		2012-03-14	1		antiemetics and antinauseants
Crizotinib	Xalkori		1	1	1	2012-04-25	1		antineoplastic agents
Fidaxomicin	Dificid		1	1		2012-06-07	1		antidiarrheals, intestinal antiinflammatory/antiinfective agents
Lurasidone	Latuda		1	1		2012-06-13	1		psycholeptics
Ruxolitinib	Jakavi		1		1	2012-06-19	1		antineoplastic agents
Collagenase clostridium histolyticum	Xiaflex	1		1		2012-07-05		1	other drugs for disorders of the musculo-skeletal system
Axitinib	Inlyta		1	1		2012-07-12	1		antineoplastic agents
Catridecacog	Tretten		1		1	2012-07-19		1	antihemorrhagics
Bendamustine	Treanda		1	1		2012-08-24	1		antineoplastic agents
Pirfenidone	Esbriet		1		1	2012-10-01			immunosuppressants

Elvitegravir, emtricitabine, tenofovir, cobicistat	Stribild		1	1			2012-11-26	1		antivirals for systemic use
Ivacaftor	Kalydeco	1			1		2012-11-26	1		other respiratory system products
Stiripentol	Diacomit		1	1			2012-12-21	1		antiepileptics
Nebivolol	Bystolic		1	1			2012-12-21	1		beta blocking agents
Ingenol	Picato		1	1			2013-01-30	1		antibiotics and chemotherapeutics for dermatological use
Brentuximab	Adcetris		1	1		1	2013-02-01		1	antineoplastic agents
Meningococcal polysaccharide groups A,C,W-135 & Y conjugate vaccine, Tetanus toxoid	Nimenrix		1	1			2013-03-05		1	vaccines
Mirabegron	Myrbetriq		1	1			2013-03-06	1		urologicals
Regorafenib	Stivarga		1		1		2013-03-11	1		antineoplastic agents
Rotigotine	Neupro		1	1			2013-03-21	1		anti-parkinson drugs
Dimethyl	Tecfidera		1	1			2013-04-03	1		other nervous system
Perampanel	Fycompa		1	1			2013-04-04	1		antiepileptics
Pertuzumab	Perjeta	1			1		2013-04-12		1	antineoplastic agents
Enzalutamide	Xtandi		1		1		2013-05-29	1		endocrine therapy
Ulipristal	Fibristal		1	1			2013-06-24	1		sex hormones and modulators of the genital system
Vismodegib	Erivedge		1	1			2013-07-12	1		antineoplastic agents
Dabrafenib	Tafinlar		1	1			2013-07-16	1		antineoplastic agents
Trametinib	Mekinist		1	1			2013-07-18	1		antineoplastic agents

Fluticasone and vilatnerol	Breo ellipta		1	1		2013-07-23	1		drugs for obstructive airway diseases
Aclidinium	Tudorza genuair		1	1		2013-07-29	1		drugs for obstructive airway diseases
Rifaximin	Zaxine		1		1	2013-08-13	1		antidiarrheals, intestinal antiinflammatory/antiinfective agents
Ocriplasmin	Jetrea	1			1	2013-08-13		1	ophthalmologicals
Trastuzumab emtansine	Kadcyla		1		1	2013-09-11		1	antineoplastic agents
Galsulfase	Naglazyme	1		1		2013-09-16		1	other alimentary tract and metabolism products
Riociguat	Adempas		1		1	2013-09-19	1		antihypertensives
Pasireotide	Signifor	1			1	2013-09-23	1		pituitary and hypothalamic hormones
Efinaconazole	Jublia		1	1		2013-10-02	1		drugs used in diabetes
Romidepsin	Istodax		1	1		1 2013-10-16	1		antineoplastic agents
Dolutegravir	Tivicay		1	1		2013-10-31	1		antivirals for systemic use
Afatinib	Giotrif		1	1		2013-11-01	1		antineoplastic agents
Macitentan	Opsumit		1	1		2013-11-06	1		antihypertensives
Aflibercept	Eylea		1	1		2013-11-08		1	antineoplastic agents
Teriflunomide	Aubagio		1	1		2013-11-14	1		immunosuppressants
Simeprevir	Galexos		1		1	2013-11-18	1		antivirals for systemic use
Alogliptin	Nesina		1	1		2013-11-27	1		drugs used in diabetes
Linaclotide	Constella		1	1		2013-12-02	1		drugs for constipation
Multicomponent meningococcal B vacine	Bexsero	1		1		2013-12-06		1	vaccines
Radium-223 dichl	Xofigo		1	1		2013-12-12		1	therapeutic radiopharmaceuticals

