

BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-023605
Article Type:	Research
Date Submitted by the Author:	14-Apr-2018
Complete List of Authors:	Lexchin, Joel; York University, School of Health Policy & Management
Keywords:	Health policy < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, accelerated approvals, Health Canada, therapeutic evaluation, therapeutic groups

SCHOLARONE™
Manuscripts

view only

1
2
3 1 **Health Canada's use of accelerated review pathways and therapeutic innovation, 1995-**
4
5 2 **2016: a cohort study**

6
7
8 3 Joel Lexchin MSc, MD^{1,2,3}

9
10 4 ¹Professor Emeritus

11
12 5 School of Health Policy and Management

13
14 6 York University

15
16 7 ²Emergency Physician

17
18 8 University Health Network

19
20 9 ³Associate Professor

21
22 10 Faculty of Medicine

23
24 11 University of Toronto

25
26 12

27
28 13 Correspondence:

29
30 14 Joel Lexchin MD

31
32 15 School of Health Policy and Management

33
34 16 York University

35
36 17 4700 Keele St.

37
38 18 Toronto, ON M3J 1P3

39
40 19 Tel: 416-964-7186

41
42 20 Email: jlexchin@yorku.ca

43
44 21 ORCID ID: 0000-0001-5120-8029

45
46 22 **Key words:**

47
48 23 accelerated approvals, Health Canada, health policy, therapeutic evaluation, therapeutic

49
50 24 group

51
52 25 **Word count:**

1
2
3 26 2790
4
5

6 27 **Structured summary**
7

8 28 **Objectives**
9

10
11 29 This study examines the use of accelerated approval pathways by Health Canada over the
12
13 30 period 1995 to 2016 inclusive and the relationship between the use of these pathways and the
14
15 31 therapeutic gain offered by new products.
16
17

18
19 32 **Design**
20

21
22 33 Cohort study.
23
24

25 34 **Data sources**
26

27
28 35 Therapeutic Products Directorate, Biologics and Genetic Therapies Directorate, Notice of
29
30 36 Compliance database, Notice of Compliance with conditions web site, Patented Medicine
31
32 37 Prices Review Board, La revue Prescrire, World Health Organization (WHO) Anatomical
33
34 38 Therapeutic Chemical (ATC) classification system.
35
36
37

38 39 **Interventions**
39

40
41 40 None
42
43
44

45 41 **Primary and secondary outcomes**
46

47
48 42 Percent of new drugs evaluated by Health Canada that went through an accelerated pathway
49
50 43 between 1995 and 2016 inclusive. Kappa values comparing the review status to assessments
51
52 44 of therapeutic value for individual drugs.
53
54

55 45 **Results**
56
57
58
59
60

1
2
3 46 438 (70.3%) drugs went through the standard pathway, 185 (29.7%) an accelerated pathway.
4
5 47 Therapeutic evaluations were available for 509 drugs. Health Canada used an accelerated
6
7 48 approval pathway for 159 of the 509 drugs whereas only 55 were judged to be therapeutically
8
9 49 innovative. The Kappa value for the entire period for all 509 drugs was 0.276 (95% CI 0.194,
10
11 50 0.359) or fair.

14 51 **Conclusion**

16
17
18 52 Health Canada's use of accelerated approvals was stable over the entire time period. Its
19
20 53 ability to predict which drugs will offer a major therapeutic gain is relatively poor. The
21
22 54 findings in this study should provoke a discussion about whether Health Canada should
23
24 55 continue to use these pathways and if so how their use can be improved.
25
26
27 56

1
2
3 57 **Article Summary**
4

5 58 *Strengths and limitations of this study*
6

- 7 59 • Examination of the use of accelerated approval pathways by Health Canada over an
8 extended period of time.
9
10 60
11 61 • Comparison of use of accelerated approval pathways to independent assessment of
12 therapeutic evaluation.
13
14 62
15 63 • Analysis of approvals and therapeutic value of therapeutic subgroups.
16
17
18 64 • Twenty percent of new drugs approved did not have therapeutic evaluations.
19

20 65
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

66 **Introduction**

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

74

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

85

86 Lexchin has examined how closely Health Canada's use of the two pathways (priority review
87 and NOC/c, hereafter collectively termed accelerated review pathways) corresponds to
88 independent assessments of the therapeutic innovation of drugs at the level of individual
89 drugs. For the period 1997-2012, the Kappa value was 0.334 (95% CI 0.220, 0.447) or fair
90 (5).

1
2
3 91
4
5 92 This current study is a further and more detailed look at how Health Canada uses its
6
7 93 accelerated review pathways, by extending previous work in a number of ways. First it
8
9 94 covers a wider time period – 1995 to 2016, inclusive. Second, it looks at the use of both of
10
11 95 the accelerated review pathways over this entire time period for the entire sample of drugs as
12
13 96 well as subgroups – small molecule drugs, biologics, and therapies for serious diseases.
14
15 97 Third, it calculates the Kappa and positive and negative predictive values for the entire
16
17 98 sample of drugs as well as the subgroups listed above. These subgroups were chosen because
18
19 99 small molecules and biologics have fundamentally different characteristics and these may
20
21 100 influence a decision to use an accelerated review pathway and how accurately Health Canada
22
23 101 can predict their therapeutic value. Similarly, when the treatment is for serious medical
24
25 102 conditions, Health Canada may be more willing to use an accelerated review pathway and
26
27 103 may be more likely to believe that the new product will provide a significant therapeutic
28
29 104 benefit.
30
31
32
33
34

35 106 **Methods**

36 107 *Data sources*

37
38
39 108 All NAS approved from 1995 to 2016 inclusive were documented using the annual reports
40
41 109 from the Therapeutic Products and the Biologics and Genetic Therapies Directorates that are
42
43 110 in charge of reviewing applications for new small molecule drugs and biologics and
44
45 111 vaccines, respectively. (Reports are available by directly contacting the directorates at
46
47 112 <publications@hc-sc.gc.ca>.) 1995 was the starting date as there are no annual reports from
48
49 113 Health Canada prior to that year. Generic and brand names along with the specific approval
50
51 114 pathway – standard, priority, NOC/c (only from 1998 onwards) – and whether the product
52
53
54
55
56
57
58
59
60

1
2
3 115 was a small molecule drug or biologic (information available only from 2000 onwards) were
4
5 116 extracted from the annual reports.

6
7 117

8
9 118 Not all of the drugs with a NOC/c are documented in the annual reports and they were
10
11 119 supplemented using four additional sources: articles by Lexchin (6) and Law (7), the Notice
12
13 120 of Compliance database (<http://webprod5.hc-sc.gc.ca/noc-ac/index-eng.jsp>) and the Notice
14
15 121 of Compliance with conditions web site ([http://www.hc-sc.gc.ca/dhp-](http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/conditions/index-eng.php)
16
17 122 [mps/prodpharma/notices-avis/conditions/index-eng.php](http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/conditions/index-eng.php)). Only drugs approved for the first
18
19 123 time under a NOC/c were considered. Drugs can receive both a priority and NOC/c review
20
21 124 and in this case they were only counted as receiving a priority review.
22
23 125

24 126 *Assessment of therapeutic innovation*

25
26
27 127 The therapeutic value of drugs was assessed using the ratings from the annual reports of the
28
29 128 Canadian Patented Medicine Prices Review Board (PMPRB) <[http://www.pmprb-](http://www.pmprb-cepmb.gc.ca/english/View.asp?x=91)
30
31 129 [cepmb.gc.ca/english/View.asp?x=91](http://www.pmprb-cepmb.gc.ca/english/View.asp?x=91)> and the French drug bulletin La revue Prescrire (8).

32
33 130 The processes that these two organizations use in arriving at their decisions about
34
35 131 therapeutically innovation have been previously described (5). For the purpose of this study,
36
37 132 products that the PMPRB deemed breakthrough and substantial improvement were termed
38
39 133 “innovative” and products in other categories were termed “not innovative” (category 3 =
40
41 134 moderate, little or no improvement over existing medicines prior to 2010; slight or no
42
43 135 improvement, moderate improvement – primary and moderate improvement – secondary
44
45 136 from 2010 onward). Prescrire uses seven categories to rate therapeutic innovation. The first
46
47 137 two, bravo (major therapeutic innovation in an area where previously no treatment was
48
49 138 available); a real advance (important therapeutic innovation but has limitations) were defined
50
51 139 as a significant therapeutic innovation and the other Prescrire categories (except judgment
52
53
54
55
56
57
58
59
60

140 reserved) were defined as no therapeutic advance.

141

142 If a drug was judged innovative by either the PMPRB and/or Prescrire, it was rated as inno-

143 vative. If both organizations evaluated the drug and the ratings were discordant, i.e., one said it

144 was not innovative and one said it was, the drug was still considered innovative. Table 1 shows

145 that there is substantial agreement among the definitions used by Health Canada, the PMPRB

146 and Prescrire in assessing therapeutic innovation. Ratings were current for PMPRB as of

147 December 31, 2016 (the annual report for 2017 was not available at the time of writing) and for

148 Prescrire as of February 20, 2018.

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

152

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

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

153

154 Adapted from: (9)

155 *Notice of Compliance with conditions

156

157 *Data analysis*

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

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

160

161 Kappa values were used to compare the review status from Health Canada to the assessments

162 for the same drug from the PMPRB/Prescrire for each year and for the 22-year period. Owing

163 to the small number of drugs approved through the NOC/c pathway, numbers from the two

164 accelerated review pathways were combined. Kappa scores measure whether there is more or

165 less agreement between different evaluations than would be expected by chance. Levels of

166 agreement were graded in accordance with the recommendations of Landis and Koch (10).

167

168 *Subgroup analyses*

169 The number and percent of small molecule drugs and biologics approved through the

170 standard, priority and NOC/c pathways were calculate and compared using the Chi-square

171 statistic. Similarly, the Kappa values were calculated separately for small molecule drugs and

172 biologics.

173

1
2
3 174 All drugs were categorized using the second level of the World Health Organization (WHO)
4
5 175 Anatomical Therapeutic Chemical (ATC) classification system (11). Drugs in three therapeutic
6
7 176 groups – antineoplastic agents, antivirals for systemic use and immunosuppressants – were
8
9 177 chosen for subgroup analyses because they are primarily used for serious life-threatening
10
11 178 diseases and because there are sufficient numbers in each group to allow for statistical analyses.
12
13 179 The number and percent of each subgroup that received an accelerated review was calculated
14
15 180 as were the Kappa values on a drug-by-drug basis and for drugs in the “all other therapeutic
16
17 181 groups”. Distribution of approval pathways in the subgroups individually and for the three
18
19 182 subgroups combined versus all other therapeutic groups was compared using the Chi-square
20
21 183 statistic. Calculations were done using Excel 2016 for Macintosh (Microsoft) and Prism 7.0
22
23 184 (GraphPad Software).

24
25 185

26 27 186 *Patient and public involvement*

28
29
30 187 No patients were involved in any aspect of this study.

31
32 188

33 34 189 *Ethics*

35
36 190 No patients were involved in this study and only publicly available data was gathered.

37
38 191 Therefore, ethics approval was not required.

39
40
41 192

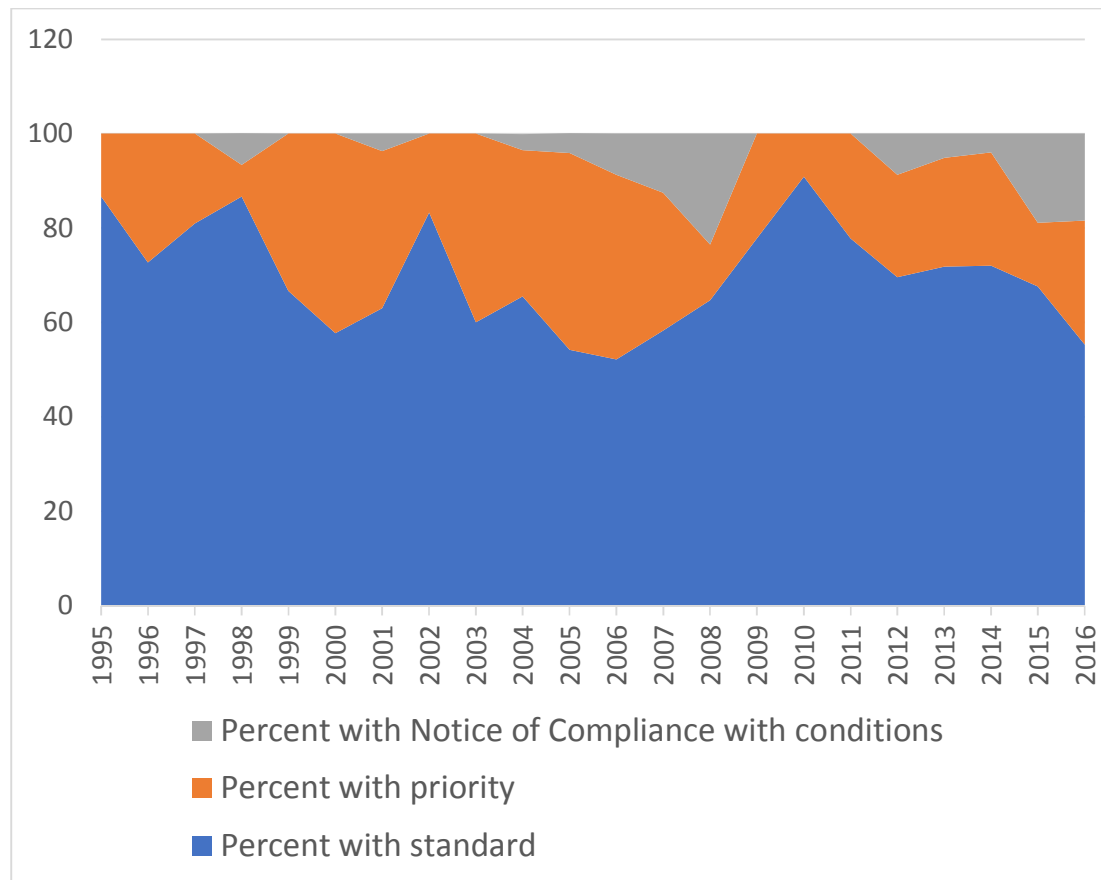
42 43 193 **Results**

44 45 194 *Review status*

46
47 195 From January 1, 1995 to December 31, 2016 Health Canada approved a total of 623 NAS. Of
48
49 196 these, 438 (70.3%) went through the standard pathway, 152 (24.4%) the priority pathway and
50
51 197 33 (5.3%) received a NOC/c. Almost 30 percent (29.7%) went through the accelerated
52
53 198 review pathways over the entire period, varying from a low of 9.1% in 2010 to a high of
54
55 199 47.8% in 2006 (Table 2). (Health Canada used both a priority and NOC/c approval for 11

200 drugs, data not shown.) Figure 1 shows that there is no trend to using accelerated review
 201 pathways more liberally or more conservatively over the time period. (Supplementary Tables
 202 1 & 2, drugs with and without therapeutic evaluations, respectively, give all of the data
 203 extracted for the 623 drugs in question.)

204 **Figure 1: Percent of drugs approved through different pathways**



205

206

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

208

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)

209

210 *Notice of Compliance with conditions

211 †Patented Medicine Prices Review Board

212

213 There were 126 biologics approved versus 323 small molecules (data only available from
 214 2000 onward). There was no difference in the distribution of the approval pathways ($p =$
 215 0.4867) (Table 3). There were 81 approvals for antineoplastic agents, 47 for antivirals for
 216 systemic use, 36 for immunosuppressants and 365 for drugs in the “all other therapeutic
 217 groups” ($n = 67$) (Supplementary Table 1). The distribution of approval pathways was
 218 significantly different for the three subgroups ($p = 0.0018$) and for the three subgroups
 219 combined versus “all other therapeutic groups” ($p < 0.00001$) (Table 3).

220 **Table 3: Subgroup comparison of review pathways**

221

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

222

223 Small molecules vs. biologics: chi-square = 1.4402 (p = 0.4867)

224 Antineoplastics vs. antivirals vs. immunosuppressants: chi-square = 17.1978 (p = 0.0018)

225 Antineoplastics + antivirals + immunosuppressants vs. all other therapeutic groups: chi-square = 97.4874 (p < 0.00001)

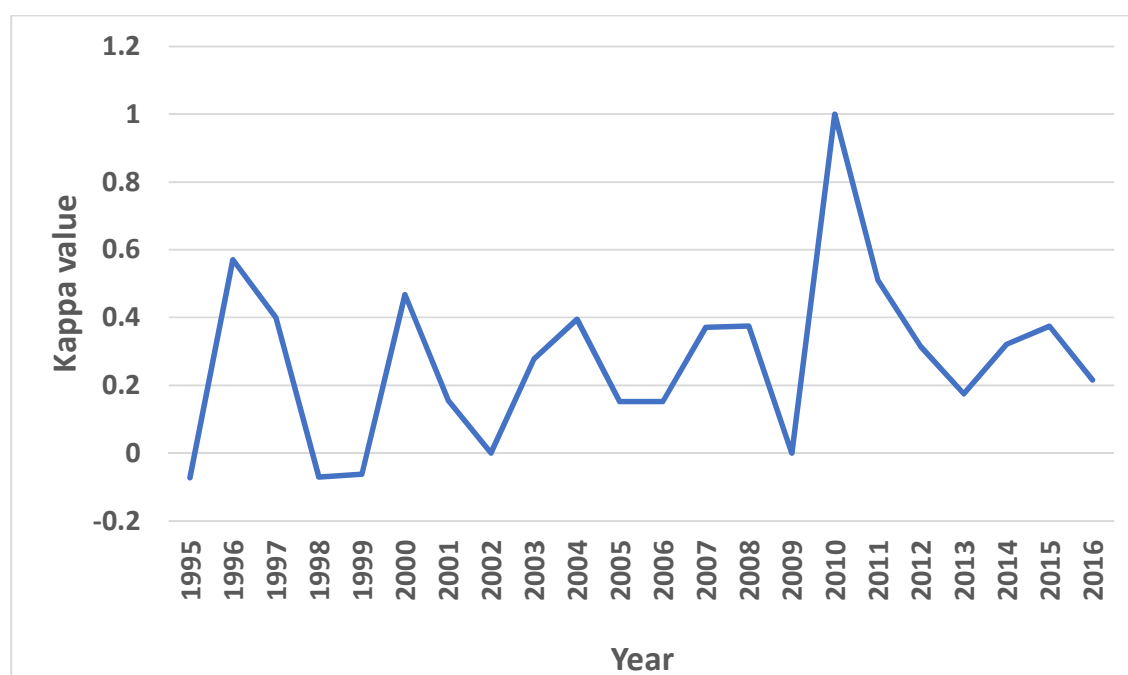
226

227

228 *Therapeutic value*

229 Out of the 623 NAS, 509 (81.7%) were evaluated for their therapeutic innovation either by
 230 the PMPRB and/or La revue Prescrire. Health Canada used an accelerated review pathway
 231 for 159 of the 509 drugs whereas only 55 were judged to be therapeutically innovative by one
 232 or both of the independent reviews (Table 4). The Kappa value for the entire period for all
 233 509 drugs was 0.276 (95% CI 0.194, 0.359) or fair. Figure 2 presents the Kappa values for
 234 each year which generally ranged from 0 (poor) to 0.4 (fair).

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



236

237

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

240

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

241

242 *New active substance

243 †Number of drugs rated as innovative as a percent of all drugs given an accelerated approval
244 review by Health Canada245 ‡Number of drugs rated as not therapeutically innovative as a percent of all drugs given a
246 standard review by Health Canada

247

248 There were 286 and 99 small molecule drugs and biologics, respectively, with therapeutic
249 ratings. The Kappa values were 0.313 (95% CI 0.205, 0.420) (fair) and 0.233 (95% CI 0.061,
250 0.405) (fair), respectively. The overlapping 95% CIs indicate no difference in the Kappa
251 values between the two groups (Table 5).

252 **Table 5: Subgroup analyses: Kappa values**

253

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)

254

255 The 509 drugs were in 57 different second level ATC groups: antineoplastic agents (71),
256 antivirals for systemic use (46), immunosuppressants (35) and “all other therapeutic groups”
257 (357) (Supplementary Table 1). Kappa values for the four groups were: 0.091 (95% CI 0.017,
258 0.200) (poor), 0.200, 0.122 (95% CI 0.011, 0.233) (poor), 0.376 (95% CI 0.075, 0.675)
259 (fair) and (95% CI 0.263, 0.506)0.385 (fair), respectively. The 95% CIs for the Kappa values

1
2
3 260 for the antineoplastic agents, antivirals for systemic use and immunosuppressants overlapped
4
5 261 indicating no difference among the groups but there was no overlap of any of these with the
6
7 262 95% CI for “all other therapeutic groups”.