Sofosbuvir	Sovaldi	1			1		2013-12-13	1		antivirals for systemic use
Umeclidinium and vilanterol	Anoro ellipta		1	1			2013-12-23	1		drugs for obstructive airway diseases
Pomalidomide	Pomalyst	1			1		2014-01-20	1		immunosuppressants
Lomitapide	Juxtapid		1	1			2014-02-04	1		lipid modifying agents
Aflibercept	Zaltrap		1	1			2014-02-12		1	antineoplastic agents
Bosutinibs	Bosulif		1	1		1	2014-03-14	1		antineoplastic agents
Recombinant human coagulation Factor IX, FC fusion protein	Alprolix		1	1			2014-03-20		1	antihemmorhagics
Tofacitinib	Xeljanz		1	1			2014-04-17	1		immunosuppressants
Tesamorelin	Egrifta		1	1			2014-04-29	1		pituitary and hypothalamic hormones
Canagliflozin	Invokana		1	1			2014-05-23	1		drugs used in diabetes
Taliglucerase Alfa	Elelyso		1	1			2014-05-29		1	other alimentary tract and metabolism products
Eslicarbazepine	Aptiom		1	1			2014-07-08	1		antiepileptics
Antihemophilic factor, FC fusion protein	Eloctate		1	1			2014-08-22		1	antihemmorhagics
Ledipasvir and sofosbuvir	Harvoni		1		1		2014-10-15	1		antivirals for systemic use
Vortioxetine	Trintellix		1	1			2014-10-22	1		psychoanaleptics
Simoctocog alfa	Nuwiq		1	1			2014-10-23		1	antihemmorhagics
Azelastine and fluticasone	Dymista		1	1			2014-10-23	1		nasal preparations
Conjugated estrogens and bazedoxifene acetate	Duavive		1	1			2014-10-23	1		sex hormones and modulators of the genital system

Apremilast	Otezla		1	1			2014-11-12	1		immunosuppressants
Ibrutinib	Imbruvica	1			1	1	2014-11-17	1		antineoplastic agents
Obinutuzumab	Gazyva	1		1			2014-11-25		1	antineoplastic agents
Siltuximab	Sylvant		1		1		2014-12-03		1	immunosuppressants
Dapagliflozin	Forxiga		1	1			2014-12-12	1		drugs used in diabetes
Ritonavir, paritaprevir, ombitasvir, dasabuvir	Holkira Pak		1		1		2014-12-22	1		antivirals for systemic use
Sodium phenylbutyrate	Pheburane		1		1		2015-01-26	1		other alimentary tract and metabolism products
Vedolizumab	Entyvio		1	1			2015-01-29		1	immunosuppressants
Human papillomavirus 9 valent vaccine, recombinant	Gardasil 9		1	1			2015-02-05		1	vaccines
Deferiprone	Ferriprox		1	1			2015-02-13	1		all other therapeutic products
Secukinumab	Cosentyx		1	1			2015-02-27		1	immunosuppressants
Tedizolid	Sivextro		1	1			2015-03-17	1		antibacterials for systemic use
Idelalisib	Zydelig		1	1		1	2015-03-27	1		antineoplastic agents
Ceritinib	Zykadia		1	1		1	2015-03-27	1		antineoplastic agents
Ponatinib	Iclusig		1	1		1	2015-04-02	1		antineoplastic agents
Carglumic Acid	Carbaglu	1			1		2015-04-10	1		other alimentary tract and metabolism products
Ivermectin	Rosiver		1	1			2015-04-22	1		anthelmintics
Levomilnacipran	Fetzima		1	1			2015-05-08	1		psychoanaleptics
Pembrolizumab	Keytruda		1	1		1	2015-05-19		1	antineoplastic agents
Naloxegol	Movantik		1	1			2015-06-02	1		drugs for constipation
Nintedanib	Ofev		1	1			2015-06-25	1		antineoplastic agents