8
9 263

10 11 264 **Discussion**

12
13 265 Almost 30% of the new active substances that Health Canada reviewed between 1995 and
14
15 266 2016 went through one of two accelerated review pathways – priority review or NOC/c,
16
17 267 primarily a priority review. There is no difference between small molecule drugs and
18
19 268 biologics in the approval pathways used indicating that for these two groups Health Canada
20
21 269 does not see one or the other being more likely to offer significant new therapeutic benefits.
22
23 270 However, the same is not true for the therapeutic subgroups. The three specifically examined
24
25 271 – antineoplastics, antivirals and immunosuppressants – were more likely to be assigned to an
26
27 272 accelerated review pathway compared to all other therapeutic groups, possibly because of the
28
29 273 nature of the diseases that they treat.

30
31
32
33 274

34
35 275 Just over 80% of the NAS approved had been assessed by the PMPRB and/or La revue
36
37 276 Prescrire for their therapeutic benefit. The Kappa value for the 509 drugs was 0.276 meaning
38
39 277 that Health Canada’s ability to predict major therapeutic gain from these drugs was only fair.
40
41 278 The relatively low Kappa value may relate to when Health Canada makes its decision about
42
43 279 what type of approval pathway to use. This assignment is at the start of the review process
44
45 280 when all of the data will not have been fully assessed. In contrast, the PMPRB and La revue
46
47 281 Prescrire make their assessments after the drug has been marketed when more information
48
49 282 about efficacy and safety is available.

50
51
52
53 283

1
2
3 284 As was the case with the assignment of an accelerated review pathway, there is no difference
4
5 285 in how Health Canada evaluates the therapeutic value of small molecule drugs and biologics.
6
7 286 Health Canada seems somewhat better at predicting the therapeutic value of drugs in the “all
8
9 287 other therapeutic groups” than it does for drugs in the antineoplastic, antiviral and
10
11 288 immunosuppressant groups although it is more likely to review these groups through an
12
13 289 accelerated review pathway.
14

15
16 290

17
18 291 How Health Canada uses its accelerated review pathways is important for a number of
19
20 292 reasons. First, their use may explicitly create an impression among clinicians and patients that
21
22 293 these drugs are likely to deliver major new therapeutic benefits despite the fact that the
23
24 294 likelihood that they will is only “fair” as measured by the Kappa value. Second, the NOC/c
25
26 295 pathway requires companies to commit to conducting post-market studies to validate the
27
28 296 efficacy of the product, but many of these studies are delayed (6, 7), leaving clinicians and
29
30 297 patients uncertain about the value of these products. In at least one case, Health Canada did
31
32 298 not suspend the sale of a drug and allowed it to stay on the market despite not fulfilling the
33
34 299 conditions required under its NOC/c. In December 2003, Iressa (gefitinib) was approved as a
35
36 300 third-line treatment for non-small cell lung cancer on the condition that the company submit a
37
38 301 study showing that it improved survival (12). When the study results were submitted to
39
40 302 Health Canada they showed no survival benefit for gefitinib compared to placebo (13).

41
42
43 303 Health Canada recognized that the conditions had not been fulfilled, but rather than removing
44
45 304 gefitinib from the market, in February 2005 it elected to allow it to continue to be sold (12).

46
47
48 305 In 2009, the drug was deemed to have met its conditions after a new study showed non-
49
50 306 inferiority, i.e., survival after taking it was no worse compared to another chemotherapeutic
51
52 307 agent (14). Third, although the priority and standard approval pathways are equivalent in
53
54 308 terms of the amount of data reviewed, the former is done in 180 days compared to 300 days
55
56
57
58
59
60

1
2
3 309 for the latter, meaning that the priority pathway is more resource intensive possibly drawing
4
5 310 resources from other Health Canada activities. Finally, drugs reviewed through both
6
7 311 accelerated review pathways are more likely to receive safety warnings once they are on the
8
9 312 market compared to drugs with a standard approval (2, 15).

10
11 313

12
13 314 As Figure 1 indicates, Health Canada is not using the accelerated review pathways more
14
15 315 liberally (or more conservatively) over time, but as Figure 2 shows it has not improved its
16
17 316 ability to predict therapeutic innovation over the 22 years evaluated in this study. The
18
19 317 Introduction describes the criteria that Health Canada uses to assign a drug to either a priority
20
21 318 review or a NOC/c review but how those criteria are applied and whether Health Canada
22
23 319 periodically reviews its performance are not known. The fact that it appears to be better at
24
25 320 predicting therapeutic innovation for some therapeutic subgroups is encouraging.

26
27 321

28
29 322 Contrary to the situation in the United States (US) where the Food and Drug Administration
30
31 323 (FDA) has been using an increasing number of expedited development or review programs,
32
33 324 Health Canada's use of its programs has been relatively stable since 1995. Between 1987 and
34
35 325 2014, 43% received a priority review from the FDA and 19% were approved through the fast
36
37 326 track program the equivalent of a NOC/c (16). (Drugs could be associated with both
38
39 327 programs.) However, when it comes to approving oncology drugs through an accelerated
40
41 328 pathway, Health Canada is only marginally better than the FDA. In the US, only 1 of 15
42
43 329 (6.7%) oncology drugs approved through an accelerated program from January 1, 2008,
44
45 330 through December 31, 2012 had a proven survival benefit compared to the other 6 and 8 that
46
47 331 either had no overall survival benefit or an unknown benefit, respectively (17). In this current
48
49 332 study, out of 42 neoplastic agents that Health Canada gave an accelerated review to, only 6
50
51 333 (14.3%) were rated as therapeutically innovative. While Health Canada used accelerated
52
53
54
55
56
57
58
59
60

1
2
3 334 approvals less often than the FDA, it used these pathways more often than the European
4
5 335 Medicines Association which applied them to only 70 (12.5%) of 558 new drugs it approved
6
7 336 from 1995 to 2009 (18).
8

9 337

10
11 338 *Limitations*

12
13 339 Almost 20% of new drugs approved by Health Canada were not evaluated for their
14
15 340 therapeutic innovation by either the PMPRB or La revue Prescrire. The absence of these
16
17 341 evaluations may have skewed both the Kappa values in either a more positive or more
18
19 342 negative direction.
20
21

22 343

23
24 344 **Conclusion**

25
26 345 Health Canada continues to use accelerated review pathways for about 30% of new drugs.
27
28 346 The rationale for using accelerated review pathways is to get important therapeutic advances
29
30 347 to patients in a timely manner, but Health Canada's ability to predict which of these drugs
31
32 348 will fulfill this expectation has not improved over a 22-year period and remains relatively
33
34 349 low. Moreover, using these pathways come with both health related and resource costs. The
35
36 350 findings in this study should provoke a discussion about whether Health Canada should
37
38 351 continue to use these pathways and if so how their use can be improved.
39
40

41
42 352
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 353 **Acknowledgements**
4

5 354 None
6

7 355 **Competing Interests**
8

9 356 In 2015-2017, Joel Lexchin received payment from two non-profit organizations for being a
10
11 357 consultant on a project looking at indication based prescribing and a second looking at which
12
13 358 drugs should be distributed free of charge by general practitioners. In 2015, he received
14
15 359 payment from a for-profit organization for being on a panel that discussed expanding drug
16
17 360 insurance in Canada. He is on the Foundation Board of Health Action International.
18
19

20 361 **Funding**
21

22 362 This research received no specific grant from any funding agency in the public, commercial
23
24 363 or not-for profit sectors.
25

26 364 **Data sharing**
27

28 365 Full data that was extracted is available from the online data repository Dryad
29
30
31 366 <http://datadryad.org> with the DOI:
32

33 367 **Author Contributions**
34

35 368 JL came up with the idea for this study, gathered and analyzed the data and wrote the
36
37 369 manuscript.
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 370 **References**

- 4
5 371 1. Health Products and Food Branch. Access to therapeutic products: the regulatory
6
7 372 process in Canada Ottawa: Health Canada; 2006 [cited 2014 July 20]. Available from:
8
9 373 http://publications.gc.ca/collections/collection_2007/hc-sc/H164-9-2006E.pdf.
10
11 374 2. Lexchin J. Post-market safety warnings for drugs approved in Canada under the
12
13 375 Notice of Compliance with conditions policy. *British Journal of Clinical Pharmacology*.
14
15 376 2015;79:847-59.
16
17 377 3. Health Canada: Health Products and Food Branch. Guidance for industry: priority
18
19 378 review of drug submissions. Ottawa: 2009.
20
21 379 4. Health Canada. Notice of compliance with conditions (NOC/c). Ottawa: 2002.
22
23 380 5. Lexchin J. Health Canada's use of its priority review process for new drugs: a cohort
24
25 381 study. *BMJ Open*. 2015;5:e006816.
26
27 382 6. Lexchin J. Notice of compliance with conditions: a policy in limbo. *Healthcare*
28
29 383 *Policy*. 2007;2:114-22.
30
31 384 7. Law M. The characteristics and fulfillment of conditional prescription drug approvals
32
33 385 in Canada. *Health Policy*. 2014;116:154-61.
34
35 386 8. Prescrire Editorial Staff. Prescrire's ratings system: gauge the usefulness of new
36
37 387 products at glance Paris2011 [cited 2015 March 11]. Available from:
38
39 388 <http://english.prescrire.org/en/81/168/46800/0/NewsDetails.aspx>.
40
41 389 9. Lexchin J. Postmarket safety in Canada: are significant therapeutic advances and
42
43 390 biologics less safe than other drugs? A cohort study. *BMJ Open*. 2014;4:e004289.
44
45 391 10. Landis JR, Koch GG. The measurement of observer agreement for categorical data.
46
47 392 *Biometrics*. 1977;33:159-74.
48
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3 393 11. WHO Collaborating Centre for Drug Statistics Methodology, Norwegian Institute of
4
5 394 Public Health. Structure and principles 2011 [cited 2018 February 20]. Available from:
6
7 395 http://www.whooc.no/atc/structure_and_principles/.
8
9 396 12. Health Canada. Clarification from Health Canada regarding the status of Iressa®
10
11 397 (gefitinib) in Canada Ottawa2005 [cited 2014 October 20]. Available from: [http://www.hc-](http://www.hc-sc.gc.ca/dhp-mpps/prodpharma/activit/fs-fi/fact_iressa-eng.php)
12
13 398 [sc.gc.ca/dhp-mpps/prodpharma/activit/fs-fi/fact_iressa-eng.php](http://www.hc-sc.gc.ca/dhp-mpps/prodpharma/activit/fs-fi/fact_iressa-eng.php).
14
15 399 13. Thatcher N, Chang A, Parikh P, Pereira J, Ciuleanu T, von Pawel J, et al. Gefitinib
16
17 400 plus best supportive care in previous treated patients with refractory advanced non-small-cell
18
19 401 lung cancer: results from a randomised, placebo-controlled, multicentre study (Iressa
20
21 402 Survival Evaluation in Lung Cancer). *Lancet*. 2005;366:1527-37.
22
23 403 14. Kim E, Hirsh V, Mok T, Socinski M, Gervais R, Wu Y-L, et al. Gefitinib versus
24
25 404 docetaxel in previously treated non-small-cell lung cancer (INTEREST): a randomised phase
26
27 405 III trial. *Lancet*. 2008;372:1809-18.
28
29 406 15. Lexchin J. New drugs and safety: what happened to new active substances approved
30
31 407 in Canada between 1995 and 2010? *Archives of Internal Medicine*. 2012;172:1680-1.
32
33 408 16. Kesselheim A, Wang B, Franklin J, Darrow J. Trends in utilization of FDA expedited
34
35 409 drug development and approval programs, 1987-2014: cohort study. *BMJ*. 2015;351:h4633.
36
37 410 17. Kim C, Prasad V. Cancer drugs approved on the basis of a surrogate end point and
38
39 411 subsequent overall survival: an analysis of 5 years of US Food and Drug Administration
40
41 412 approvals. *JAMA Internal Medicine*. 2015;175:1992-4.
42
43 413 18. Boon W, Moors E, Meijer A, Schellekens H. Conditional approval and approval
44
45 414 under exceptional circumstances as regulatory instruments for stimulating responsible drug
46
47 415 innovation in Europe. *Clinical Pharmacology & Therapeutics*. 2010;88:848-53.
48
49
50
51
52
53
54
55
56
57
58
59
60

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

Generic name	Brand name	PMPRB breakthrough, substantial improvement and/or	PMPRB and/or Prescribe 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	

1					
2					
3	Valacyclovir	Valtrex	1	1	
4	Quinagolide	Norprolac	1	1	
5	Meropenem	Merrem	1	1	
6					
7					
8	Abciximab	Reopro	1	1	
9	Anastrozole	Arimidex	1	1	
10	Ritonavir	Norvir	1		1
11	Raltitrexed	Tomudex	1		1
12	Indinavir	Crixivan	1		1
13	Insulin lispro	Humalog	1	1	
14	Dirithromycin	Dynabac	1	1	
15					
16					
17					
18	Olanzapine	Zyprexa	1	1	
19	Nalmefene	Revex	1	1	
20	Zolpidem	Ambien	1	1	
21	Desflurane	Suprane	1	1	
22	Gemcitabine	Gemzar	1	1	
23	Ropivacaine	Naropin injections	1	1	
24	Imiglucerase	Cerezyme	1		1
25					
26					
27					
28	Atorvastatin	Lipitor	1		1
29	Topiramate	Topamax	1	1	
30	Formoterol	Foradil dry	1	1	
31		powder capsules			
32					
33	Epoprostenol	Flolan	1		1
34	Coagulation factor IX	Benefix	1		1
35					
36					
37	Topotecan	Hycamtin	1	1	
38	Dolasetron	Anzemet	1	1	
39					
40					
41	Letrozole	Femara	1	1	
42	Fexofenadine	Allegra	1	1	
43					
44					
45	Latanoprost	Xalatan	1	1	
46	Carbetocin	Duratocin	1	1	
47					
48					
49	Follitropin beta	Puregon	1	1	
50					
51					
52	Irinotecan	Camptosar	1	1	
53	Donepezil	Aricept	1	1	
54	Ropinirole	Requip	1	1	
55					
56					
57					
58					
59					
60					

1							
2							
3	Ibandronate	Bondronat	1	1			
4							
5	Glatiramer	Copaxone for	1	1			
6		injection					
7	Tolcapone	Tasmar	1	1			
8	Zafirlukast	Accolate	1	1			
9							
10							
11	Valsartan	Diovan	1	1			
12							
13							
14	Levofloxacin	Levaquin	1	1			
15							
16	Brimonidine	Alphagan	1	1			
17		ophthalmic solution					
18	Quetiapine	Seroquel	1	1			
19	Pramipexole	Mirapex	1	1			
20	Interferon Beta-1A	Rebif	1	1			
21	Emedastine	Emadine	1	1			
22		ophthalmic					
23	Cerivastatin	Baycol	1	1			
24	Grepafloxacin	Raxar	1	1			
25							
26							
27	Naratriptan	Amerge	1	1			
28	Bupropion	Wellbutrin SR	1	1			
29	Irbesartan	Avapro	1	1			
30							
31							
32							
33							
34	Tamsulosin	Flomax	1	1			
35	Montelukast	Singulair	1	1			
36							
37							
38	Delavirdine	Rescriptor	1	1			1
39	Nelfinavir	Viracept	1		1		
40	Zolmitriptan	Zomig	1	1			
41	Capecitabine	Xeloda	1		1		
42	Nevirapine	Viramune	1	1			1
43	Clopidogrel	Plavix	1	1			
44	Brinzolamide	Azopt ophthalmic	1	1			
45		suspension					
46	Raloxifene	Evista	1	1			
47							
48							
49							
50							
51							
52	Candesartan	Atacand	1	1			
53							
54	Tolterodine	Detrol	1	1			
55	Varicella vaccine	Varivax	1	1			
56							
57							
58							
59							
60							

1						
2						
3	Alatrofloxacin	Trovan (IV)	1	1		
4						
5	Trovafloracin	Trovan (tablets)	1	1		
6						
7						
8	Becaplermin gel	Regranex	1	1		
9						
10						
11	Tizanidine	Zanaflex	1	1		
12	Penciclovir	Denavir	1	1		
13	Citalopram	Celexa	1	1		
14	Recombinant	Niastase	1		1	1
15	factor VIIa					
16	Modafinil	Alertec	1	1		
17	Sildenafil	Viagra	1	1		
18						
19	Recombinant-	Infergen	1		1	
20	methionyl					
21	interferon					
22	consensus 1					
23	Efavirenz	Sustiva	1		1	
24	Repaglinide	Gluconorm	1	1		
25	Celecoxib	Celebrex	1		1	
26						
27						
28						
29	Triptorelin	Trelstar	1	1		
30	Ancestim	Stemgen	1	1		
31	Orlistat	Xenical	1	1		
32	Abacavir	Ziagen	1		1	1
33	Eptifibatide	Integrilin	1	1		
34	Eprosartan	Teveten	1	1		
35						
36						
37						
38	Cidofovir	Vistide	1	1		
39	Rizatriptan	Maxalt	1	1		
40	Trastuzumab	Herceptin	1		1	
41	Telmisartan	Micardis	1	1		
42						
43						
44	Risedronate	Actonel	1	1		
45						
46						
47	Tirofiban	Aggrastat	1	1		
48	Icodextrin	Extraneal	1	1		
49						
50						
51	Varicella zoster	Varilrix	1		1	
52	vaccine					
53	Temozolomide	Temodal	1	1		
54	Rofecoxib	Vioxx	1		1	
55						
56						
57						
58						
59						
60						

1						
2						
3	Zanamivir	Relenza			1	1
4	Melanoma	Melacine			1	1
5	theracine					
6						
7	Gadobutrol	Gadovist			1	1
8	Dalfopristin	Synercid			1	1
9						
10						
11	Oseltamivir	Tamiflu			1	1
12	Daclizumab	Zenaprax			1	1
13	Leflunomide	Arava			1	1
14	Rituximab	Rituxan	1			1
15	Rosiglitazone	Avandia			1	1
16	Oxcarbazepine	Trileptal			1	1
17	Rivastigmine	Exelon			1	1
18	Zaleplon	Starnoc			1	1
19	Verteporfin	Visudyne	1			1
20	Cabergoline	Dostinex			1	1
21	Exemestane	Aromasin			1	1
22	Pioglitazone	Actos			1	1
23	Zoledronic acid	Zometa			1	1
24						
25						
26						
27						
28	Riluzole	Rilutek	1			1
29	Meloxicam	Mobic			1	1
30						
31						
32	Basiliximab	Simulect			1	1
33	Moxifloxacin	Avelox			1	1
34						
35						
36	Peginterferon Alfa-2b	Peg-intron			1	1
37						
38	Etanercept	Enbrel	1			1
39	Gadoversetamide	Optimark			1	1
40	Sibutramine	Meridia			1	1
41	Sirolimus	Rapamune			1	1
42	Gatifloxacin	Tequin			1	1
43						
44						
45						
46	Glucagon, rDNA origin	Glucagon			1	1
47						
48	Mequinol/tretinoin	Solage			1	1
49						
50						
51	Amprenavir	Agenerase			1	1
52	Lopinavir/ritonavir	Kaletra			1	1
53	Linezolid	Zyvoxam			1	1
54						
55						
56	Iron	Venofer			1	1
57						
58						
59						
60						

1						
2						
3	Doxercalciferol	Hectorol	1	1		
4	Rabeprazole	Pariet	1	1		
5						
6						
7	Entacapone	Comtan	1	1		
8	Eflornithine	Vaniqa	1	1		
9	Mirtazapine	Remeron	1	1		
10	Desloratadine	Aerius	1	1		
11						
12						
13	Infliximab	Remicade	1	1		
14	Caspofungin	Cancidas	1		1	
15						
16						
17	Galantamine	Reminyl	1	1		
18	Esomeprazole	Nexium	1	1		
19						
20						
21	Imatinib	Gleevec	1		1	1
22	Tenecteplase	Tnkase	1	1		
23	Travoprost	Travatan	1	1		
24	Bosentan	Tracleer	1		1	
25	Meningococcal	Neisvac-C	1		1	
26	group C					
27	polysaccharide,					
28	tetanus toxoid					
29						
30						
31	Glimepiride	Amaryl	1	1		
32	Nateglinide	Starlix	1	1		
33	Alfuzosin	Xatral	1	1		
34	Tegaserod	Zelnorm	1	1		
35	Ganirelix	Orgalutran	1	1		
36						
37						
38	Valganciclovir	Valcyte	1	1		
39	Palivizumab	Synagis	1	1		
40						
41						
42	Docosanol	Abreva	1	1		
43						
44						
45						
46	Bimatoprost	Lumigan	1	1		
47	Anakinra	Kineret	1		1	
48	Moroctocog alpha	Refacto	1		1	
49	Peginterferon Alfa-	Pegatron	1	1		
50	2b ribavirin					
51	Fondaparinux	Arixtra	1		1	
52	Hetastarch	Hextend	1	1		
53						
54						
55	Darbepoetin alpha	Aranesp	1	1		
56						
57						
58						
59						
60						