Ramucirumab	Cyramza		1	1			2015-07-16		1	antineoplastic agents
Empagliflozin	Jardiance		1	1			2015-07-23	1		drugs used in diabetes
Mifepristone and Misoprostol	Mifegymiso		1	1			2015-07-29	1		sex hormones and modulators of the genital system
Daclatasvir	Daklinza		1	1		1	2015-08-13	1		antivirals for systemic use
Asfotase Alfa	Strensiq	1		1		1	2015-08-14		1	other alimentary tract and metabolism products
Teduglutide	Revestive		1		1		2015-09-04		1	other alimentary tract and metabolism products
Evolocumab	Repatha		1	1			2015-09-10		1	lipid modifying agents
Nivolumab	Opdivo	1			1		2015-09-25		1	antineoplastic agents
Ceftolozane Sulfate and Tazobactam Sodium	Zerbaxa		1	1			2015-09-30	1		antibacterials for systemic use
Sacubitril, Valsartan	Entresto	1			1		2015-10-02	1		agents acting on the renin-angiotensin system
Dulaglutide	Trulicity		1	1			2015-11-10		1	drugs used in diabetes
Elvitegravir, Cobicistat, Emtricitabine, Tenofovir Alafenamide Hemifumarate	Genvoya		1	1			2015-11-27	1		antivirals for systemic use
Mepolizumab	Nucala		1	1			2015-12-03		1	drugs for obstructive airway diseases
Lenvatinib	Lenvima		1	1			2015-12-22	1		antineoplastic agents
Blinatumomab	Blincyto		1	1		1	2015-12-22		1	antineoplastic agents
Carfilzomib	Kyprolis		1		1		2016-01-15	1		antineoplastic agents

Elbasvir, Grazoprevir	Zepatier		1		1		2016-01-19	1		antivirals for systemic use
Selexipag	Uptravi		1	1			2016-01-20	1		antithrombotic agents
Ivacaftor, Lumacaftor	Orkambi		1		1		2016-01-26	1		other respiratory system products
Sugammadex	Bridion		1	1			2016-02-05	1		all other therapeutic products
Cobimetinib	Cotellic		1	1			2016-02-22	1		antineoplastic agents
Brivaracetam	Brivlera		1	1			2016-03-09	1		antiepileptics
Asunaprevir	Sunvepra		1	1			2016-03-09	1		antivirals for systemic use
Palbociclib	Ibrance		1	1		1	2016-03-16	1		antineoplastic agents
Alirocumab	Praluent		1	1			2016-04-11		1	lipid modifying agents
Bilastine	Blexten		1	1			2016-04-21	1		antihistamines for systemic use
Idarucizumab	Praxbind		1	1		1	2016-04-29		1	all other therapeutic products
Olaparib	Lynparza		1	1		1	2016-04-29	1		antineoplastic agents
Ixekizumab	Taltz		1	1			2016-05-25		1	immunosuppressants
Osimertinib	Tagrisso		1	1		1	2016-07-05	1		antineoplastic agents
Sofosbuvir + Velpatasvir	Epclusa		1		1		2016-07-11	1		antivirals for systemic use
Ixazomib	Ninlaro		1		1		2016-08-04	1		antineoplastic agents
Nitisinone	MDK-Nitisinone	1			1		2016-09-20	1		other alimentary tract and metabolism products
Venetoclax	Venclexta		1	1		1	2016-09-30	1		antineoplastic agents
Edoxaban	Lixiana		1	1			2016-11-04	1		antithrombotic agents
Nitisinone	Nitisinone	1			1		2016-11-04	1		other alimentary tract and metabolism products
Daclizumab beta	Zinbryta		1	1			2016-12-08		1	immunosuppressants

Nitisinone	Orfadin	1				1		2016-12-13	1		other alimentary tract and metabolism products
Ivabradine	Lancora		1	1				2016-12-23	1		cardiac therapy
		55	454	379	130	42			286	99	