1								
2								
3	Norelgestromin/et	Evra		1	1			
4	hinyl estradiol							
5								
6								
7	Treprostinil	Remodulin		1			1	
8	Bivalirudin	Angiomax		1	1			
9	Tiotropium	Spiriva		1	1			
10								
11								
12	Valdecoxib	Betra		1	1			
13								
14	Drotrecogin Alfa	Xigris	1				1	
15	Rosuvastatin	Crestor		1	1			
16	Recombinant	Dukoral		1			1	
17	cholera toxin B							
18	subunit							
19								
20	Levetiracetam	Keppra		1	1			
21	Tenofovir	Viread		1			1	1
22	Pimecrolimus	Elidel		1	1			
23								
24								
25								
26	Ertapenem	Invanz		1	1			
27								
28	Ezetimibe	Ezetrol		1	1			
29	Telithromycin	Ketek		1	1			
30								
31								
32	Enfuvirtide	Fuzeon	1				1	
33	Dutasteride	Avodart		1	1			
34	Peginterferon Alfa-	Pegasys		1	1			
35	2a							
36	Cetorelix	Cetrotide		1	1			
37								
38								
39	Adefovir	Hepsera		1			1	
40	Tadalafil	Cialis		1	1			
41	Almotriptan	Axert		1	1			
42								
43								
44	Rasburicase	Fasturtec		1			1	
45								
46								
47	Atazanavir	Reyataz		1			1	
48	Gefitinib	Iressa		1			1	1
49	Agalsidase Beta	Fabrazyme		1			1	
50								
51								
52	Agalsidase	Replagal	1				1	1
53								
54								
55	Fulvestrant	Faslodex		1	1			
56								
57								
58								
59								
60								

1					
2					
3	Gemifloxacin	Factive		1	1
4					
5					
6	Pegfilgrastim	Neulasta		1	1
7	Vardenafil	Levitra		1	1
8	Gadobenate	Multihance		1	1
9	Miglustat	Zavesca		1	1
10					
11					
12	Botulinum Toxin	Myobloc		1	1
13	Type B				
14	Peginterferon Alfa-	Pegasys RBV		1	1
15	2A Ribavirin				
16	Ethinyl	Nuvaring		1	1
17	estradiol/etonoge				
18	strel				
19					
20	Pemetrexed	Alimta		1	1
21	Laronidase	Adlurazyme	1		1
22					
23					
24	Teriparatide	Forteo		1	1
25	Cinacalcet	Sensipar	1		1
26	Eletriptan	Relpax		1	1
27	Voriconazole	Vfend		1	1
28					
29					
30					
31	Frovatriptan	Frova		1	1
32	Adalimumab	Humira		1	1
33	Alefacept	Amevive		1	1
34	Omalizumab	Xolair		1	1
35					
36					
37	Memantine	Ebixa		1	1
38	Fosamprenavir	Telzir		1	1
39	Drospirenone/ethi	Yasmin 21/28		1	1
40	nyl estradiol				
41					
42					
43	Atomoxetine	Strattera		1	1
44	Escitalopram	Cipralex		1	1
45	Bortezomib	Velcade		1	1
46	Paricalcitol	Zemplar		1	1
47	Pantoprazole	Pantaloc M		1	1
48					
49					
50					
51	Pegaptanib	Macugen	1		1
52	Ibritumomab	Zevalin		1	1
53					
54	Pregabalin	Lyrica		1	1
55					
56					
57					
58					
59					
60					

1								
2								
3	Lutropin Alfa	Luveris		1	1			
4								
5								
6								
7	Erlotinib	Tarceva		1			1	
8	Tramadol	Tramacet		1	1			
9	Sodium oxybate	Xyrem		1	1			
10	Perindopril	Coversyl		1	1			
11								
12								
13	Bevacizumab	Avastin		1			1	
14	Cetuximab	Erbitux		1			1	
15	Insulin detemir	Levemir		1	1			
16	Pegvisomant	Somavert		1			1	
17								
18								
19	Efalizumab	Raptiva		1	1			
20	Darifenacin	Enablex		1	1			
21	Emtricitabine	Emtriva		1	1			
22	Tipranavir	Aptivus		1			1	
23	Alemtuzumab	Mabcampath	1		1			
24	Palifermin	Kepivance	1				1	
25								
26								
27								
28	Trospium	Trosec		1	1			
29	Solifenacin	Vesicare		1	1			
30	Histrelin	Vantas		1	1			
31	Insulin glulisine	Apidra		1	1			
32	Sunitinib	Sutent		1			1	1
33	Entecavir	Baraclude		1			1	
34								
35								
36								
37	Abatacept	Orencia		1			1	
38	Recombinant	Gardasil	1				1	
39	human							
40	papillomavirus							
41	Lanreotide	Somatuline		1	1			
42		autogel						
43								
44	Sorafenib	Nexavar		1	1			
45	Darunavir	Prezista		1	1			1
46	Rotaviruses	Rotateq	1		1			
47	Alglucosidase Alfa	Myozyme	1				1	
48								
49								
50								
51	Rasagiline	Azilect		1	1			
52	Ciclesonide	Alvesco		1	1			
53								
54								
55								
56								
57								
58								
59								
60								

1					
2					
3	Tigecycline	Tygalil	1	1	
4					
5	Natalizumab	Tysabri	1		1
6	Lanthanum	Fosrenol	1	1	
7					
8					
9	Deferasirox	Exjade	1		1
10					1
11	Gadofosveset	Vasovist	1	1	
12	Telbivudine	Sebivo	1		1
13	Varenicline	Champix	1	1	
14	Acamprosate	Campral	1	1	
15	Dasatinib	Sprycell	1	1	1
16	Posaconazole	Spriafil (Posanol)	1		1
17					
18	Micafungin	Mycamine	1	1	
19					
20	Sitaxentan	Thelin	1	1	
21	Idursulfase	Elaprase	1		1
22					
23	Oxaliplatin	Eloxatin	1		1
24	Ranibizumab	Lucentis	1		1
25	Fluticasone	Avamys	1	1	
26					
27	Aprepitant	Emend	1	1	
28					
29	Maraviroc	Celsentri	1		1
30	Daptomycin	Cubicin	1	1	
31					
32	Paliperidone	Invega	1	1	
33	Duloxetine	Cymbalta	1	1	
34	Nesiritide	Natrecor	1	1	1
35	Aliskiren	Rasilez	1	1	
36					
37	Anidulafungin	Eraxis	1	1	
38					
39	Raltegravir	Isentress	1		1
40	Rivastigmine	Exelon patch	1	1	1
41	Sitagliptin	Januvia	1	1	
42	Temsirolimus	Torisel	1		1
43	Lenalidomide	Revlimid	1	1	1
44	Ambrisentan	Volibris	1	1	
45	Etravirine	Intence	1		1
46					
47					
48					
49					
50					
51					
52					
53					
54					
55					
56					
57					
58					
59					
60					

1						
2						
3	Methylalntrexone	Relistor	1		1	
4	Panitumumab	Vectibix		1	1	1
5	Nepafenac	Nevanac		1	1	
6	Dabigatran	Pradaxa		1	1	
7	Ceftobiprole	Zeftera		1	1	
8						
9						
10						
11	Idebenone	Catena		1	1	1
12	Nilotinib	Tasigna		1	1	1
13	Rivaroxaban	Xarelto		1	1	
14	Olmesartan	Olmetec		1	1	
15						
16						
17	Capsular	Synflorix		1	1	
18	polysaccharide					
19	Ustekinumab	Stelara		1	1	
20	Loteprednol	Alrex		1	1	
21	Eculizumab	Soliris		1		1
22	Desvenlafaxine	Pristiq		1	1	
23	Lisdexamfetamine	Vyvanse		1	1	
24						
25						
26						
27	Romiplostim	Nplate		1		1
28	Methyl	Metvix		1	1	
29	aminolevulinate					
30						
31	Eplerenone	Inspra		1	1	
32	Fosaprepitant	Emend IV		1	1	
33	Golimumab	Simponi		1	1	
34	Lapatinib	Tykerb		1	1	
35	Vorinostat	Zolinza		1	1	
36	Aripiprazole	Abilify		1	1	
37	Clofarabine	Clolar		1	1	
38	Dronedarone	Multaq		1		1
39	Certolizumab	Cimzia		1	1	
40	Doripenem	Doribax		1	1	
41						
42						
43						
44	Aztreonam	Cayston		1		1
45						
46						
47	Saxagliptin	Onglyza		1	1	
48	Besifloxacin	Besivance		1	1	
49	Azacitidine	Vidaza		1		1
50	Japanese	Ixiaro		1	1	
51	encephalitis					
52	vaccine					
53						
54	Alitretinoin	Toctino		1	1	
55	Degarelix	Firmagon		1	1	
56						
57						
58						
59						
60						

1					
2					
3	Dexmedetomidine	Precedex	1	1	
4	Everolimus	Afinitor	1	1	1
5	Thrombin alfa	Recothrom	1	1	
6	Pneumococcal	Prevnar	1		1
7	conjugate				
8	Gadoxetate	Primovist	1	1	
9	Recombinant	Cervarix	1	1	
10	human				
11	papillomavirus				
12	Canakinumab	Ilaris	1		1
13	Prasugrel	Effient	1	1	
14	Tocilizumab	Actemra	1	1	
15	Sapropterin	Kuvan	1		1
16					
17	Trabectedin	Yondelis	1	1	
18	Liraglutide	Victoza - 1.2 mg	1	1	
19		pen-injector			
20	Meningococcal	Menveo	1	1	
21	oligosaccharides				
22	conjugated				
23	Pazopanib	Votrient	1	1	
24	Paliperidone	Invega sustenna	1	1	
25	Sevelamer	Renvela	1	1	
26					
27	Dexlansoprazole	Dexilant	1	1	
28					
29	Denosumab	Prolia	1	1	
30					
31	Febuxostat	Uloric	1	1	
32	Lacosamide	Vimpat	1	1	
33	Velaglucerase alfa	VPRIV	1	1	
34					
35	Roflumilast	Daxas	1	1	
36					
37	Tapentadol	Nucynta CR	1	1	
38	Silodosin	Rapaflo	1	1	
39	Eltrombopag	Revolade	1	1	
40	Exenatide	Byetta	1	1	
41	Fingolimod	Gilenya	1	1	
42	Ticagrelor	Brilinta	1		1
43	Cabazitaxel	Jevtana	1	1	
44	Rufinamide	Banzel	1	1	
45	Belimumab	Benlysta	1	1	
46					
47					
48					
49					
50					
51					
52					
53					
54					
55					
56					
57					
58					
59					
60					

1					
2					
3	Rilpivirine	Edurant	1	1	
4	Tolvaptan	Samsca	1	1	
5	Abiraterone	Zytiga	1		1
6	Linagliptin	Trajenta	1	1	
7	Boceprevir	Victrelis	1		1
8	Boceprevir,	Victrelis Triple	1		1
9	peginterferon alfa-				
10	2b, ribavirin				
11	Telaprevir	Incivek	1		1
12	Colesevelam	Lodalis	1	1	
13	Senapine	Saphris	1	1	
14	Dienogest	Visanne	1	1	
15					
16					
17	Indacaterol	Onbrez breezhaler	1	1	
18					
19	Prucalopride	Resotran	1	1	
20	Plerixafor	Mozobil	1	1	
21	Eribulin	Halaven	1	1	
22	Apixaban	Eliquis	1	1	
23	Vandetanib	Caprelsa	1	1	
24	Ipilimumab	Yervoy	1	1	
25	Fesoterodine	Toviaz	1	1	
26	Fampridine	Fampyra	1	1	
27	Vemurafenib	Zelboraf	1		1
28	Azilsartan	Edarbi	1	1	
29					
30	Ofatumumab	Arzerra	1	1	
31	Palonosetron	Aloxi	1	1	
32					
33	Crizotinib	Xalkori	1	1	1
34	Fidaxomicin	Dificid	1	1	
35					
36					
37	Lurasidone	Latuda	1	1	
38	Ruxolitinib	Jakavi	1		1
39	Collagenase	Xiaflex	1	1	
40	clostridium				
41	histolyticum				
42	Axitinib	Inlyta	1	1	
43	Catridecacog	Tretten	1		1
44	Bendamustine	Treanda	1	1	
45	Pirfenidone	Esbriet	1		1
46					
47					
48					
49					
50					
51					
52					
53					
54					
55					
56					
57					
58					
59					
60					

1					
2					
3	Elvitegravir,	Stribild		1	1
4	emtricitabine,				
5	tenofovir,				
6	Ivacaftor	Kalydeco	1		1
7					
8					
9	Stiripentol	Diacomit		1	1
10	Nebivolol	Bystolic		1	1
11	Ingenol	Picato		1	1
12					
13					
14					
15	Brentuximab	Adcetris		1	1
16	Meningococcal	Nimenrix		1	1
17	polysaccharide				
18	groups A,C,W-135				
19	& Y conjugate				
20	vaccine, Tetanus				1
21	toxoid				
22	Mirabegron	Myrbetriq		1	1
23	Regorafenib	Stivarga		1	1
24	Rotigotine	Neupro		1	1
25	Dimethyl	Tecfidera		1	1
26	Perampanel	Fycompa		1	1
27	Pertuzumab	Perjeta	1		1
28	Enzalutamide	Xtandi		1	1
29	Ulipristal	Fibristal		1	1
30					
31					
32	Vismodegib	Erivedge		1	1
33	Dabrafenib	Tafinlar		1	1
34	Trametinib	Mekinist		1	1
35	Fluticasone and	Breo ellipta		1	1
36	vilatnerol				
37	Aclidinium	Tudorza genuair		1	1
38					
39	Rifaximin	Zaxine		1	1
40					
41	Ocriplasmin	Jetrea	1		1
42	Trastuzumab	Kadcyla		1	1
43	emtansine				
44	Galsulfase	Naglazyme	1		1
45					
46	Riociguat	Adempas		1	1
47					
48					
49					
50					
51					
52					
53					
54					
55					
56					
57					
58					
59					
60					

1					
2					
3	Pasireotide	Signifor	1	1	
4					
5					
6	Efinaconazole	Jublia	1	1	
7	Romidepsin	Istodax	1	1	1
8	Dolutegravir	Tivicay	1	1	
9	Afatinib	Giotrif	1	1	
10	Macitentan	Opsumit	1	1	
11	Aflibercept	Eylea	1	1	
12	Teriflunomide	Aubagio	1	1	
13	Simeprevir	Galexos	1		1
14	Alogliptin	Nesina	1	1	
15	Linaclotide	Constella	1	1	
16	Multicomponent	Bexsero	1	1	
17	meningococcal B				
18	vacine				
19	Radium-223 dichloride	Xofigo	1	1	
20					
21					
22	Sofosbuvir	Sovaldi	1		1
23	Umeclidinium and vilanterol	Anoro ellipta	1	1	
24					
25	Pomalidomide	Pomalyst	1		1
26	Lomitapide	Juxtapid	1	1	
27	Aflibercept	Zaltrap	1	1	
28	Bosutinibs	Bosulif	1	1	1
29	Recombinant human coagulation Factor IX, FC fusion protein	Alprolix	1	1	
30					
31	Tofacitinib	Xeljanz	1	1	
32	Tesamorelin	Egrifta	1	1	
33					
34	Canagliflozin	Invokana	1	1	
35	Taliglucerase Alfa	Elelyso	1	1	
36					
37	Eslicarbazepine	Aptiom	1	1	
38	Antihemophilic factor, FC fusion protein	Eloctate	1	1	
39					
40	Ledipasvir and sofosbuvir	Harvoni	1		1
41					
42	Vortioxetine	Trintellix	1	1	
43	Simoctocog alfa	Nuwiq	1	1	
44					
45					
46					
47					
48					
49					
50					
51					
52					
53					
54					
55					
56					
57					
58					
59					
60					

1						
2						
3	Azelastine and	Dymista		1	1	
4	fluticasone					
5	Conjugated	Duavive		1	1	
6	estrogens and					
7	bazedoxifene					
8	acetate					
9	Apremilast	Otezla		1	1	
10	Ibrutinib	Imbruvica	1			1
11	Obinutuzumab	Gazyva	1		1	1
12	Siltuximab	Sylvant		1		1
13	Dapagliflozin	Forxiga		1	1	
14	Ritonavir,	Holkira Pak		1		1
15	paritaprevir,					
16	ombitasvir,					
17	dasabuvir					
18	Sodium	Pheburane		1		1
19	phenylbutyrate					
20	Vedolizumab	Entyvio		1	1	
21	Human	Gardasil 9		1	1	
22	papillomavirus 9					
23	valent vaccine,					
24	recombinant					
25	Deferiprone	Ferriprox		1	1	
26						
27	Secukinumab	Cosentyx		1	1	
28	Tedizolid	Sivextro		1	1	
29						
30	Idelalisib	Zydelig		1	1	1
31	Ceritinib	Zykadia		1	1	1
32	Ponatinib	Iclusig		1	1	1
33	Carglumic Acid	Carbaglu	1			1
34						
35	Ivermectin	Rosiver		1	1	
36	Levomilnacipran	Fetzima		1	1	
37	Pembrolizumab	Keytruda		1	1	1
38	Naloxegol	Movantik		1	1	
39	Nintedanib	Ofev		1	1	
40	Ramucirumab	Cyramza		1	1	
41	Empagliflozin	Jardiance		1	1	
42	Mifepristone and	Mifegymiso		1	1	
43	Misoprostol					
44						
45	Daclatasvir	Daklinza		1	1	1
46						
47						
48						
49						
50						
51						
52						
53						
54						
55						
56						
57						
58						
59						
60						

1						
2						
3	Asfotase Alfa	Strensiq	1	1		1
4						
5						
6	Teduglutide	Revestive		1	1	
7						
8	Evolocumab	Repatha		1	1	
9	Nivolumab	Opdivo	1			1
10	Ceftolozane	Zerbaxa		1	1	
11	Sulfate and					
12	Tazobactam					
13						
14	Sacubitril,	Entresto	1			1
15	Valsartan					
16	Dulaglutide	Trulicity		1	1	
17	Elvitegravir,	Genvoya		1	1	
18	Cobicistat,					
19	Emtricitabine,					
20	Tenofovir					
21	Alafenamide					
22	Hemifumarate					
23	Mepolizumab	Nucala		1	1	
24						
25						
26	Lenvatinib	Lenvima		1	1	
27	Blinatumomab	Blinicyto		1	1	1
28	Carfilzomib	Kyprolis		1		1
29	Elbasvir,	Zepatier		1		1
30	Grazoprevir					
31	Selexipag	Uptravi		1	1	
32	Ivacaftor,	Orkambi		1		1
33	Lumacaftor					
34	Sugammadex	Bridion		1	1	
35						
36	Cobimetinib	Cotellic		1	1	
37	Brivaracetam	Brivlera		1	1	
38	Asunaprevir	Sunvepra		1	1	
39	Palbociclib	Ibrance		1	1	1
40	Alirocumab	Praluent		1	1	
41	Bilastine	Blexten		1	1	
42						
43						
44	Idarucizumab	Praxbind		1	1	1
45						
46	Olaparib	Lynparza		1	1	1
47	Ixekizumab	Taltz		1	1	
48	Osimertinib	Tagrisso		1	1	1
49						
50						
51						
52						
53						
54						
55						
56						
57						
58						
59						
60						

1						
2						
3	Sofosbuvir +	Epclusa		1		1
4	Velpatasvir					
5						
6	Ixazomib	Ninlaro		1		1
7	Nitisinone	MDK-Nitisinone	1			1
8						
9	Venetoclax	Venclexta		1	1	
10						1
11	Edoxaban	Lixiana		1	1	
12	Nitisinone	Nitisinone	1			1
13						
14	Daclizumab beta	Zinbryta		1	1	
15						
16	Nitisinone	Orfadin	1			1
17						
18	Ivabradine	Lancora		1	1	
19						
20			55	454	379	130
21						42

***Prescribe evaluations as of February 20, 2018; PMPRB evaluations as of December 31, 2016; Prescri**

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

1
2
3 1996-05-01 antivirals for systemic use
4 1996-06-25 other gynecologicals
5 1996-07-02 antibacterials for systemic
6 use
7
8 1996-07-04 antithrombotic agents
9 1996-08-01 endocrine therapy
10 1996-08-14 antivirals for systemic use
11 1996-09-12 antineoplastic agents
12 1996-09-13 antivirals for systemic use
13 1996-10-08 drugs used in diabetes
14 1996-10-28 antibacterials for systemic
15 use
16 1996-10-28 psycholeptics
17 1996-11-06 other nervous system
18 1996-11-20 psycholeptics
19 1996-12-03 anesthetics
20 1996-12-23 antineoplastic agents
21 1996-12-24 anesthetics
22 1997-02-12 other alimentary tract and
23 metabolism products
24 1997-02-19 lipid modifying agents
25 1997-03-06 antiepileptics
26 1997-03-06 drugs for obstructive
27 airway diseases
28 1997-03-06 antithrombotic agents
29 1997-03-21 antihemorrhagics
30
31 1997-04-15 antineoplastic agents
32 1997-05-21 antiemetics and
33 antinauseants
34 1997-05-21 endocrine therapy
35 1997-06-11 antihistamines for
36 systemic use
37 1997-06-16 ophthalmologicals
38 1997-06-24 pituitary and hypothalamic
39 hormones and analogues
40 1997-07-02 sex hormones and
41 modulators of the genital
42 system
43 1997-07-04 antineoplastic agents
44 1997-08-12 psychoanaleptics
45 1997-08-19 anti-parkinson drugs
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1		
2		
3	1997-08-27	drugs for treatment of
4		bone disease
5	1997-09-04	immunostimulants
6		
7		
8	1997-10-08	anti-parkinson drugs
9	1997-10-21	drugs for obstructive
10		airway diseases
11	1997-11-03	agents acting on the renin-
12		angiotensin system
13	1997-11-14	antibacterials for systemic
14		use
15	1997-11-24	ophthalmologicals
16		
17		
18	1997-12-02	psycholeptics
19	1998-01-29	anti-parkinson drugs
20	1998-02-05	immunostimulants
21	1998-02-16	ophthalmologicals
22		
23	1998-02-18	lipid modifying agents
24	1998-04-09	antibacterials for systemic
25		use
26	1998-04-28	analgesics
27	1998-04-28	psychoanaleptics
28	1998-06-01	agents acting on the renin-
29		angiotensin system
30	1998-06-01	urologicals
31	1998-06-17	drugs for obstructive
32		airway diseases
33	1998-07-22	antivirals for systemic use
34	1998-08-11	antivirals for systemic use
35	1998-08-24	analgesics
36	1998-08-31	antineoplastic agents
37	1998-09-04	antivirals for systemic use
38	1998-10-07	antithrombotic agents
39	1998-10-23	ophthalmologicals
40		
41	1998-11-06	sex hormones and
42		modulators of the genital
43		system
44	1998-11-20	agents acting on the renin-
45		angiotensin system
46	1998-11-20	urologicals
47	1998-12-02	vaccines
48		
49		
50		
51		
52		
53		
54		
55		
56		
57		
58		
59		
60		

1
2
3 1998-12-04 antibacterials for systemic
4 use
5
6 1998-12-04 antibacterials for systemic
7 use
8 1998-12-30 preparations for wounds
9 and ulcers
10
11 1999-01-25 muscle relaxants
12 1999-02-02 antivirals for systemic use
13 1999-02-05 psychoanaleptics
14 1999-02-12 antihemorrhagics
15
16
17 1999-02-26 psychoanaleptics
18 1999-03-08 urologicals
19 1999-03-11 immunostimulants
20
21
22
23
24 1999-03-19 antivirals for systemic use
25 1999-04-06 drugs used in diabetes
26 1999-04-14 antiinflammatoary and
27 antirheumatic products
28
29 1999-05-06 endocrine therapy
30 1999-05-20 immunostimulants
31 1999-06-03 antiobesity preparations
32 1999-06-04 antivirals for systemic use
33 1999-06-11 antithrombotic agents
34 1999-07-09 agents acting on the renin-
35 angiotensin system
36 1999-07-13 antivirals for systemic use
37 1999-07-16 analgesics
38 1999-08-13 antineoplastic agents
39 1999-08-16 agents acting on the renin-
40 angiotensin system
41 1999-08-18 drugs for treatment of
42 bone disease
43 1999-08-19 antithrombotic agents
44 1999-09-17 blood substitutes and
45 perfusion solutions
46 1999-10-13 vaccines
47
48 1999-10-25 antineoplastic agents
49 1999-10-25 antiinflammatoary and
50 antirheumatic products
51
52
53
54
55
56
57
58
59
60

1			
2			
3	1999-11-02		antivirals for systemic use
4	1999-11-04		immunostimulants
5			
6			
7	1999-11-08		contrast media
8	1999-12-10		antibacterials for systemic
9			use
10			
11	1999-12-23		antivirals for systemic use
12	2000-01-04	1	antineoplastic agents
13	2000-03-16	1	immunosuppressants
14	2000-03-17	1	immunosuppressants
15	2000-03-21	1	drugs used in diabetes
16	2000-04-13	1	antiepileptics
17	2000-04-13	1	psychoanaleptics
18	2000-05-11	1	psycholeptics
19	2000-05-31	1	ophthalmologicals
20	2000-06-30	1	anti-parkinson drugs
21	2000-08-17	1	endocrine therapy
22	2000-08-17	1	drugs used in diabetes
23	2000-08-21	1	drugs for treatment of
24			bone disease
25			
26	2000-08-30	1	other nervous system
27	2000-08-31	1	antiinflammatory and
28			antirheumatic products
29			
30	2000-09-01	1	immunosuppressants
31	2000-10-19	1	antibacterials for systemic
32			use
33			
34	2000-10-20	1	immunostimulants
35			
36			
37			
38	2000-12-01	1	immunosuppressants
39	2000-12-11	1	contrast media
40	2000-12-28	1	antiobesity preparations
41	2001-01-05	1	immunosuppressants
42	2001-01-09	1	antibacterials for systemic
43			use
44			
45	2001-01-11	1	pancreatic hormones
46			
47			
48	2001-01-17	1	other dermatological
49			preparations
50			
51	2001-03-01	1	antivirals for systemic use
52	2001-03-09	1	antivirals for systemic use
53	2001-04-02	1	antibacterials for systemic
54			use
55			
56	2001-04-17	1	antianemic preparations
57			
58			
59			
60			

1			
2			
3	2001-04-30	1	calcium homeostasis
4	2001-05-07	1	drugs for acid related
5			disorders
6			
7	2001-05-08	1	anti-parkinson drugs
8	2001-05-10	1	antiprotozoals
9	2001-05-18	1	psychoanaleptics
10	2001-05-29	1	antihistamines for
11			systemic use
12			
13	2001-06-06	1	immunosuppressants
14	2001-07-29	1	antimycotics for systemic
15			use
16			
17	2001-07-31	1	psychoanaleptics
18	2001-08-17	1	drugs for acid related
19			disorders
20			
21	2001-09-20	1	antineoplastic agents
22	2001-10-17	1	antithrombotic agents
23	2001-11-09	1	ophthalmologicals
24	2001-11-30	1	antihypertensives
25	2001-12-18	1	vaccines
26			
27			
28			
29			
30			
31	2002-01-25	1	drugs used in diabetes
32	2002-02-13	1	drugs used in diabetes
33	2002-02-21		urologicals
34	2002-03-12	1	drugs for constipation
35	2002-05-01	1	pituitary and hypothalamic
36			hormones and analogues
37			
38	2002-05-03	1	antivirals for systemic use
39	2002-05-15	1	immune sera and
40			immunoglobulins
41			
42	2002-05-24	1	antibiotics and
43			chemotherapeutics for
44			dermatological use
45			
46	2002-05-24	1	ophthalmologicals
47	2002-05-24	1	immunosuppressants
48	2002-05-28	1	antihemorrhagics
49	2002-05-31	1	immunostimulants
50			
51			
52	2002-06-13	1	antithrombotic agents
53	2002-07-08	1	blood substitutes and
54			perfusion solutions
55			
56	2002-08-02	1	antianemic preparations
57			
58			
59			
60			

1			
2			
3	2002-08-20	1	sex hormones and
4			modulators of the genital
5			system
6			
7	2002-10-04	1	antithrombotic agents
8	2002-10-09	1	antithrombotic agents
9	2002-11-20	1	drugs for obstructive
10			airway diseases
11			
12	2002-12-11	1	antiinflammatoary and
13			antirheumatic products
14	2003-01-31	1	antithrombotic agents
15	2003-02-18	1	lipid modifying agents
16	2003-02-21	1	vaccines
17			
18			
19			
20			
21	2003-03-06	1	antiepileptics
22	2003-03-18	1	antivirals for systemic use
23	2003-03-19	1	other dermatological
24			preparations
25			
26	2003-05-12	1	antibacterials for systemic
27			use
28	2003-05-12	1	lipid modifying agents
29	2003-05-28	1	antibacterials for systemic
30			use
31			
32	2003-07-14	1	antivirals for systemic use
33	2003-07-22	1	urologicals
34	2003-08-13	1	immunostimulants
35			
36			
37	2003-08-13	1	pituitary and hypothalamic
38			hormones and analogues
39	2003-08-27	1	antivirals for systemic use
40	2003-09-17	1	urologicals
41	2003-10-01	1	agents acting on the renin-
42			angiotensin system
43			
44	2003-10-29	1	all other therapeutic
45			products
46			
47	2003-12-05	1	antivirals for systemic use
48	2003-12-17	1	antineoplastic agents
49	2004-01-23	1	other alimentary tract and
50			metabolism products
51			
52	2004-02-06	1	other alimentary tract and
53			metabolism products
54	2004-02-17	1	endocrine therapy
55			
56			
57			
58			
59			
60			

1			
2			
3	2004-03-09	1	antibacterials for systemic
4			use
5			
6	2004-03-12		1 immunostimulants
7	2004-03-17	1	urologicals
8	2004-03-31	1	contrast media
9	2004-03-31	1	other alimentary tract and
10			metabolism products
11			
12	2004-04-16		1 muscle relaxants
13			
14	2004-05-10		1 immunostimulants
15			
16			
17	2004-05-11	1	sex hormones and
18			modulators of the genital
19			system
20			
21	2004-05-21	1	antineoplastic agents
22	2004-05-31		1 other alimentary tract and
23			metabolism products
24			
25	2004-06-03		1 calcium homeostasis
26	2004-08-04	1	calcium homeostasis
27	2004-08-05	1	analgesics
28	2004-08-20	1	antimycotics for systemic
29			use
30			
31	2004-09-03	1	analgesics
32	2004-09-24		1 immunosuppressants
33	2004-10-06		1 immunosuppressants
34	2004-11-18		1 drugs for obstructive
35			airway diseases
36			
37	2004-12-08	1	psychoanaleptics
38	2004-12-10	1	antivirals for systemic use
39	2004-12-10	1	sex hormones and
40			modulators of the genital
41			system
42			
43	2004-12-24	1	psychoanaleptics
44	2004-12-24	1	psychoanaleptics
45	2005-01-27	1	antineoplastic agents
46	2005-03-31	1	calcium homeostasis
47	2005-04-22	1	drugs for acid related
48			disorders
49			
50			
51	2005-05-02	1	ophthalmologicals
52	2005-05-10		1 therapeutic
53			radiopharmaceuticals
54	2005-06-03	1	antiepileptics
55			
56			
57			
58			
59			
60			

1			
2			
3	2005-06-24	1	sex hormones and
4			modulators of the genital
5			system
6			
7	2005-07-07	1	antineoplastic agents
8	2005-07-20	1	analgesics
9	2005-08-05	1	other nervous system
10			
11	2005-08-23	1	agents acting on the renin-
12			angiotensin system
13	2005-09-09	1	antineoplastic agents
14	2005-09-09	1	antineoplastic agents
15	2005-09-29	1	drugs used in diabetes
16	2005-10-17	1	pituitary and hypothalamic
17			hormones and analogues
18			
19	2005-10-24	1	immunosuppressants
20	2005-11-14	1	urologicals
21	2005-11-21	1	antivirals for systemic use
22	2005-11-21	1	antivirals for systemic use
23	2005-11-21	1	antivirals for systemic use
24	2005-11-30	1	immunosuppressants
25	2005-12-09	1	all other therapeutic
26			products
27			
28	2006-01-10	1	urologicals
29	2006-02-20	1	urologicals
30	2006-03-10	1	endocrine therapy
31	2006-04-12	1	drugs used in diabetes
32	2006-05-26	1	antineoplastic agents
33	2006-06-16	1	pituitary and hypothalamic
34			hormones and analogues
35			
36	2006-06-29	1	immunosuppressants
37	2006-07-10	1	vaccines
38			
39			
40			
41			
42	2006-07-17	1	antivirals for systemic use
43			
44			
45	2006-07-28	1	antineoplastic agents
46	2006-07-28	1	antivirals for systemic use
47	2006-08-01	1	vaccines
48	2006-08-14	1	other alimentary tract and
49			metabolism products
50			
51	2006-08-17	1	anti-parkinson drugs
52	2006-09-11	1	drugs for obstructive
53			airway diseases
54			
55			
56			
57			
58			
59			
60			

1			
2			
3	2006-09-14	1	antibacterials for systemic
4			use
5	2006-09-28	1	immunosuppressants
6	2006-10-17	1	all other therapeutic
7			products
8	2006-10-18	1	all other therapeutic
9			products
10	2006-10-31	1	contrast media
11	2006-11-28	1	antivirals for systemic use
12	2007-01-24	1	other nervous system
13	2007-03-16	1	other nervous system
14	2007-03-26	1	antineoplastic agents
15	2007-03-26	1	antimycotics for systemic
16			use
17	2007-05-22	1	antimycotics for systemic
18			use
19	2007-05-30	1	antihypertensives
20	2007-06-13	1	other alimentary tract and
21			metabolism products
22	2007-06-15	1	antineoplastic agents
23	2007-06-26	1	ophthalmologicals
24	2007-08-14	1	drugs for obstructive
25			airway diseases
26	2007-08-24	1	antiemetics and
27			antinauseants
28	2007-09-21	1	antivirals for systemic use
29	2007-09-24	1	antibacterials for systemic
30			use
31	2007-09-26	1	psycholeptics
32	2007-11-01	1	psychoanaleptics
33	2007-11-08	1	cardiac therapy
34	2007-11-14	1	agents acting on the renin-
35			angiotensin system
36	2007-11-14	1	antimycotics for systemic
37			use
38	2007-11-27	1	antivirals for systemic use
39	2007-11-29	1	psychoanaleptics
40	2007-12-14	1	drugs used in diabetes
41	2007-12-21	1	antineoplastic agents
42	2008-01-17	1	immunosuppressants
43	2008-03-20	1	antihypertensives
44	2008-03-27	1	antivirals for systemic use
45			
46			
47			
48			
49			
50			
51			
52			
53			
54			
55			
56			
57			
58			
59			
60			

1			
2			
3	2008-03-28	1	drugs for constipation
4	2008-04-03		1 antineoplastic agents
5	2008-04-17	1	ophthalmologicals
6	2008-06-10	1	antithrombotic agents
7	2008-06-26	1	antibacterials for systemic
8			use
9			
10			
11	2008-07-23	1	psychoanaleptics
12	2008-09-09	1	antineoplastic agents
13	2008-09-15	1	antithrombotic agents
14	2008-10-28	1	agents acting on the renin-
15			angiotensin system
16			
17	2008-12-11		1 vaccines
18			
19			
20	2008-12-12		1 immunosuppressants
21	2008-12-23	1	ophthalmologicals
22	2009-01-28		1 immunosuppressants
23	2009-02-04	1	psychoanaleptics
24	2009-02-19	1	psychoanaleptics
25			
26			
27	2009-02-19		1 antihemorrhagics
28	2009-02-26	1	antineoplastic agents
29			
30			
31	2009-02-26	1	diuretics
32	2009-04-01	1	antivirals for systemic use
33	2009-04-07		1 immunosuppressants
34	2009-05-15	1	antineoplastic agents
35	2009-06-11	1	antineoplastic agents
36	2009-07-09	1	psycholeptics
37	2009-07-16	1	antineoplastic agents
38	2009-08-11	1	cardiac therapy
39	2009-08-12		1 immunosuppressants
40	2009-09-02	1	antibacterials for systemic
41			use
42			
43	2009-09-11	1	antibacterials for systemic
44			use
45			
46	2009-09-14	1	drugs used in diabetes
47	2009-10-23	1	ophthalmologicals
48	2009-10-23	1	antineoplastic agents
49	2009-10-29		1 vaccines
50			
51			
52			
53			
54			
55	2009-11-13	1	antineoplastic agents
56	2009-11-16	1	endocrine therapy
57			
58			
59			
60			

1			
2			
3	2009-12-09	1	psycholeptics
4	2009-12-14	1	antineoplastic agents
5			
6	2009-12-15		1 antihemorrhagics
7	2009-12-21		1 vaccines
8			
9			
10	2010-01-14	1	contrast media
11	2010-02-03		1 vaccines
12			
13			
14			
15	2010-02-26		1 immunosuppressants
16	2010-04-16	1	antithrombotic agents
17	2010-04-30		1 immunosuppressants
18	2010-04-30	1	other alimentary tract and
19			metabolism products
20			
21	2010-05-13	1	antineoplastic agents
22	2010-05-21		1 drugs used in diabetes
23			
24			
25	2010-05-21		1 vaccines
26			
27			
28	2010-05-27	1	antineoplastic agents
29	2010-06-30	1	psycholeptics
30	2010-07-07	1	all other therapeutic
31			products
32			
33	2010-07-22	1	drugs for acid related
34			disorders
35			
36	2010-08-06		1 drugs for treatment of
37			bone disease
38	2010-09-22	1	antigout preparations
39	2010-09-30	1	antiepileptics
40			
41	2010-10-01		1 other alimentary tract and
42			metabolism products
43	2010-11-23	1	drugs for obstructive
44			airway diseases
45			
46	2010-12-02	1	analgesics
47	2011-01-11	1	urologicals
48	2011-01-12	1	antihemorrhagics
49	2011-01-13	1	drugs used in diabetes
50			
51	2011-03-09	1	immunosuppressants
52	2011-05-30	1	antithrombotic agents
53	2011-06-16	1	antineoplastic agents
54	2011-06-22	1	antiepileptics
55			
56	2011-07-06		1 immunosuppressants
57			
58			
59			
60			

1			
2			
3	2011-07-21	1	antivirals for systemic use
4	2011-07-25	1	diuretics
5	2011-07-27	1	endocrine therapy
6	2011-07-28	1	drugs used in diabetes
7	2011-07-29	1	antivirals for systemic use
8	2011-08-10	1	immunostimulants
9			
10			
11			
12			
13	2011-08-16	1	antivirals for systemic use
14	2011-09-22	1	lipid modifying agents
15	2011-10-07	1	psycholeptics
16	2011-10-12	1	sex hormones and
17			modulators of the genital
18			system
19			
20			
21	2011-12-06	1	drugs for obstructive
22			airway diseases
23	2011-12-07	1	drugs for constipation
24	2011-12-08	1	immunostimulants
25	2011-12-14	1	antineoplastic agents
26	2011-12-16	1	antithrombotic agents
27	2012-01-12	1	antineoplastic agents
28	2012-02-01	1	antineoplastic agents
29	2012-02-09	1	urologicals
30	2012-02-10	1	other nervous system
31	2012-02-15		antineoplastic agents
32	2012-03-08	1	agents acting on the renin-
33			angiotensin system
34	2012-03-09	1	antineoplastic agents
35	2012-03-14	1	antiemetics and
36			antinauseants
37	2012-04-25	1	antineoplastic agents
38	2012-06-07	1	antidiarrheals, intestinal
39			antiinflammatory/antiinfec
40			tive agents
41	2012-06-13	1	psycholeptics
42	2012-06-19	1	antineoplastic agents
43	2012-07-05	1	other drugs for disorders of
44			the musculo-skeletal
45			system
46	2012-07-12	1	antineoplastic agents
47	2012-07-19	1	antihemorrhagics
48	2012-08-24	1	antineoplastic agents
49	2012-10-01		immunosuppressants
50			
51			
52			
53			
54			
55			
56			
57			
58			
59			
60			