***Prescrire evaluations as of February 20, 2018; PMPRB evaluations as of December 31, 2016; Prescrire ratings - offers an advantage, possibly helpful, nothing new, not acceptable; PMPRB ratings - category 3 = moderate, little or no improvement (prior to 2010), slight or no improvement, moderate improvement - primary, moderate improvement - secondary (2010 onwards)**

Supplementary Table 2: All drugs approved between 1995-2016 that did not receive therapeutic assessments

Generic name	Brand name	Review status			Notice of compliance or Notice of compliance with conditions date	Small molecule	Biologic	ATC group (second level)
		Standard	Priority	Notice of compliance with conditions				
Levocarnitine	Carnitor		1		1995-01-19			other alimentary tract and metabolism products
Losoxantrone	Bianda	1			1995-02-19			antineoplastic agents
Carvedilol	Dilatrend	1			1995-02-27			beta blocking agents
Carvedilol	Kredex	1			1995-02-27			beta blocking agents
Halofantrine	Halfan	1			1995-03-29			antiprotozoals
Ceftibuten	Cedax	1			1995-05-09			antibacterials for systemic use
Sermorelin	Geref	1			1995-06-08			pituitary and hypothalamic hormones and analogues
Tetrabenazine	Nitoman	1			1995-12-29			other nervous system drugs
Iron dextran	Dexferrum		1		1996-01-09			antianemic preparations
Rimexolone	Vexol	1			1996-01-17			corticosteroids for systemic use
Measles virus vaccine/Rubella virus vaccine	Moru-Viraten		1		1996-02-26			vaccines
Ferumoxsil	Gastromark	1			1996-03-15			contrast media
Saquinavir	Saquinavir		1		1996-03-22			antivirals for systemic use
Pantoprazole	Panto-Byk	1			1996-07-05			drugs for acid related disorders
Dexfenfluramine	Redux	1			1996-07-29			antiobesity preparations
Palmitic acid/Galactose	Levovist	1			1996-07-31			contrast media
Fleroxacin	Megalone	1			1996-08-21			antibacterials for systemic use

Reviparin	Clivarine	1		1996-09-10	antithrombotic agents
Diptheria, tetanus & acellular pertussis vaccine	Infanrix		1	1996-12-17	vaccines
Cisatracurium	Nimbex injectior	1		1996-12-18	muscle relaxants
Remifentanil	Ultiva injection	1		1996-12-24	anesthetics
Tiludronate	Skelid	1		1997-02-06	drugs for treatment of bone disease
Tazarotene	Tazorac Gel	1		1997-02-25	antipsoriatics
Praziquantel	Biltricide	1		1997-03-07	anthelmintics
Molgramostim	Leucomax		1	1997-03-10	immunostimulants
Fosphenytoin	Cerebyx injectio	1		1997-03-20	antiepileptics
Butenafine	Dr. Scholl's athle	1		1997-04-15	antifungals for dermatological use
Troglitazone	Rezulin		1	1997-05-09	drugs used in diabetes
Trandolapril	Odrik	1		1997-05-15	agents acting on the renin-angiotensin system
Follitropin alpha	Gonal-F	1		1997-06-06	sex hormones and modulators of the genital system
Kit for preparation of indium in 111 imciromab pentetate	Myoscint	1		1997-07-02	diagnotic radiopharmaceuticals
Cytomegalovirus immune globulin	Cytogam	1		1997-08-01	immune sera and immunoglobulins
Oxiconazole	Oxizole	1		1997-08-08	antifungals for dermatological use
Respiratory syncytial virus immune globulin	Respigam		1	1997-08-20	immune sera and immunoglobulins
Arcitumomab	CEA-Scan	1		1997-09-16	diagnotic radiopharmaceuticals