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

1			
2			
3	2013-09-23	1	pituitary and hypothalamic
4			hormones and analogues
5			
6	2013-10-02	1	drugs used in diabetes
7	2013-10-16	1	antineoplastic agents
8	2013-10-31	1	antivirals for systemic use
9			
10	2013-11-01	1	antineoplastic agents
11	2013-11-06	1	antihypertensives
12	2013-11-08	1	antineoplastic agents
13	2013-11-14	1	immunosuppressants
14	2013-11-18	1	antivirals for systemic use
15	2013-11-27	1	drugs used in diabetes
16	2013-12-02	1	drugs for constipation
17	2013-12-06	1	vaccines
18			
19			
20			
21			
22	2013-12-12	1	therapeutic
23			radiopharmaceuticals
24	2013-12-13	1	antivirals for systemic use
25	2013-12-23	1	drugs for obstructive
26			airway diseases
27			
28	2014-01-20	1	immunosuppressants
29	2014-02-04	1	lipid modifying agents
30	2014-02-12	1	antineoplastic agents
31	2014-03-14	1	antineoplastic agents
32	2014-03-20	1	antihemorrhagics
33			
34			
35			
36			
37			
38	2014-04-17	1	immunosuppressants
39	2014-04-29	1	pituitary and hypothalamic
40			hormones and analogues
41			
42	2014-05-23	1	drugs used in diabetes
43	2014-05-29	1	other alimentary tract and
44			metabolism products
45			
46	2014-07-08	1	antiepileptics
47	2014-08-22	1	antihemorrhagics
48			
49			
50			
51	2014-10-15	1	antivirals for systemic use
52			
53	2014-10-22	1	psychoanaleptics
54	2014-10-23	1	antihemorrhagics
55			
56			
57			
58			
59			
60			

1			
2			
3	2014-10-23	1	nasal preparations
4			
5	2014-10-23	1	sex hormones and
6			modulators of the genital
7			system
8			
9			
10	2014-11-12	1	immunosuppressants
11	2014-11-17	1	antineoplastic agents
12			
13	2014-11-25	1	antineoplastic agents
14			
15	2014-12-03	1	immunosuppressants
16	2014-12-12	1	drugs used in diabetes
17	2014-12-22	1	antivirals for systemic use
18			
19			
20			
21			
22	2015-01-26	1	other alimentary tract and
23			metabolism products
24	2015-01-29	1	immunosuppressants
25			
26	2015-02-05	1	vaccines
27			
28			
29			
30			
31	2015-02-13	1	all other therapeutic
32			products
33	2015-02-27	1	immunosuppressants
34			
35	2015-03-17	1	antibacterials for systemic
36			use
37	2015-03-27	1	antineoplastic agents
38	2015-03-27	1	antineoplastic agents
39	2015-04-02	1	antineoplastic agents
40	2015-04-10	1	other alimentary tract and
41			metabolism products
42			
43	2015-04-22	1	antihelmintics
44	2015-05-08	1	psychoanaleptics
45			
46	2015-05-19	1	antineoplastic agents
47	2015-06-02	1	drugs for constipation
48	2015-06-25	1	antineoplastic agents
49			
50	2015-07-16	1	antineoplastic agents
51	2015-07-23	1	drugs used in diabetes
52	2015-07-29	1	sex hormones and
53			modulators of the genital
54			system
55			
56	2015-08-13	1	antivirals for systemic use
57			
58			
59			
60			

1			
2			
3	2015-08-14	1	other alimentary tract and
4			metabolism products
5	2015-09-04	1	other alimentary tract and
6			metabolism products
7	2015-09-10	1	lipid modifying agents
8	2015-09-25	1	antineoplastic agents
9	2015-09-30	1	antibacterials for systemic
10			use
11			
12			
13			
14	2015-10-02	1	agents acting on the renin-
15			angiotensin system
16	2015-11-10	1	drugs used in diabetes
17	2015-11-27	1	antivirals for systemic use
18			
19			
20			
21			
22			
23			
24			
25			
26	2015-12-03	1	drugs for obstructive
27			airway diseases
28	2015-12-22	1	antineoplastic agents
29	2015-12-22	1	antineoplastic agents
30	2016-01-15	1	antineoplastic agents
31	2016-01-19	1	antivirals for systemic use
32			
33			
34	2016-01-20	1	antithrombotic agents
35	2016-01-26	1	other respiratory system
36			products
37	2016-02-05	1	all other therapeutic
38			products
39	2016-02-22	1	antineoplastic agents
40	2016-03-09	1	antiepileptics
41	2016-03-09	1	antivirals for systemic use
42	2016-03-16	1	antineoplastic agents
43	2016-04-11	1	lipid modifying agents
44	2016-04-21	1	antihistamines for
45			systemic use
46	2016-04-29	1	all other therapeutic
47			products
48	2016-04-29	1	antineoplastic agents
49	2016-05-25	1	immunosuppressants
50	2016-07-05	1	antineoplastic agents
51			
52			
53			
54			
55			
56			
57			
58			
59			
60			

1			
2			
3	2016-07-11	1	antivirals for systemic use
4			
5			
6	2016-08-04	1	antineoplastic agents
7	2016-09-20	1	other alimentary tract and
8			metabolism products
9			
10	2016-09-30	1	antineoplastic agents
11	2016-11-04	1	antithrombotic agents
12	2016-11-04	1	other alimentary tract and
13			metabolism products
14	2016-12-08	1	immunosuppressants
15			
16	2016-12-13	1	other alimentary tract and
17			metabolism products
18	2016-12-23	1	cardiac therapy
19		286	99
20			

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

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

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	

1			
2			
3	Fomepizole	Antizol	1
4	Iron dextran	Dexferrum	1
5			
6	Tegafur/uracil and	Orzel	1
7	leucovorin calcium		
8			
9	Aminolevulinic acid	Levulan	1
10			
11	Losoxantrone	Bianda	1
12	Pegaspargase	Oncaspar	1
13	Valrubicin	Valstar	1
14	Nelarabine	Atriance	
15	Alectinib	Alecensaro	
16	Elotuzumab	Empliciti	1
17			
18	Daratumumab	Darzalex	
19			
20			
21			
22	Anagrelide as	Agrylin	1
23	hydrochloride		
24	Dexfenfluramine	Redux	1
25	Halofantrine	Halfan	1
26	Tazarotene	Tazorac Gel	1
27	Vorapaxar	Zontivity	1
28	Reviparin	Clivarine	1
29			
30			
31	Nadroparin	Fraxiparine	1
32			
33			
34	Argatroban	Argatroban	1
35	Saquinavir	Saquinavir	1
36			
37	Carvedilol	Dilatrend	1
38			
39	Carvedilol	Kredex	1
40			
41	Clevidipine	Cleviprex	1
42	Ibutilide	Corvert injection	1
43	Mangafodipir	Teslascan	1
44			
45	Sulfur Hexafluoride	Sonovue	1
46			
47	Gadoterate Meglumine	Dotarem	1
48			
49	Ferumoxsil	Gastromark	1
50	Palmitic acid/Galactose	Levovist	1
51			
52			
53	Gadolinium (III)	Gadolite	1
54	Ioxilan	Oxilan	1
55	Rimexolone	Vexol	1
56			
57			
58			
59			
60			

1				
2				
3	Difluprednate	Durezol	1	
4				
5				
6	Thyrotropin	Thyrogen	1	
7	Methacholine	Methacoline	1	
8	Sulesomab	Leukoscan	1	
9	Kit for preparation of	Myoscint	1	
10	indium in 111			
11	imciromab pentetate			
12				
13	Arcitumomab	CEA-Scan	1	
14	Bicisate	OncoScint	1	
15				
16	Pantoprazole	Panto-Byk	1	
17	Lubiprostone	Amitiza	1	
18	Olodaterol	Striverdi respimat	1	
19				
20	Reslizumab	Cinqair	1	
21				
22	Tiludronate	Skelid	1	
23				
24	Albiglutide	Eperzan	1	
25	Miglitol	Glyset	1	
26	Toremifene	Fareston	1	
27	Botulinium antitoxin	BAT	1	
28				
29	Cytomegalovirus	Cytogam	1	
30	immune globulin			
31				
32				
33	Peginterferon Beta-1A	Plegridy	1	
34	F-Fluorodeoxyglucose	Cantrace		1
35	Rubidium chloride rb	Ruby-fill		1
36	82			
37				
38	Troglitazone	Rezulin		1
39	Respiratory syncytial	Respigam		1
40	virus immune globulin			
41				
42	Molgramostim	Leucomax		1
43				
44	Anti-thymocyte	Thymoglobulin	1	
45	globulin			
46				
47	Infliximab	Remicade		1
48	Cisatracurium	Nimbex injection	1	
49	Unoprostone isopropyl	Rescula	1	
50				
51	Tafluprost	Saflutan	1	
52	Bromfenac	Prolensa	1	
53	Olopatadine	Patanol	1	
54	Human C1 esterase	Berinerter	1	
55	inhibitor			
56				
57				
58				
59				
60				

1			
2			
3	Tetrabenazine	Nitoman	1
4	Finafloxacin	Xtoro	1
5	Sermorelin	Geref	1
6			
7			
8	Dextromethylphenidate	Attenade	1
9			
10			
11	Vilazodone	Viibryd	1
12			
13	Choriogonadotropin Alfa	Ovidrel	1
14			
15	Follitropin alpha	Gonal-F	1
16			
17	Amlexanox	Aphthera	1
18	Lexidronam	Quadramet	1
19			
20	Zucapsaicin	Civanex (Zuacta)	1
21			
22	Rotavirus vaccine	Rotarix	1
23	Influenza vaccine	Flumist	1
24			
25	Haemagglutinin-Strain A	Arepranrix H5N1	1
26			
27			
28	Polidocanol	Varithena	1
29	Glycerol	Ravicti	1
30			
31	Elosulfase Alfa	Vimizim	1
32			
33	Levocarnitine	Carnitor	1
34			
35	Alitretinoin	Panretin	1
36			
37	Nitric oxide	Inomax	1
38	Yttrium-90	Yttrium-90	1
39			
40	Tositumomab	Bexxar	1
41			
42	Remestemcel-L	Prochymal	1
43	Measles virus	Moru-Viraten	1
44			
45	Diphtheria, tetanus &	Infanrix	1
46	Lipoprotein-OspA	Lymerix	1
47			
48			
49			
50			
51			
52			
53			
54			
55			
56			
57			
58			
59			
60			

Therapeutic assessments

	Notice of compliance or Notice of compliance with conditions	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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

	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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

11/4/2013	1	corticosteroids, dermatological preparations
5/31/2002	1	diagnostic agents
2/25/1999		diagnostic agents
1/17/2005	1	diagnostic radiopharmaceuticals
7/2/1997		diagnostic radiopharmaceuticals
9/16/1997		diagnostic radiopharmaceuticals
1/16/1998		diagnostic 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	diagnostic radiopharmaceuticals
9/20/2011	1	diagnostic 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

1				
2				
3	12/29/1995			other nervous system drugs
4	3/11/2016	1		otologicals
5	6/8/1995			pituitary and hypothalamic hormones
6				and analogues
7				
8	8/12/2003	1		psychoanaleptics
9				
10				
11	7/16/2015	1		psychoanaleptics
12				
13	12/16/2004		1	sex hormones and modulators of the
14				genital system
15	6/6/1997			sex hormones and modulators of the
16				
17	12/11/2000	1		stomatological preparations
18	6/22/1998			therapeutic radiopharmaceuticals
19	7/15/2010	1		topical products for joint and
20				muscular pain
21				
22	10/9/2007		1	vaccines
23	6/22/2010		1	vaccines
24				
25	2/13/2013		1	vaccines
26				
27				
28	8/4/2015	1		vasoprotectives
29	3/16/2016	1		other alimentary tract and
30				
31	7/2/2014		1	other alimentary tract and
32				
33	1/19/1995			other alimentary tract and
34				metabolism products
35	6/11/1999			other dermatological preparations
36	9/23/2005	1		other respiratory system products
37				
38	12/2/2004		1	therapeutic radiopharmaceuticals
39	8/18/2005		1	therapeutic radiopharmaceuticals
40				
41	5/17/2012		1	unassigned
42	2/26/1996			vaccines
43				
44	12/17/1996			vaccines
45				
46	12/2/1998			vaccines
47				
48				
49				
50				
51				
52				
53				
54				
55				
56				
57				
58				
59				
60				

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	Title, 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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	Methods, pages 6, 7
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed	Not relevant
		<i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed	
		<i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	
		(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) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	Not relevant
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	Results, pages 11-15
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	
		<i>Cross-sectional study</i> —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

1			
2	Generalisability	21	Discuss the generalisability (external validity) of the study
3			results
4	<hr/>		

5 **Other information**

6	Funding	22	Give the source of funding and the role of the funders for the	Page 20
7			present study and, if applicable, for the original study on which	
8			the present article is based	

9

10 *Give information separately for cases and controls in case-control studies and, if applicable, for exposed and

11 unexposed groups in cohort and cross-sectional studies.

12

13

14 **Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and

15 published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely

16 available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at

17 <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is

18 available at www.strobe-statement.org.

19

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-023605.R1
Article Type:	Research
Date Submitted by the Author:	18-Jun-2018
Complete List of Authors:	Lexchin, Joel; York University, School of Health Policy & Management
Primary Subject Heading:	Health policy
Secondary Subject Heading:	Health services research, Pharmacology and therapeutics
Keywords:	Health policy < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, accelerated approvals, Health Canada, therapeutic evaluation, therapeutic groups

SCHOLARONE™
Manuscripts

Peer Review Only

1
2
3 1 **Health Canada's use of expedited review pathways and therapeutic innovation, 1995-**
4
5 2 **2016: cross sectional analysis**
6

7
8 3 Joel Lexchin MSc, MD^{1,2,3}
9

10 4 ¹Professor Emeritus

11
12 5 School of Health Policy and Management

13
14 6 York University

15
16 7 ²Emergency Physician

17
18 8 University Health Network

19
20 9 ³Associate Professor

21
22 10 Faculty of Medicine

23
24 11 University of Toronto

25
26 12

27
28 13 Correspondence:

29
30 14 Joel Lexchin MD

31
32 15 School of Health Policy and Management

33
34 16 York University

35
36 17 4700 Keele St.

37
38 18 Toronto, ON M3J 1P3

39
40 19 Tel: 416-964-7186

41
42 20 Email: jlexchin@yorku.ca

43
44 21 ORCID ID: 0000-0001-5120-8029

45
46 22 **Key words:**

47
48 23 expedited approvals, Health Canada, health policy, therapeutic evaluation, therapeutic group

49
50 24 **Word count:**

51
52 25 3030
53
54
55
56
57
58
59
60

1
2
3 26 **Structured summary**
4

5 27 **Objectives**
6
7

8 28 This study examines the use of expedited approval pathways by Health Canada over the
9
10 29 period 1995 to 2016 inclusive and the relationship between the use of these pathways and the
11
12 30 therapeutic gain offered by new products.
13
14

15
16 31 **Design**
17

18
19 32 Cross sectional study.
20
21

22 33 **Data sources**
23

24
25 34 Therapeutic Products Directorate, Biologics and Genetic Therapies Directorate, Notice of
26
27 35 Compliance database, Notice of Compliance with conditions web site, Patented Medicine
28
29 36 Prices Review Board, La revue Prescrire, World Health Organization (WHO) Anatomical
30
31 37 Therapeutic Chemical (ATC) classification system.
32
33

34
35 38 **Interventions**
36

37
38 39 None
39
40

41
42 40 **Primary and secondary outcomes**
43

44
45 41 Percent of new drugs evaluated by Health Canada that went through an expedited pathway
46
47 42 between 1995 and 2016 inclusive. Kappa values comparing the review status to assessments
48
49 43 of therapeutic value for individual drugs.
50
51

52 44 **Results**
53
54
55
56
57
58
59
60

1
2
3 45 Of 623 drugs approved by Health Canada between 1995 and 2016, 438 (70.3%) drugs went
4
5 46 through the standard pathway, 185 (29.7%) an expedited pathway. Therapeutic evaluations
6
7 47 were available for 509 drugs. Health Canada used an expedited approval pathway for 159 of
8
9 48 the 509 drugs whereas only 55 were judged to be therapeutically innovative. Forty-two of the
10
11 49 55 therapeutically innovative drugs received an expedited review and 13 received a standard
12
13 50 review. The Kappa value for the entire period for all 509 drugs was 0.276 (95% CI 0.194,
14
15 51 0.359) indicating “fair” agreement between Health Canada’s use of expedited pathways and
16
17 52 independent evaluations of therapeutic innovation.
18
19
20

21 **Conclusion**

22
23
24 54 Health Canada’s use of expedited approvals was stable over the entire time period. Its ability
25
26 55 to predict which drugs will offer a major therapeutic gain is poor. The findings in this study
27
28 56 should provoke a discussion about whether Health Canada should continue to use these
29
30 57 pathways and if so how their use can be improved.
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58

1
2
3 59 **Article Summary**
4

5 60 *Strengths and limitations of this study*
6

- 7 61 • Cross sectional analysis of the use of expedited approval pathways by Health Canada
8
9 62 over an extended period of time.
10
11 63 • Comparison of use of expedited approval pathways to independent assessment of
12
13 64 therapeutic evaluation.
14
15 65 • Analysis of approvals and therapeutic value of therapeutic subgroups.
16
17
18 66 • Twenty percent of new drugs approved did not have therapeutic evaluations.
19

20 67
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 68 • **Acknowledgements**
4

5 69 • None
6

7 70 • **Competing Interests**
8

9 71 • In 2015-2017, Joel Lexchin received payment from two non-profit organizations for
10
11 being a consultant on a project looking at indication-based prescribing and a second
12
13 looking at which drugs should be distributed free of charge by general practitioners. In
14
15 2015, he received payment from a for-profit organization for being on a panel that
16
17 discussed expanding drug insurance in Canada. He is on the Foundation Board of Health
18
19 Action International.
20
21 76

22 77 • **Funding**
23

24 78 • This research received no specific grant from any funding agency in the public,
25
26 commercial or not-for profit sectors.
27
28 79

29 80 • **Data sharing statement**
30

31 81 • Full data that was extracted is available from the online data repository Dryad
32
33 <http://datadryad.org> with the DOI: doi:10.5061/dryad.0bf6000.
34
35 82

36 83 • **Contributorship statement**
37

38 84 • JL came up with the idea for this study, gathered and analyzed the data and wrote the
39
40 manuscript.
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

86 **Introduction**

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

94
95 In an effort to ensure that promising therapies for serious, life-threatening or debilitating
96 illnesses reach Canadians in a timely manner, Health Canada has developed two other
97 pathways for approving NAS. These are described in detail elsewhere [2], but briefly, the
98 first of these is a priority review that involves the company submitting a complete NDS but
99 with a review period of 180 days [3]. The second is the Notice of Compliance with conditions
100 (NOC/c) [4] whereby Health Canada will give a conditional approval based on limited
101 evidence – Phase II clinical trials or trials with only surrogate markers. In return for NOC/c
102 status, companies commit to further studies that definitively establish efficacy and submit the
103 results of these to Health Canada. A failure to complete these studies or negative results from
104 them could lead to the marketing authorization being cancelled.

105
106 Lexchin has examined how closely Health Canada's use of the two pathways (priority review
107 and NOC/c, hereafter collectively termed expedited review pathways) corresponds to
108 independent assessments of the therapeutic innovation of drugs at the level of individual
109 drugs. For the period 1997-2012, the Kappa value was 0.334 (95% CI 0.220, 0.447) or fair
110 [5].

1
2
3 111

4
5 112 This current study is a further and more detailed look at how Health Canada uses its
6
7 113 expedited review pathways, by extending previous work in a number of ways. First it covers
8
9 114 a wider time period – 1995 to 2016, inclusive. Second, it looks at the use of both of the
10
11 115 expedited review pathways over this entire time period for the entire sample of drugs as well
12
13 116 as subgroups – small molecule drugs, biologics, and therapies for serious diseases. Third, it
14
15 117 calculates the Kappa values for the entire sample of drugs as well as the subgroups listed
16
17 118 above. These subgroups were chosen because small molecules and biologics have
18
19 119 fundamentally different characteristics and these may influence a decision to use an
20
21 120 expedited review pathway and how accurately Health Canada can predict their therapeutic
22
23 121 value. Similarly, when the treatment is for serious medical conditions, Health Canada may be
24
25 122 more willing to use an expedited review pathway and may be more likely to believe that the
26
27 123 new product will provide a significant therapeutic benefit.
28
29

30
31 12432
33 125 **Methods**34
35 126 *Data sources*

36
37 127 All NAS approved from 1995 to 2016 inclusive were documented using the annual reports
38
39 128 from the Therapeutic Products and the Biologics and Genetic Therapies Directorates that are
40
41 129 in charge of reviewing applications for new small molecule drugs and biologics and vaccines,
42
43 130 respectively. (Reports are available by directly contacting the directorates at
44
45 131 publications@hc-sc.gc.ca.) A starting year of 1995 was selected as there are no annual
46
47 132 reports from Health Canada prior to that year. Generic and brand names along with the
48
49 133 specific approval pathway – standard, priority, NOC/c (only from 1998 onwards) – and
50
51 134 whether the product was a small molecule drug or biologic (information available only from
52
53 135 2000 onwards) were manually extracted from the annual reports by the author.
54
55
56
57
58
59

1
2
3 136

4
5 137 Not all of the drugs with a NOC/c are documented in the annual reports and they were
6
7 138 supplemented using four additional sources: articles by Lexchin [6] and Law [7], the Notice
8
9 139 of Compliance database (<http://webprod5.hc-sc.gc.ca/noc-ac/index-eng.jsp>) and the Notice
10
11 140 of Compliance with conditions web site (<http://www.hc-sc.gc.ca/dhp->
12
13 141 [mps/prodpharma/notices-avis/conditions/index-eng.php](http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/conditions/index-eng.php)). Only NAS approved for the first
14
15 142 time under a NOC/c were considered. Drugs can receive both a priority and NOC/c review
16
17 143 and in this case they were only counted as receiving a priority review.
18
19

20 144

21
22 145 *Assessment of therapeutic innovation*

23
24 146 The therapeutic value of drugs was assessed using the ratings from the annual reports of the
25
26 147 Canadian Patented Medicine Prices Review Board (PMPRB) (<http://www.pmprb->
27
28 148 [cepmb.gc.ca/english/View.asp?x=91](http://www.pmprb-cepmb.gc.ca/english/View.asp?x=91)) and Prescrire International, the English language
29
30 149 translation of the French drug bulletin La revue Prescrire [8]. The processes that these two
31
32 150 organizations use in arriving at their decisions about therapeutic innovation have been
33
34 151 previously described [5]. For the purpose of this study, products that the PMPRB deemed
35
36 152 breakthrough and substantial improvement were termed “innovative” and products in other
37
38 153 categories were termed “not innovative” (category 3 = moderate, little or no improvement
39
40 154 over existing medicines prior to 2010; slight or no improvement, moderate improvement –
41
42 155 primary and moderate improvement – secondary from 2010 onward). Prescrire uses seven
43
44 156 categories to rate therapeutic innovation. The first two, bravo (major therapeutic innovation
45
46 157 in an area where previously no treatment was available); a real advance (important
47
48 158 therapeutic innovation but has limitations) were defined as a significant therapeutic
49
50 159 innovation and the other Prescrire categories (except judgment reserved) were defined as no
51
52 160 therapeutic advance.
53
54
55
56
57
58
59
60

161

162 If both the PMPRB and Prescrire evaluated the drug and the ratings were discordant, i.e., one
 163 said it was not innovative and one said it was, the drug was still considered innovative. Table
 164 1 shows that there is substantial agreement among the definitions used by Health Canada, the
 165 PMPRB and Prescrire in assessing therapeutic innovation. Ratings were current for PMPRB
 166 as of December 31, 2016 (the annual report for 2017 was not available at the time of writing)
 167 and for Prescrire as of February 20, 2018.

168 **Table 1: Criteria used by Health Canada in determination of priority review or Notice**
 169 **of Compliance with conditions pathway and by Human Drug Advisory Panel and**
 170 **Prescrire in determining innovation status**
 171

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

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

172

173 Adapted from: [9]

174 *Notice of Compliance with conditions

175

176 *Data analysis*

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

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

179

180 Kappa values were used to compare the review status from Health Canada to the assessments

181 for the same drug from the PMPRB and/or Prescrire for each year and for the 22-year period.

182 Drugs approved through the priority review and NOC/c pathways were analyzed together as a

183 single group. Kappa scores measure whether there is more or less agreement between

184 different evaluations than would be expected by chance. Levels of agreement were graded in

185 accordance with the recommendations of Landis and Koch where < 0 indicates no agreement,

186 0 – 0.20 slight agreement, 0.21 – 0.40 fair agreement, 0.41 – 0.60 moderate agreement, 0.61 –

187 0.80 substantial agreement, and 0.81–1.0 almost perfect agreement [10].

188

189 *Subgroup analyses*

190 The number and percent of small molecule drugs and biologics approved through the

191 standard, priority and NOC/c pathways were calculate and compared using the Chi-square

192 statistic. Similarly, the Kappa values were calculated separately for small molecule drugs and

193 biologics.

194

1
2
3 195 All drugs were categorized using the second level of the World Health Organization (WHO)
4
5 196 Anatomical Therapeutic Chemical (ATC) classification system [11]. Drugs in three therapeutic
6
7 197 groups – antineoplastic agents (L01), antivirals for systemic use (J05) and immunosuppressants
8
9 198 (L04) – were chosen for subgroup analyses because they are primarily used for serious life-
10
11 199 threatening diseases and because there are sufficient numbers in each group to allow for
12
13 200 statistical analyses. The number and percent of each subgroup that received an expedited
14
15 201 review was calculated as were the Kappa values on a drug-by-drug basis and for drugs in the
16
17 202 “all other therapeutic groups”. Distribution of approval pathways in the subgroups individually
18
19 203 and for the three subgroups combined versus all other therapeutic groups was compared using
20
21 204 the Chi-square statistic. Calculations were done using Excel 2016 for Macintosh (Microsoft)
22
23 205 and Prism 7.0 (GraphPad Software).
24

25 206

27 207 *Patient and public involvement*

28
29
30 208 No patients were involved in any aspect of this study.
31

32 209

34 210 *Ethics*

35
36 211 No patients were involved in this study and only publicly available data was gathered.
37

38 212 Therefore, ethics approval was not required.
39

40 213

42 214 **Results**

44 215 *Review status*

45
46
47 216 From January 1, 1995 to December 31, 2016 Health Canada approved a total of 623 NAS. Of
48
49 217 these, 438 (70.3%) went through the standard pathway, 152 (24.4%) the priority pathway and
50
51 218 33 (5.3%) received a NOC/c. Almost 30 percent (29.7%) went through the expedited review
52
53 219 pathways over the entire period, varying from a low of 9.1% in 2010 to a high of 47.8% in
54
55 220 2006 (Table 2). (Health Canada used both a priority and NOC/c approval for 11 drugs, data
56
57
58
59
60

221 not shown.) Figure 1 shows that there is no trend to using expedited review pathways more
 222 liberally or more conservatively over the time period. (Supplementary Tables 1 & 2, drugs
 223 with and without therapeutic evaluations, respectively, give all of the data extracted for the
 224 623 drugs in question.)

225
 226
 227

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*	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)

228
 229
 230
 231

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

232 There were 126 biologics approved versus 323 small molecules (data only available from
 233 2000 onward). There was no difference in the distribution of the approval pathways ($p =$
 234 0.4867) (Table 3). There were 81 approvals for antineoplastic agents, 47 for antivirals for
 235 systemic use, 36 for immunosuppressants and 365 for drugs in the “all other 68 therapeutic
 236 groups” (Supplementary Table 1). The distribution of approval pathways was significantly
 237 different for the three subgroups ($p = 0.0018$) and for the three subgroups combined versus
 238 “all other therapeutic groups” ($p < 0.00001$) (Table 3).

239 **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

241
 242 Small molecules vs. biologics: chi-square = 1.4402 ($p = 0.4867$)
 243 Antineoplastics vs. antivirals vs. immunosuppressants: chi-square = 17.1978 ($p = 0.0018$)
 244 Antineoplastics + antivirals + immunosuppressants vs. all other therapeutic groups: chi-
 245 square = 97.4874 ($p < 0.00001$)
 246

247 *Therapeutic value*

248 Out of the 623 NAS, 509 (81.7%) were evaluated for their therapeutic innovation either by
 249 the PMPRB and/or Prescrire. Health Canada used an expedited review pathway for 159 of the
 250 509 drugs whereas only 55 were judged to be therapeutically innovative by one or both of the
 251 independent reviews. Forty-two of the 55 drugs that were therapeutic innovations received an
 252 expedited review, 13 received a standard review and 117 (159 – 42) that were not therapeutic
 253 innovations also received an expedited review (Table 4). The Kappa value for the entire

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

256

257

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

260

Year	Number (%) of NAS* with a therapeutic assessment from Patented Medicine Prices Review Board and/or Prescribe	Number of NAS with an expedited review	Number of NAS rated as therapeutic innovation by either Patented Medicine Prices Review Board and/or Prescribe	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

261

262 *New active substance

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

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

267

268 There were 286 and 99 small molecule drugs and biologics, respectively, with therapeutic
 269 ratings. The Kappa values were 0.313 (95% CI 0.205, 0.420) (fair) and 0.233 (95% CI 0.061,
 270 0.405) (fair), respectively. The overlapping 95% CIs indicate no difference in the Kappa
 271 values between the two groups (Table 5).

272 **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)

274
 275 The 509 drugs were in 58 different second level ATC groups (drugs in 13 ATC groups did
 276 not have therapeutic evaluations): antineoplastic agents (71), antivirals for systemic use (46),
 277 immunosuppressants (35) and “all other therapeutic groups” (357) (Supplementary Table 1).
 278 Kappa values for the four groups were: 0.091 (95% CI 0.017, 0.200) (slight), 0.122
 279 (95% CI 0.011, 0.233) (slight), 0.376 (95% CI 0.075, 0.675) (fair) and (95% CI 0.263,
 280 0.506)0.385 (fair), respectively. The 95% CIs for the Kappa values for the antineoplastic
 281 agents, antivirals for systemic use and immunosuppressants overlapped indicating no
 282 difference among the groups but there was no overlap of any of these with the 95% CI for
 283 “all other therapeutic groups”. Drugs in the three therapeutic subgroups were much less likely
 284 to receive a standard review than were drugs in “all other therapeutic groups”, 43.7% versus
 285 79.3% (data not shown).

286

1
2
3 287 **Discussion**

4
5 288 Almost 30% of the 623 new active substances that Health Canada reviewed between 1995
6
7 289 and 2016 went through at least one of two expedited review pathways – priority review or
8
9 290 NOC/c, primarily a priority review. There is no difference between small molecule drugs and
10
11 291 biologics in the approval pathways used indicating that for these two groups Health Canada
12
13 292 does not see one or the other being more likely to offer significant new therapeutic benefits.
14
15 293 However, the same is not true for the therapeutic subgroups. Drugs in the three specifically
16
17 294 examined – antineoplastics, antivirals and immunosuppressants – were collectively more
18
19 295 likely to be assigned to an expedited review pathway (56%) compared to drugs in “all other
20
21 296 therapeutic groups” (20.5%), possibly because of the nature of the diseases that they treat.
22
23

24 297

25
26 298 Just over 80% of the NAS approved had been assessed by the PMPRB and/or Prescrire for
27
28 299 their therapeutic benefit. The Kappa value for the 509 drugs was 0.276 meaning that Health
29
30 300 Canada’s ability to predict major therapeutic gain from these drugs was only fair.

31
32 301 Furthermore, almost 25% (13/55) of the drugs that were therapeutic innovations did not
33
34 302 receive an expedited review underscoring that Health Canada is not reliably able to predict
35
36 303 which drugs will offer major therapeutic gains. The relatively low Kappa value may relate to
37
38 304 when Health Canada makes its decision about what type of approval pathway to use. This
39
40 305 assignment is at the start of the review process when all of the data will not have been fully
41
42 306 assessed. In contrast, the PMPRB and Prescrire make their assessments after the drug has
43
44 307 been marketed when more information about efficacy and safety is available.
45
46

47 308

48
49 309 As was the case with the assignment of an expedited review pathway, there is no difference
50
51 310 in how accurately Health Canada predicts the therapeutic value of small molecule drugs and
52
53 311 biologics as measured by Kappa values. The Kappa value for drugs in “all other therapeutic
54
55
56
57
58
59
60

1
2
3 312 groups” is higher than the value for drugs in the antineoplastic, antiviral and
4
5 313 immunosuppressant groups. This difference may be because Health Canada is better able to
6
7 314 predict these drugs are less likely to be therapeutic innovations than drugs in the
8
9 315 antineoplastic, antiviral and immunosuppressant groups. Out of the 357 drugs that had
10
11 316 therapeutic evaluations in the “all other therapeutic groups,” 79.3% received a standard
12
13 317 review compared to 43.7% of the 151 drugs in the three therapeutic subgroups.
14
15
16 318
17
18 319 How Health Canada uses its expedited review pathways is important for a number of reasons.
19
20 320 First, their use may explicitly create an impression among clinicians and patients that these
21
22 321 drugs are likely to deliver major new therapeutic benefits despite the fact that the likelihood
23
24 322 that they will is only “fair” as measured by the Kappa value. Second, the NOC/c pathway
25
26 323 requires companies to commit to conducting post-market studies to validate the efficacy of
27
28 324 the product, but many of these studies are delayed [6, 7], leaving clinicians and patients
29
30 325 uncertain about the value of these products. In at least one case, Health Canada did not
31
32 326 suspend the sale of a drug and allowed it to stay on the market despite not fulfilling the
33
34 327 conditions required under its NOC/c. In December 2003, Iressa (gefitinib) was approved as a
35
36 328 third-line treatment for non-small cell lung cancer on the condition that the company submit a
37
38 329 study showing that it improved survival [12]. When the study results were submitted to
39
40 330 Health Canada they showed no survival benefit for gefitinib compared to placebo [13].
41
42 331 Health Canada recognized that the conditions had not been fulfilled, but rather than removing
43
44 332 gefitinib from the market, in February 2005 it elected to allow it to continue to be sold [12].
45
46 333 In 2009, the drug was deemed to have met its conditions after a new study showed non-
47
48 334 inferiority, i.e., survival after taking it was no worse compared to another chemotherapeutic
49
50 335 agent [14]. Third, although the priority and standard approval pathways are equivalent in
51
52 336 terms of the amount of data reviewed, the former is done in 180 days compared to 300 days
53
54
55
56
57
58
59
60

1
2
3 337 for the latter, meaning that the priority pathway is more resource intensive possibly drawing
4
5 338 resources from other Health Canada activities. Finally, drugs reviewed through both
6
7 339 expedited review pathways are more likely to receive safety warnings once they are on the
8
9 340 market compared to drugs with a standard approval [2, 15].
10

11 341

12
13 342 As Figure 1 indicates, Health Canada is not using the expedited review pathways more
14
15 343 liberally (or more conservatively) over time, but as Figure 2 shows it has not improved its
16
17 344 ability to predict therapeutic innovation over the 22 years evaluated in this study. The
18
19 345 Introduction describes the criteria that Health Canada uses to assign a drug to either a priority
20
21 346 review or a NOC/c review but how those criteria are applied and whether Health Canada
22
23 347 periodically reviews its performance are not known.
24
25

26 348

27
28 349 Contrary to the situation in the United States (US) where the Food and Drug Administration
29
30 350 (FDA) has been using an increasing number of expedited development or review programs,
31
32 351 Health Canada's use of its programs has been relatively stable since 1995. Between 1987 and
33
34 352 2014, 43% received a priority review from the FDA and 19% were approved through the fast
35
36 353 track program which approximately corresponds to a NOC/c [16]. (Drugs could be associated
37
38 354 with both programs.) However, when it comes to approving oncology drugs through an
39
40 355 expedited pathway, Health Canada is only marginally better than the FDA. In the US, only 1
41
42 356 of 15 (6.7%) oncology drugs approved through an expedited program from January 1, 2008,
43
44 357 through December 31, 2012 had a proven survival benefit compared to the other 6 and 8 that
45
46 358 either had no overall survival benefit or an unknown benefit, respectively [17]. In this current
47
48 359 study, out of 42 antineoplastic agents that Health Canada gave an expedited review, only 6
49
50 360 (14.3%) were rated as therapeutically innovative. The European Medicines Agency (EMA)
51
52 361 does not have the equivalent of a priority review but its exceptional conditions (EC) and
53
54
55
56
57
58
59
60

1
2
3 362 conditional approvals (CA) pathways are roughly equivalent to a NOC/c. These were used
4
5 363 for 12.5% (70/558) new drugs it approved from 1995 to 2009 [18], while Health Canada used
6
7 364 a NOC/c for 5.3% (33/623) approvals between 1995 and 2016.
8

9 365

11 366 *Limitations*

13 367 Almost 20% of new drugs approved by Health Canada were not evaluated for their
14
15 368 therapeutic innovation by either the PMPRB or La revue Prescrire. The absence of these
16
17 369 evaluations may have skewed the Kappa values in either a more positive or more negative
18
19 370 direction. The lack of the availability of reports from Health Canada reviewers means that the
20
21 371 reasons why drugs were assigned to a specific review pathway cannot be evaluated.
22
23

24 372

26 373 **Conclusion**

28 374 Health Canada continues to use expedited review pathways for about 30% of new drugs.
29
30 375 Other regulatory authorities such as the Australian Therapeutic Goods Administration and the
31
32 376 EMA are in the process of either implementing or expanding expedited review pathways [19-
33
34 377 21] and should study the example of what has happened in Canada. The rationale for using
35
36 378 expedited review pathways is to get important therapeutic advances to patients in a timely
37
38 379 manner, but Health Canada's ability to predict which of these drugs will fulfill this
39
40 380 expectation has not improved over a 22-year period and remains relatively low. Moreover,
41
42 381 use of these pathways comes with both health related and resource costs. The findings in this
43
44 382 study should provoke a discussion about whether Health Canada should continue to use these
45
46 383 pathways and if so how their use can be improved.
47
48
49
50
51
52
53
54
55
56
57
58
59

1
2
3 384 **Figure 1 legend**

4
5 385 Grey – Percent with Notice of Compliance with conditions

6 386

7 387 Orange – Percent with priority

8 388

9 389 Blue – Percent with standard

10 390

11
12 391 **Figure 2 legend**

13
14 392 Kappa values:

15
16 393 < 0 = no agreement

17 394

18 395 0 – 0.20 = slight agreement

19 396

20 397 0.21 – 0.40 = fair agreement

21 398

22 399 0.41 – 0.60 = moderate agreement

23 400

24 401 0.61 – 0.80 = substantial agreement

25 402

26 403 0.81 – 1.0 = almost perfect agreement

27 404

28
29 405
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

406 **References**

- 407 1. Health Products and Food Branch. Access to therapeutic products: the regulatory
408 process in Canada Ottawa: Health Canada; 2006 [cited 2014 July 20]. Available from:
409 http://publications.gc.ca/collections/collection_2007/hc-sc/H164-9-2006E.pdf.
- 410 2. Lexchin J. Post-market safety warnings for drugs approved in Canada under the
411 Notice of Compliance with conditions policy. *British Journal of Clinical Pharmacology*.
412 2015;79:847-59.
- 413 3. Health Canada: Health Products and Food Branch. Guidance for industry: priority
414 review of drug submissions. Ottawa: 2009.
- 415 4. Health Canada. Notice of compliance with conditions (NOC/c). Ottawa: 2002.
- 416 5. Lexchin J. Health Canada's use of its priority review process for new drugs: a cohort
417 study. *BMJ Open*. 2015;5:e006816.
- 418 6. Lexchin J. Notice of compliance with conditions: a policy in limbo. *Healthcare*
419 *Policy*. 2007;2:114-22.
- 420 7. Law M. The characteristics and fulfillment of conditional prescription drug approvals
421 in Canada. *Health Policy*. 2014;116:154-61.
- 422 8. Prescrire Editorial Staff. Prescrire's ratings system: gauge the usefulness of new
423 products at a glance Paris2011 [cited 2015 March 11]. Available from:
424 <http://english.prescrire.org/en/81/168/46800/0/NewsDetails.aspx>.
- 425 9. Lexchin J. Postmarket safety in Canada: are significant therapeutic advances and
426 biologics less safe than other drugs? A cohort study. *BMJ Open*. 2014;4:e004289.
- 427 10. Landis JR, Koch GG. The measurement of observer agreement for categorical data.
428 *Biometrics*. 1977;33:159-74.