Olopatadine	Patanol	1		1997-09-16		ophthalmologicals
Pegaspargase	Oncaspar	1		1997-11-19		antineoplastic agents
Anagrelide as hydrochloride	Agrylin		1	1997-11-19		antineoplastic agents
Nadroparin	Fraxiparine	1		1997-11-27		antithrombotic agents
Bicisate	OncoScint	1		1998-01-16		diagnotic radiopharmaceuticals
Gadolinium (III)	Gadolite	1		1998-04-08		contrast media
Lexidronam	Quadramet	1		1998-06-22		therapeutic radiopharmaceuticals
Miglitol	Glyset	1		1998-07-22		drugs used in diabetes
Lipoprotein-OspA antigen recombinant	Lymerix		1	1998-12-02		vaccines
Toremifene	Fareston	1		1998-12-14		endocrine therapy
Cefdinir	Omnicef	1		1999-02-05		antibacterials for systemic use
Methacholine	Methacoline	1		1999-02-25		diagnostic agents
Fosfomycin	Monurol	1		1999-04-12		antibacterials for systemic use
Alitretinoin	Panretin		1	1999-06-11		other dermatological preparations
Ioxilan	Oxilan	1		1999-10-05		contrast media
Mangafodipir	Teslascan	1		2000-02-09	1	contrast media
Sevelamer	Renagel	1		2000-02-24	1	all other therapeutic products
Valrubicin	Valstar		1	2000-07-04	1	antineoplastic agents
Ibutilide	Corvert injection	1		2000-07-14	1	cardiac therapy
Fomepizole	Antizol		1	2000-11-30	1	all other therapeutic products
Amlexanox	Apthera	1		2000-12-11	1	stomatological preparations
Tegafur/uracil and leucovorin calcium	Orzel	1		2001-04-06	1	antineoplastic agents
Argatroban	Argatroban		1	2001-06-04	1	antithrombotic agents

Aminolevulinic acid	Levulan	1			2001-06-20	1		antineoplastic agents
Infliximab	Remicade		1		2001-09-27		1	immunosuppressants
Levobupivacaine	Chirocaine	1			2002-03-20	1		anesthetics
Unoprostone isopropyl	Rescula	1			2002-04-03	1		ophthalmologicals
Thyrotropin	Thyrogen	1			2002-05-31		1	diagnostic agents
Anti-thymocyte globulin	Thymoglobulin	1			2002-11-20		1	immunosuppressants
Dextromethylpheni date	Attenade	1			2003-08-12	1		psychoanaleptics
Sulfur Hexafluoride	Sonovue	1			2004-02-12	1		contrast media
Yttrium-90	Yttrium-90		1		2004-12-02		1	therapeutic radiopharmaceuticals
Choriogonadotropin Alfa	Ovidrel	1			2004-12-16		1	sex hormones and modulators of the genital system
Sulesomab	Leukoscan	1			2005-01-17		1	diagnotic radiopharmaceuticals
Tositumomab	Bexxar		1		2005-08-18		1	therapeutic radiopharmaceuticals
Nitric oxide	Inomax		1		2005-09-23	1		other respiratory system products
F-Fluorodeoxyglucose	Cantrace		1		2006-07-27		1	diagnotic radiopharmaceuticals
Lumiracoxib	Prexige	1			2006-11-02	1		antiinflammatory and antirheumatic products
Nelarabine	Atriance			1	2007-09-22	1		antineoplastic agents
Rotavirus vaccine	Rotarix	1			2007-10-09		1	vaccines
Retapamulin	Altargo	1			2008-03-19	1		antibiotics and chemotherapeutics for dermatological use