- 1
2
3 429 11. WHO Collaborating Centre for Drug Statistics Methodology, Norwegian Institute of
4
5 430 Public Health. Structure and principles 2011 [cited 2018 February 20]. Available from:
6
7 431 http://www.whooc.no/atc/structure_and_principles/.
8
9 432 12. Health Canada. Clarification from Health Canada regarding the status of Iressa®
10
11 433 (gefitinib) in Canada Ottawa2005 [cited 2014 October 20]. Available from: [http://www.hc-](http://www.hc-sc.gc.ca/dhp-mpps/prodpharma/activit/fs-fi/fact_iressa-eng.php)
12
13 434 [sc.gc.ca/dhp-mpps/prodpharma/activit/fs-fi/fact_iressa-eng.php](http://www.hc-sc.gc.ca/dhp-mpps/prodpharma/activit/fs-fi/fact_iressa-eng.php).
14
15 435 13. Thatcher N, Chang A, Parikh P, Pereira J, Ciuleanu T, von Pawel J, et al. Gefitinib
16
17 436 plus best supportive care in previous treated patients with refractory advanced non-small-cell
18
19 437 lung cancer: results from a randomised, placebo-controlled, multicentre study (Iressa
20
21 438 Survival Evaluation in Lung Cancer). *Lancet*. 2005;366:1527-37.
22
23 439 14. Kim E, Hirsh V, Mok T, Socinski M, Gervais R, Wu Y-L, et al. Gefitinib versus
24
25 440 docetaxel in previously treated non-small-cell lung cancer (INTEREST): a randomised phase
26
27 441 III trial. *Lancet*. 2008;372:1809-18.
28
29 442 15. Lexchin J. New drugs and safety: what happened to new active substances approved
30
31 443 in Canada between 1995 and 2010? *Archives of Internal Medicine*. 2012;172:1680-1.
32
33 444 16. Kesselheim A, Wang B, Franklin J, Darrow J. Trends in utilization of FDA expedited
34
35 445 drug development and approval programs, 1987-2014: cohort study. *BMJ*. 2015;351:h4633.
36
37 446 17. Kim C, Prasad V. Cancer drugs approved on the basis of a surrogate end point and
38
39 447 subsequent overall survival: an analysis of 5 years of US Food and Drug Administration
40
41 448 approvals. *JAMA Internal Medicine*. 2015;175:1992-4.
42
43 449 18. Boon W, Moors E, Meijer A, Schellekens H. Conditional approval and approval
44
45 450 under exceptional circumstances as regulatory instruments for stimulating responsible drug
46
47 451 innovation in Europe. *Clinical Pharmacology & Therapeutics*. 2010;88:848-53.
48
49 452 19. European Medicines Agency. Final report on the adaptive pathways pilot. London:
50
51 453 2016.
52
53
54
55
56
57
58
59
60

1
2
3 454 20. Department of Health Therapeutic Goods Administration. Consultation: provisional
4
5 455 approval pathway for prescription medicines. Proposed registration process and post-market
6
7 456 requirements. Woden, ACT: 2017.

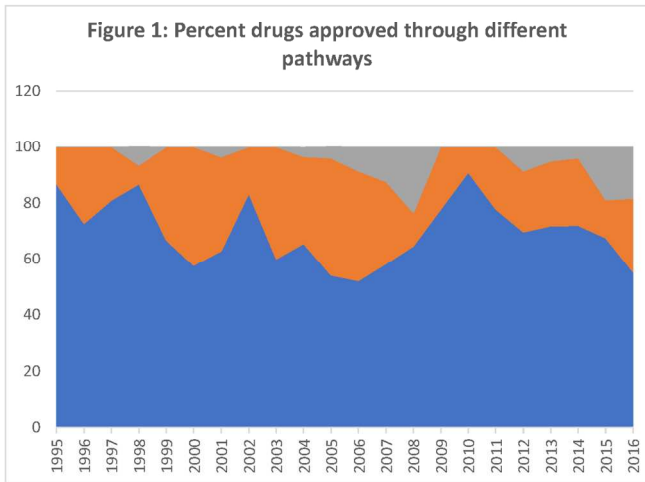
8
9 457 21. Department of Health Therapeutic Goods Administration. Consultation: expedited
10
11 458 pathways for prescription medicines. Eligibility criteria and designation process. Woden,
12
13 459 ACT: 2016.

14
15
16 460

17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

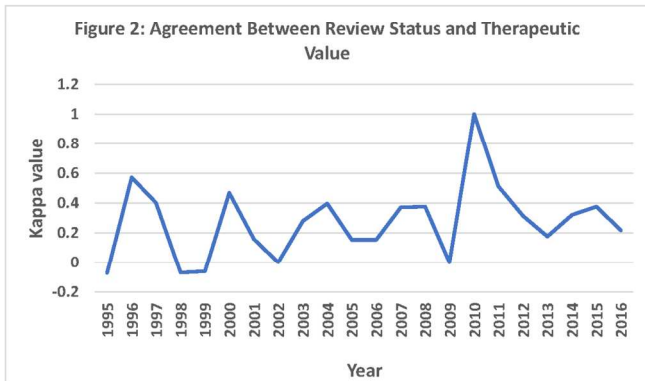
For peer review only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



148x209mm (300 x 300 DPI)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



148x209mm (300 x 300 DPI)

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 Standard Priority	Notice of compliance with conditions	Notice of compliance or notice of compliance with conditions date	Small molecule	Biologic	ATC group (second level)
Adapalene	Differin		1	1		1995-01-24			anti-acne preparation
Dexrazoxane	Zinocard	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		1	1		1995-04-24			psycholeptics
Zuclopenthixol	acuphase 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 svstemic use
Sevoflurane	Sevorane		1	1		1995-09-18			anesthetics

1						
2						
3	Losartan	Cozaar	1	1	1995-09-28	agents acting on the
4						renin-angiotensin system
5	Iotrolan	Osmovist 280	1	1	1995-10-04	contrast media
6	Bicalutamide	Casodex	1	1	1995-11-02	endocrine therapy
7	Acarbose	Prandase	1	1	1995-11-15	drugs used in diabetes
8	Mycophenolate	Cellcept	1	1	1995-11-15	immunosuppressants
9	Tacrolimus	Prograf	1	1	1995-12-06	immunosuppressants
10	Lamivudine	3TC	1	1	1995-12-08	antivirals for systemic
11						use
12	Alendronate	Fosamax	1	1	1995-12-20	drugs for treatment of
13						bone disease
14	Stavudine	Zerit	1	1	1996-03-26	antivirals for systemic
15						use
16	Acellular	Acel-P	1	1	1996-03-29	vaccines
17	pertussis vaccine					
18	adsorbed					
19						
20	Dorzolamide	Trusopt	1	1	1996-04-25	ophthalmologicals
21	Amifostine	Ethyol	1	1	1996-04-25	all other therapeutic
22						products
23	Valacyclovir	Valtrex	1	1	1996-05-01	antivirals for systemic
24						use
25	Quinagolide	Norprolac	1	1	1996-06-25	other gynecologicals
26	Meropenem	Merrem	1	1	1996-07-02	antibacterials for
27						systemic use
28	Abciximab	Reopro	1	1	1996-07-04	antithrombotic agents
29	Anastrozole	Arimidex	1	1	1996-08-01	endocrine therapy
30	Ritonavir	Norvir	1	1	1996-08-14	antivirals for systemic
31						use
32	Raltitrexed	Tomudex	1	1	1996-09-12	antineoplastic agents
33	Indinavir	Crixivan	1	1	1996-09-13	antivirals for systemic
34						use
35	Insulin lispro	Humalog	1	1	1996-10-08	drugs used in diabetes
36						
37						
38						
39						
40						
41						
42						
43						
44						
45						
46						
47						

1						
2						
3	Dirithromycin	Dynabac	1	1	1996-10-28	antibacterials for
4						systemic use
5	Olanzapine	Zyprexa	1	1	1996-10-28	psycholeptics
6	Nalmefene	Revox	1	1	1996-11-06	other nervous system
7	Zolpidem	Ambien	1	1	1996-11-20	psycholeptics
8	Desflurane	Suprane	1	1	1996-12-03	anesthetics
9	Gemcitabine	Gemzar	1	1	1996-12-23	antineoplastic agents
10	Ropivacaine	Naropin	1	1	1996-12-24	anesthetics
11		injections				
12	Imiglucerase	Cerezyme	1	1	1997-02-12	other alimentary tract
13						and metabolism products
14	Atorvastatin	Lipitor	1	1	1997-02-19	lipid modifying agents
15	Topiramate	Topamax	1	1	1997-03-06	antiepileptics
16	Formoterol	Foradil dry	1	1	1997-03-06	drugs for obstructive
17		powder				airway diseases
18		capsules				
19	Epoprostenol	Flolan	1	1	1997-03-06	antithrombotic agents
20	Coagulation	Benefix	1	1	1997-03-21	antihemorrhagics
21	factor IX					
22	Topotecan	Hycamtin	1	1	1997-04-15	antineoplastic agents
23	Dolasetron	Anzemet	1	1	1997-05-21	antiemetics and
24						antinauseants
25	Letrozole	Femara	1	1	1997-05-21	endocrine therapy
26	Fexofenadine	Allegra	1	1	1997-06-11	antihistamines for
27						systemic use
28	Latanoprost	Xalatan	1	1	1997-06-16	ophthalmologicals
29	Carbetocin	Duratocin	1	1	1997-06-24	pituitary and
30						hypothalamic hormones
31						and analogues
32	Follitropin beta	Puregon	1	1	1997-07-02	sex hormones and
33						modulators of the genital
34						svstem
35						
36						
37						
38						
39						
40						
41						
42						
43						
44						
45						
46						
47						

1						
2						
3	Irinotecan	Camptosar	1	1	1997-07-04	antineoplastic agents
4	Donepezil	Aricept	1	1	1997-08-12	psychoanaleptics
5	Ropinirole	Requip		1	1997-08-19	anti-parkinson drugs
6	Ibandronate	Bondronat		1	1997-08-27	drugs for treatment of
7						bone disease
8						immunostimulants
9	Glatiramer	Copaxone for		1	1997-09-04	
10		injection				
11	Tolcapone	Tasmar		1	1997-10-08	anti-parkinson drugs
12	Zafirlukast	Accolate		1	1997-10-21	drugs for obstructive
13						airway diseases
14	Valsartan	Diovan		1	1997-11-03	agents acting on the
15						renin-angiotensin system
16						
17						
18	Levofloxacin	Levaquin		1	1997-11-14	antibacterials for
19						systemic use
20	Brimonidine	Alphagan		1	1997-11-24	ophthalmologicals
21		ophthalmic				
22	Quetiapine	Seroquel		1	1997-12-02	psycholeptics
23	Pramipexole	Mirapex		1	1998-01-29	anti-parkinson drugs
24	Interferon Beta-	Rebif		1	1998-02-05	immunostimulants
25	Emedastine	Emadine		1	1998-02-16	ophthalmologicals
26		ophthalmic				
27						
28						
29	Cerivastatin	Baycol		1	1998-02-18	lipid modifying agents
30	Grepafloxacin	Raxar		1	1998-04-09	antibacterials for
31						systemic use
32	Naratriptan	Amerge		1	1998-04-28	analgesics
33	Bupropion	Wellbutrin SR		1	1998-04-28	psychoanaleptics
34	Irbesartan	Avapro		1	1998-06-01	agents acting on the
35						renin-angiotensin system
36						
37						
38	Tamsulosin	Flomax		1	1998-06-01	urologicals
39	Montelukast	Singulair		1	1998-06-17	drugs for obstructive
40						airway diseases
41						
42						
43						
44						
45						
46						
47						

1							
2							
3	Delavirdine	Rescriptor	1	1	1	1998-07-22	antivirals for systemic
4							use
5	Nelfinavir	Viracept	1		1	1998-08-11	antivirals for systemic
6							use
7	Zolmitriptan	Zomig	1	1		1998-08-24	analgesics
8	Capecitabine	Xeloda	1		1	1998-08-31	antineoplastic agents
9	Nevirapine	Viramune	1	1	1	1998-09-04	antivirals for systemic
10							use
11	Clopidogrel	Plavix	1	1		1998-10-07	antithrombotic agents
12	Brinzolamide	Azopt	1	1		1998-10-23	ophthalmologicals
13		ophthalmic					
14		suspension					
15	Raloxifene	Evista	1	1		1998-11-06	sex hormones and
16							modulators of the genital
17							system
18	Candesartan	Atacand	1	1		1998-11-20	agents acting on the
19							renin-angiotensin system
20	Tolterodine	Detrol	1	1		1998-11-20	urologicals
21	Varicella vaccine	Varivax	1	1		1998-12-02	vaccines
22							
23	Alatrofloxacin	Trovan (IV)	1	1		1998-12-04	antibacterials for
24							systemic use
25	Trovafloxacin	Trovan (tablets)	1	1		1998-12-04	antibacterials for
26							systemic use
27	Becaplermin gel	Regranex	1	1		1998-12-30	preparations for wounds
28							and ulcers
29	Tizanidine	Zanaflex	1	1		1999-01-25	muscle relaxants
30	Penciclovir	Denavir	1	1		1999-02-02	antivirals for systemic
31							use
32	Citalopram	Celexa	1	1		1999-02-05	psychoanaleptics
33	Recombinant	Niastase	1		1	1999-02-12	antihemorrhagics
34	factor VIIa						
35	Modafinil	Alertec	1	1		1999-02-26	psychoanaleptics
36							
37							
38							
39							
40							
41							
42							
43							
44							
45							
46							
47							

1							
2							
3	Sildenafil	Viagra	1	1		1999-03-08	urologicals
4	Recombinant-	Infergen		1	1	1999-03-11	immunostimulants
5	methionyl						
6	interferon						
7	consensus 1						
8	Efavirenz	Sustiva	1	1		1999-03-19	antivirals for systemic
9							use
10	Repaglinide	Gluconorm	1	1		1999-04-06	drugs used in diabetes
11	Celecoxib	Celebrex	1		1	1999-04-14	antiinflammatoary and
12							antirheumatic products
13	Triptorelin	Trelstar	1	1		1999-05-06	endocrine therapy
14	Ancestim	Stemgen	1	1		1999-05-20	immunostimulants
15	Orlistat	Xenical	1	1		1999-06-03	antiobesity preparations
16	Abacavir	Ziagen	1		1	1	antivirals for systemic
17							use
18	Eptifibatide	Integrilin	1	1		1999-06-11	antithrombotic agents
19	Eprosartan	Teveten	1	1		1999-07-09	agents acting on the
20							renin-angiotensin system
21							
22	Cidofovir	Vistide	1	1		1999-07-13	antivirals for systemic
23							use
24	Rizatriptan	Maxalt	1	1		1999-07-16	analgesics
25	Trastuzumab	Herceptin	1		1	1999-08-13	antineoplastic agents
26	Telmisartan	Micardis	1	1		1999-08-16	agents acting on the
27							renin-angiotensin system
28							
29	Risedronate	Actonel	1	1		1999-08-18	drugs for treatment of
30							bone disease
31	Tirofiban	Aggrastat	1	1		1999-08-19	antithrombotic agents
32	Icodextrin	Extraneal	1	1		1999-09-17	blood substitutes and
33							perfusion solutions
34	Varicella zoster	Varilrix	1		1	1999-10-13	vaccines
35	vaccine						
36	Temozolomide	Temodal	1	1		1999-10-25	antineoplastic agents
37							
38							
39							
40							
41							
42							
43							
44							
45							
46							
47							

1								
2								
3	Rofecoxib	Vioxx	1	1	1999-10-25			antiinflammaotory and
4								antirheumatic products
5	Zanamivir	Relenza	1	1	1	1999-11-02		antivirals for systemic
6								use
7	Melanoma	Melacine	1	1	1999-11-04			immunostimulants
8	theracine							
9	Gadobutrol	Gadovist	1	1	1999-11-08			contrast media
10	Dalfopristin	Synercid	1	1	1999-12-10			antibacterials for
11								systemic use
12	Oseltamivir	Tamiflu	1	1	1999-12-23			antivirals for systemic
13								use
14	Daclizumab	Zenaprax	1	1	2000-01-04		1	antineoplastic agents
15	Leflunomide	Arava	1	1	2000-03-16		1	immunosuppressants
16	Rituximab	Rituxan	1	1	2000-03-17		1	immunosuppressants
17	Rosiglitazone	Avandia	1	1	2000-03-21		1	drugs used in diabetes
18	Oxcarbazepine	Trileptal	1	1	2000-04-13		1	antiepileptics
19	Rivastigmine	Exelon	1	1	2000-04-13		1	psychoanaleptics
20	Zaleplon	Starnoc	1	1	2000-05-11		1	psycholeptics
21	Verteporfin	Visudyne	1	1	2000-05-31		1	ophthalmologicals
22	Cabergoline	Dostinex	1	1	2000-06-30		1	anti-parkinson drugs
23	Exemestane	Aromasin	1	1	2000-08-17		1	endocrine therapy
24	Pioglitazone	Actos	1	1	2000-08-17		1	drugs used in diabetes
25	Zoledronic acid	Zometa	1	1	2000-08-21		1	drugs for treatment of
26								bone disease
27	Riluzole	Rilutek	1	1	1	2000-08-30	1	other nervous system
28	Meloxicam	Mobic	1	1	2000-08-31		1	antiinflammaotory and
29								antirheumatic products
30	Basiliximab	Simulect	1	1	2000-09-01		1	immunosuppressants
31	Moxifloxacin	Avelox	1	1	2000-10-19		1	antibacterials for
32								systemic use
33	Peginterferon	Peg-intron	1	1	2000-10-20		1	immunostimulants
34	Alfa-2b							
35	Etanercept	Enbrel	1	1	2000-12-01		1	immunosuppressants
36								
37								
38								
39								
40								
41								
42								
43								
44								
45								
46								
47								

1							
2							
3	Gadoversetamid	Optimark	1	1		2000-12-11	1 contrast media
4	e						
5	Sibutramine	Meridia	1	1		2000-12-28	1 antiobesity preparations
6	Sirolimus	Rapamune	1	1		2001-01-05	1 immunosuppressants
7	Gatifloxacin	Tequin	1	1		2001-01-09	1 antibacterials for systemic use
8							
9							
10	Glucagon, rDNA origin	Glucagon	1		1	2001-01-11	1 pancreatic hormones
11							
12	Mequinol/tretinoin	Solage	1	1		2001-01-17	1 other dermatological preparations
13							
14	Amprenavir	Agenerase	1	1	1	2001-03-01	1 antivirals for systemic use
15							
16	Lopinavir/ritonavir	Kaletra	1		1	2001-03-09	1 antivirals for systemic use
17							
18	Linezolid	Zyvoxam	1	1		2001-04-02	1 antibacterials for systemic use
19							
20							
21	Iron	Venoferr	1		1	2001-04-17	1 antianemic preparations
22	Doxercalciferol	Hectorol	1	1		2001-04-30	1 calcium homeostasis
23	Rabeprazole	Pariet	1	1		2001-05-07	1 drugs for acid related disorders
24							
25	Entacapone	Comtan	1	1		2001-05-08	1 anti-parkinson drugs
26	Eflornithine	Vaniqa	1	1		2001-05-10	1 antiprotozoals
27	Mirtazapine	Remeron	1	1		2001-05-18	1 psychoanaleptics
28	Desloratadine	Aerius	1	1		2001-05-29	1 antihistamines for systemic use
29							
30							
31	Infliximab	Remicade	1	1		2001-06-06	1 immunosuppressants
32	Caspofungin	Cancidas	1		1	2001-07-29	1 antimycotics for systemic use
33							
34							
35	Galantamine	Reminyl	1	1		2001-07-31	1 psychoanaleptics
36	Esomeprazole	Nexium	1	1		2001-08-17	1 drugs for acid related disorders
37							
38	Imatinib	Gleevec			1	2001-09-20	1 antineoplastic agents
39	Tenecteplase	Tnkase	1	1		2001-10-17	1 antithrombotic agents
40	Travoprost	Travatan	1	1		2001-11-09	1 ophthalmologicals
41							
42							
43							
44							
45							
46							
47							