Methoxy Polyethylene glycol-epoetin beta	Mircera	1		2008-03-31		1	antianemic preparations
Telavancin	Vibativ	1		2009-09-29	1		antibacterials for systemic use
Human C1 esterase inhibitor	Berinert	1		2010-05-31		1	other hematological agents
Influenza vaccine	Flumist	1		2010-06-22		1	vaccines
Zucapsaicin	Civanex (Zuacta	1		2010-07-15	1		topical products for joint and muscular pain
Clevidipine	Cleviprex	1		2011-04-15	1		calcium channel blockers
Rubidium chloride rb 82	Ruby-fill		1	2011-09-20		1	diagnotic radiopharmaceuticals
Doxycycline	Efracea	1		2011-11-14	1		antibacterials for systemic use
Ferumoxytol	Feraheme	1		2011-12-08	1		antianemic preparations
Remestemcel-L	Prochymal		1	2012-05-17		1	unassigned
Ezogabine	Potiga	1		2012-10-08	1		antiepileptics
Haemagglutinin-Strain A	Arepranrix H5N1	1		2013-02-13		1	vaccines
Olodaterol	Striverdi respima	1		2013-06-11	1		drugs for obstructive airway diseases
Difluprednate	Durezol	1		2013-11-04	1		corticosteroids, dermatological preparations
Tafluprost	Saflutan	1		2014-05-26	1		ophthalmologicals
Elosulfase Alfa	Vimizim		1	2014-07-02		1	other alimentary tract and metabolism products
Turoctocog alfa	Zonovate	1		2014-12-08		1	antihemorrhagics
Bromfenac	Prolensa	1		2015-03-26	1		ophthalmologicals
Albiglutide	Eperzan	1		2015-07-15		1	drugs used in diabetes
Vilazodone	Viibryd	1		2015-07-16	1		psychoanaleptics
Polidocanol	Varithena	1		2015-08-04	1		vasoprotectives
Peginterferon Beta-1A	Plegridy	1		2015-08-10		1	immunostimulants

Antihemophilic Factor (Recombinant) Porcine Sequence	Obizur	1			2015-10-14		1	antihemorrhagics
Lubiprostone	Amitiza	1			2015-10-14	1		drugs for constipation
Albutrepenonacog Alfa	Idelvion	1			2016-01-26		1	antihemorrhagics
Finafloxacin	Xtoro	1			2016-03-11	1		otologicals
Glycerol Phenylbutyrate	Ravicti		1		2016-03-16	1		other alimentary tract and metabolism products
Vorapaxar	Zontivity	1			2016-05-13	1		antithrombotic agents
Elotuzumab	Empliciti		1		2016-06-21		1	antineoplastic agents
Daratumumab	Darzalex			1	2016-06-29		1	antineoplastic agents
Rupatadine	Rupall	1			2016-07-20	1		antihistamines for systemic use
Reslizumab	Cinqair	1			2016-07-20		1	drugs for obstructive airway diseases
Bepotastine	Bepreve	1			2016-07-27	1		antihistamines for systemic use
Alectinib	Alecensaro			1	2016-09-29	1		antineoplastic agents
Antihemophilic Factor (Recombinant), PEGylated	Adynovate	1			2016-11-17		1	antihemorrhagics
Gadoterate Meglumine	Dotarem	1			2016-11-25	1		contrast media
Botulinium antitoxin serotypes A, B,C, D, E, F and G	BAT	1			2016-12-08		1	immune sera and immunoglobulins
Lonoctocog Alfa	Afstyla	1			2016-12-12		1	antihemorrhagics

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Location in study
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Ttile, page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Structured summary, pages 2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Introduction, page 5
Objectives	3	State specific objectives, including any prespecified hypotheses	Introduction, page 6
Methods			
Study design	4	Present key elements of study design early in the paper	Methods, pages 6-8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Methods, pages 6-8, 10
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	Methods, pages 6, 7
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Methods, pages 8-10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Methods, pages 7-10
Bias	9	Describe any efforts to address potential sources of bias	Not relevant
Study size	10	Explain how the study size was arrived at	Not relevant
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Not relevant
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Methods, page 10
		(*b*) Describe any methods used to examine subgroups and interactions	Methods, pages 9, 10

		(*c*) Explain how missing data were addressed	Not relevant
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	Not relevant
		(*e*) Describe any sensitivity analyses	Not relevant
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Results, pages 10-12
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	Not relevant
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Not relevant
		(b) Indicate number of participants with missing data for each variable of interest	Results, page 13
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	Not relevant
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	Results, pages 11-15
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	Not relevant
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not relevant
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Not relevant
Discussion			
Key results	18	Summarise key results with reference to study objectives	Discussion, page 16
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Limitations, page 19
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Conclusion, page 19

Generalisability	21	Discuss the generalisability (external validity) of the study results	Not relevant
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 20

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.