1							
2							
3	Bosentan	Tracleer	1	1	2001-11-30	1	antihypertensives
4	Meningococcal	Neisvac-C	1	1	2001-12-18	1	vaccines
5	group C						
6	polysaccharide,						
7	tetanus toxoid						
8	Glimepiride	Amaryl	1	1	2002-01-25	1	drugs used in diabetes
9	Nateglinide	Starlix	1	1	2002-02-13	1	drugs used in diabetes
10	Alfuzosin	Xatral	1	1	2002-02-21		urologicals
11	Tegaserod	Zelnorm	1	1	2002-03-12	1	drugs for constipation
12	Ganirelix	Orgalutran	1	1	2002-05-01	1	pituitary and
13							hypothalamic hormones
14	Valganciclovir	Valcyte	1	1	2002-05-03	1	antivirals for systemic
15							use
16	Palivizumab	Synagis	1	1	2002-05-15	1	immune sera and
17							immunoglobulins
18	Docosanol	Abreva	1	1	2002-05-24	1	antibiotics and
19							chemotherapeutics for
20							dermatological use
21	Bimatoprost	Lumigan	1	1	2002-05-24	1	ophthalmologicals
22	Anakinra	Kineret	1	1	2002-05-24	1	immunosuppressants
23	Moroctocog	Refacto	1	1	2002-05-28	1	antihemorrhagics
24	alpha						
25	Peginterferon	Pegetron	1	1	2002-05-31	1	immunostimulants
26	Alfa-2b ribavirin						
27	Fondaparinux	Arixtra	1	1	2002-06-13	1	antithrombotic agents
28	Hetastarch	Hextend	1	1	2002-07-08	1	blood substitutes and
29							perfusion solutions
30	Darbepoetin	Aranesp	1	1	2002-08-02	1	antianemic preparations
31	alpha						
32	Norelgestromin/	Evra	1	1	2002-08-20	1	sex hormones and
33	ethinyl estradiol						modulators of the genital
34							system
35	Treprostinil	Remodulin	1	1	2002-10-04	1	antithrombotic agents
36	Bivalirudin	Angiomax	1	1	2002-10-09	1	antithrombotic agents
37							
38							
39							
40							
41							
42							
43							
44							
45							
46							
47							

1								
2								
3	Tiotropium	Spiriva	1	1		2002-11-20	1	drugs for obstructive
4								airway diseases
5	Valdecoxib	Betra	1	1		2002-12-11	1	antiinflammatoory and
6								antirheumatic products
7								antithrombotic agents
8	Drotrecogin Alfa	Xigris	1			2003-01-31		1
9	Rosuvastatin	Crestor		1		2003-02-18	1	lipid modifying agents
10	Recombinant	Dukoral		1		2003-02-21		1
11	cholera toxin B							vaccines
12	subunit							
13	Levetiracetam	Keppra		1		2003-03-06	1	antiepileptics
14	Tenofovir	Viread		1	1	2003-03-18	1	antivirals for systemic
15								use
16	Pimecrolimus	Elidel		1		2003-03-19	1	other dermatological
17								preparations
18	Ertapenem	Invanz		1		2003-05-12	1	antibacterials for
19								systemic use
20	Ezetimibe	Ezetrol		1		2003-05-12	1	lipid modifying agents
21	Telithromycin	Ketek		1		2003-05-28	1	antibacterials for
22								systemic use
23	Enfuvirtide	Fuzeon	1			2003-07-14	1	antivirals for systemic
24								use
25	Dutasteride	Avodart		1		2003-07-22	1	urologicals
26	Peginterferon	Pegasys		1		2003-08-13		1
27	Alfa-2a							immunostimulants
28	Cetrorelix	Cetrotide		1		2003-08-13	1	pituitary and
29								hypothalamic hormones
30	Adefovir	Hepsera		1		2003-08-27	1	antivirals for systemic
31								use
32	Tadalafil	Cialis		1		2003-09-17	1	urologicals
33	Almotriptan	Axert		1		2003-10-01	1	agents acting on the
34								renin-angiotensin system
35								
36	Rasburicase	Fasturtec		1		2003-10-29		1
37								all other therapeutic
38								products
39								
40								
41								
42								
43								
44								
45								
46								
47								

1								
2								
3	Atazanavir	Reyataz	1	1	2003-12-05	1		antivirals for systemic
4								use
5	Gefitinib	Iressa	1	1	1	2003-12-17	1	antineoplastic agents
6	Agalsidase Beta	Fabrazyme	1	1	2004-01-23		1	other alimentary tract
7								and metabolism products
8								
9								
10	Agalsidase	Replagal	1	1	1	2004-02-06	1	other alimentary tract
11								and metabolism products
12								
13	Fulvestrant	Faslodex	1	1	2004-02-17	1		endocrine therapy
14	Gemifloxacin	Factive	1	1	2004-03-09	1		antibacterials for
15								systemic use
16	Pegfilgrastim	Neulasta	1	1	2004-03-12		1	immunostimulants
17	Vardenafil	Levitra	1	1	2004-03-17	1		urologicals
18	Gadobenate	Multihance	1	1	2004-03-31	1		contrast media
19	Miglustat	Zavesca	1	1	2004-03-31	1		other alimentary tract
20								and metabolism products
21								
22								
23	Botulinum Toxin	Myobloc	1	1	2004-04-16		1	muscle relaxants
24	Type B							
25	Peginterferon	Pegasys RBV	1	1	2004-05-10		1	immunostimulants
26	Alfa-2A Ribavirin							
27								
28								
29	Ethinyl	Nuvaring	1	1	2004-05-11	1		sex hormones and
30	estradiol/etonog							modulators of the genital
31	estrel							svstem
32	Pemetrexed	Alimta	1	1	2004-05-21	1		antineoplastic agents
33	Laronidase	Adlurazyme	1	1	2004-05-31		1	other alimentary tract
34								and metabolism products
35								
36	Teriparatide	Forteo	1	1	2004-06-03		1	calcium homeostasis
37	Cinacalcet	Sensipar	1	1	2004-08-04	1		calcium homeostasis
38	Eletriptan	Relpax	1	1	2004-08-05	1		analgesics
39								
40								
41								
42								
43								
44								
45								
46								
47								

1							
2							
3	Voriconazole	Vfend	1	1		2004-08-20	1 antimycotics for systemic
4							use
5	Frovatriptan	Frova	1	1		2004-09-03	1 analgesics
6	Adalimumab	Humira	1	1		2004-09-24	1 immunosuppressants
7	Alefacept	Amevive	1	1		2004-10-06	1 immunosuppressants
8	Omalizumab	Xolair	1	1		2004-11-18	1 drugs for obstructive
9							airway diseases
10	Memantine	Ebixa	1	1	1	2004-12-08	1 psychoanaleptics
11	Fosamprenavir	Telzir	1	1		2004-12-10	1 antivirals for systemic
12							use
13	Drospirenone/et	Yasmin 21/28	1	1		2004-12-10	1 sex hormones and
14	hinyI estradiol						modulators of the genital
15							svstem
16	Atomoxetine	Strattera	1	1		2004-12-24	1 psychoanaleptics
17	Escitalopram	Cipralax	1	1		2004-12-24	1 psychoanaleptics
18	Bortezomib	Velcade	1	1	1	2005-01-27	1 antineoplastic agents
19	Paricalcitol	Zemplar	1	1		2005-03-31	1 calcium homeostasis
20	Pantoprazole	Pantaloc M	1	1		2005-04-22	1 drugs for acid related
21							disorders
22	Pegaptanib	Macugen	1	1		2005-05-02	1 ophthalmologicals
23	Ibritumomab	Zevalin	1	1		2005-05-10	1 therapeutic
24							radiopharmaceuticals
25	Pregabalin	Lyrica	1	1		2005-06-03	1 antiepileptics
26	Lutropin Alfa	Luveris	1	1		2005-06-24	1 sex hormones and
27							modulators of the genital
28							svstem
29	Erlotinib	Tarceva	1	1		2005-07-07	1 antineoplastic agents
30	Tramadol	Tramacet	1	1		2005-07-20	1 analgesics
31	Sodium oxybate	Xyrem	1	1		2005-08-05	1 other nervous system
32	Perindopril	Coversyl	1	1		2005-08-23	1 agents acting on the
33							renin-angiotensin system
34	Bevacizumab	Avastin	1	1		2005-09-09	1 antineoplastic agents
35							
36							
37							
38							
39							
40							
41							
42							
43							
44							
45							
46							
47							

1								
2								
3	Cetuximab	Erbix	1		1	2005-09-09		1 antineoplastic agents
4	Insulin detemir	Levemir	1	1		2005-09-29		1 drugs used in diabetes
5	Pegvisomant	Somavert	1		1	2005-10-17		1 pituitary and
6								hypothalamic hormones
7								
8	Efalizumab	Raptiva	1	1		2005-10-24		1 immunosuppressants
9	Darifenacin	Enablex	1	1		2005-11-14	1	urologicals
10	Emtricitabine	Emtriva	1	1		2005-11-21	1	antivirals for systemic
11								use
12	Tipranavir	Aptivus	1		1	2005-11-21	1	antivirals for systemic
13								use
14	Alemtuzumab	Mabcampath	1	1		2005-11-30		1 immunosuppressants
15	Palifermin	Kepivance	1		1	2005-12-09		1 all other therapeutic
16								products
17	Trospium	Trosec	1	1		2006-01-10	1	urologicals
18	Solifenacin	Vesicare	1	1		2006-02-20	1	urologicals
19	Histrelin	Vantas	1	1		2006-03-10	1	endocrine therapy
20	Insulin glulisine	Apidra	1	1		2006-04-12		1 drugs used in diabetes
21	Sunitinib	Sutent	1		1	2006-05-26	1	antineoplastic agents
22	Entecavir	Baraclude	1		1	2006-06-16	1	pituitary and
23								hypothalamic hormones
24								and analogues
25	Abatacept	Orencia	1		1	2006-06-29		1 immunosuppressants
26	Recombinant	Gardasil	1		1	2006-07-10		1 vaccines
27	human							
28	papillomavirus							
29	Lanreotide	Somatuline	1	1		2006-07-17	1	antivirals for systemic
30		autogel						use
31	Sorafenib	Nexavar	1	1		2006-07-28	1	antineoplastic agents
32	Darunavir	Prezista	1	1	1	2006-07-28	1	antivirals for systemic
33								use
34	Rotaviruses	Rotateq	1	1		2006-08-01		1 vaccines
35								
36								
37								
38								
39								
40								
41								
42								
43								
44								
45								
46								
47								

1								
2								
3	Alglucosidase	Myozyme	1		1	2006-08-14	1	other alimentary tract
4	Alfa							and metabolism products
5								
6	Rasagiline	Azilect		1	1	2006-08-17	1	anti-parkinson drugs
7	Ciclesonide	Alvesco		1	1	2006-09-11	1	drugs for obstructive
8								airway diseases
9	Tigecycline	Tygacil		1	1	2006-09-14	1	antibacterials for
10								systemic use
11	Natalizumab	Tysabri		1	1	2006-09-28		immunosuppressants
12	Lanthanum	Fosrenol		1	1	2006-10-17	1	all other therapeutic
13								products
14	Deferasirox	Exjade		1	1	1	2006-10-18	1
15								all other therapeutic
16								products
17	Gadofosveset	Vasovist		1	1		2006-10-31	1
18	Telbivudine	Sebivo		1	1		2006-11-28	1
19								antivirals for systemic
20								use
21	Varenicline	Champix		1	1		2007-01-24	1
22								other nervous system
23	Acamprosate	Campral		1	1		2007-03-16	1
24								other nervous system
25	Dasatinib	Sprycell	1		1	1	2007-03-26	1
26	Posaconazole	Spriafil	1			1	2007-03-26	1
27		(Posanol)						antimycotics for systemic
28	Micafungin	Mycamine		1	1		2007-05-22	1
29								use
30	Sitaxentan	Thelin		1	1		2007-05-30	1
31								antihypertensives
32	Idursulfase	Elaprase		1		1	2007-06-13	1
33								other alimentary tract
34								and metabolism products
35	Oxaliplatin	Eloxatin		1		1	2007-06-15	1
36								antineoplastic agents
37	Ranibizumab	Lucentis	1			1	2007-06-26	1
38								ophthalmologicals
39	Fluticasone	Avamys		1	1		2007-08-14	1
40								drugs for obstructive
41								airway diseases
42	Aprepitant	Emend		1	1		2007-08-24	1
43								antiemetics and
44								antinauseants

1								
2								
3	Maraviroc	Celsentri	1	1	2007-09-21	1		antivirals for systemic
4								use
5	Daptomycin	Cubicin	1	1	2007-09-24	1		antibacterials for
6								systemic use
7	Paliperidone	Invega	1	1	2007-09-26	1		psycholeptics
8	Duloxetine	Cymbalta	1	1	2007-11-01	1		psychoanaleptics
9	Nesiritide	Natrecor	1	1	2007-11-08		1	cardiac therapy
10	Aliskiren	Rasilez	1	1	2007-11-14	1		agents acting on the
11								renin-angiotensin system
12								
13								
14	Anidulafungin	Eraxis	1	1	2007-11-14	1		antimycotics for systemic
15								use
16	Raltegravir	Isentress	1	1	2007-11-27	1		antivirals for systemic
17								use
18	Rivastigmine	Exelon patch	1	1	2007-11-29	1		psychoanaleptics
19	Sitagliptin	Januvia	1	1	2007-12-14	1		drugs used in diabetes
20	Temsirolimus	Torisel	1	1	2007-12-21	1		antineoplastic agents
21	Lenalidomide	Revlimid	1	1	2008-01-17	1		immunosuppressants
22	Ambrisentan	Volibris	1	1	2008-03-20	1		antihypertensives
23	Etravirine	Intelence	1	1	2008-03-27	1		antivirals for systemic
24								use
25	Methylnaltrexon	Relistor	1	1	2008-03-28	1		drugs for constipation
26								
27	e							
28	Panitumumab	Vectibix	1	1	2008-04-03		1	antineoplastic agents
29	Nepafenac	Nevanac	1	1	2008-04-17	1		ophthalmologicals
30	Dabigatran	Pradaxa	1	1	2008-06-10	1		antithrombotic agents
31	Ceftobiprole	Zeftera	1	1	2008-06-26	1		antibacterials for
32								systemic use
33	Idebenone	Catena	1	1	2008-07-23	1		psychoanaleptics
34	Nilotinib	Tasigna	1	1	2008-09-09	1		antineoplastic agents
35	Rivaroxaban	Xarelto	1	1	2008-09-15	1		antithrombotic agents
36								
37								
38								
39								
40								
41								
42								
43								
44								
45								
46								
47								

1								
2								
3	Olmesartan	Olmotec	1	1		2008-10-28	1	agents acting on the
4								renin-angiotensin system
5								
6	Capsular	Synflorix	1	1		2008-12-11		1 vaccines
7	polysaccharide							
8	Ustekinumab	Stelara	1	1		2008-12-12		1 immunosuppressants
9	Loteprednol	Alrex	1	1		2008-12-23	1	ophthalmologicals
10	Eculizumab	Soliris	1		1	2009-01-28		1 immunosuppressants
11	Desvenlafaxine	Pristiq	1	1		2009-02-04	1	psychoanaleptics
12	Lisdexamfetami	Vyvanse	1	1		2009-02-19	1	psychoanaleptics
13	ne							
14	Romiplostim	Nplate	1		1	2009-02-19		1 antihemorrhagics
15	Methyl	Metvix	1	1		2009-02-26	1	antineoplastic agents
16	aminolevulinate							
17	Eplerenone	Inspra	1	1		2009-02-26	1	diuretics
18	Fosaprepitant	Emend IV	1	1		2009-04-01	1	antivirals for systemic
19								use
20	Golimumab	Simponi	1	1		2009-04-07		1 immunosuppressants
21	Lapatinib	Tykerb	1	1		2009-05-15	1	antineoplastic agents
22	Vorinostat	Zolinza	1	1		2009-06-11	1	antineoplastic agents
23	Aripiprazole	Abilify	1	1		2009-07-09	1	psycholeptics
24	Clofarabine	Clolar	1	1		2009-07-16	1	antineoplastic agents
25	Dronedarone	Multaq	1		1	2009-08-11	1	cardiac therapy
26	Certolizumab	Cimzia	1	1		2009-08-12		1 immunosuppressants
27	Doripenem	Doribax	1	1		2009-09-02	1	antibacterials for
28								systemic use
29	Aztreonam	Cayston	1		1	2009-09-11	1	antibacterials for
30								systemic use
31	Saxagliptin	Onglyza	1	1		2009-09-14	1	drugs used in diabetes
32	Besifloxacin	Besivance	1	1		2009-10-23	1	ophthalmologicals
33	Azacitidine	Vidaza	1		1	2009-10-23	1	antineoplastic agents
34								
35								
36								
37								
38								
39								
40								
41								
42								
43								
44								
45								
46								
47								

1								
2								
3	Japanese	Ixiaro	1	1	2009-10-29		1	vaccines
4	encephalitis							
5	vaccine							
6	Alitretinoin	Toctino	1	1	2009-11-13		1	antineoplastic agents
7	Degarelix	Firmagon	1	1	2009-11-16		1	endocrine therapy
8	Dexmedetomidine	Precedex	1	1	2009-12-09		1	psycholeptics
9	Everolimus	Afinitor	1	1	2009-12-14	1	1	antineoplastic agents
10	Thrombin alfa	Recothrom	1	1	2009-12-15		1	antihemorrhagics
11	Pneumococcal conjugate	Prevnar	1		2009-12-21	1	1	vaccines
12	Gadoxetate	Primovist	1	1	2010-01-14		1	contrast media
13	Recombinant human papillomavirus	Cervarix	1	1	2010-02-03		1	vaccines
14	Canakinumab	Ilaris	1		2010-02-26		1	immunosuppressants
15	Prasugrel	Effient	1	1	2010-04-16		1	antithrombotic agents
16	Tocilizumab	Actemra	1	1	2010-04-30		1	immunosuppressants
17	Sapropterin	Kuvan	1		2010-04-30	1	1	other alimentary tract and metabolism products
18	Trabectedin	Yondelis	1	1	2010-05-13		1	antineoplastic agents
19	Liraglutide	Victoza - 1.2 mg pen-injector	1	1	2010-05-21		1	drugs used in diabetes
20	Meningococcal oligosaccharides conjugated	Menveo	1	1	2010-05-21		1	vaccines
21	Pazopanib	Votrient	1	1	2010-05-27		1	antineoplastic agents
22	Paliperidone	Invega sustenna	1	1	2010-06-30		1	psycholeptics
23	Sevelamer	Renvela	1	1	2010-07-07		1	all other therapeutic products
24	Dexlansoprazole	Dexilant	1	1	2010-07-22		1	drugs for acid related disorders
25								
26								
27								
28								
29								
30								
31								
32								
33								
34								
35								
36								
37								
38								
39								
40								
41								
42								
43								
44								
45								
46								
47								

1								
2								
3	Denosumab	Prolia	1	1	2010-08-06		1	drugs for treatment of
4								bone disease
5	Febuxostat	Uloric	1	1	2010-09-22		1	antigout preparations
6	Lacosamide	Vimpat	1	1	2010-09-30		1	antiepileptics
7	Velaglucerase alf.	VPRIV	1	1	2010-10-01		1	other alimentary tract
8								and metabolism products
9								
10								
11	Roflumilast	Daxas	1	1	2010-11-23		1	drugs for obstructive
12								airway diseases
13	Tapentadol	Nucynta CR	1	1	2010-12-02		1	analgesics
14	Sildenafil	Rapaflo	1	1	2011-01-11		1	urologicals
15	Eltrombopag	Revolade	1	1	2011-01-12		1	antihemorrhagics
16	Exenatide	Byetta	1	1	2011-01-13		1	drugs used in diabetes
17	Fingolimod	Gilenya	1	1	2011-03-09		1	immunosuppressants
18	Ticagrelor	Brilinta	1	1	2011-05-30		1	antithrombotic agents
19	Cabazitaxel	Jevtana	1	1	2011-06-16		1	antineoplastic agents
20	Rufinamide	Banzel	1	1	2011-06-22		1	antiepileptics
21	Belimumab	Benlysta	1	1	2011-07-06		1	immunosuppressants
22	Rilpivirine	Edurant	1	1	2011-07-21		1	antivirals for systemic
23								use
24	Tolvaptan	Samsca	1	1	2011-07-25		1	diuretics
25	Abiraterone	Zytiga	1	1	2011-07-27		1	endocrine therapy
26	Linagliptin	Trajenta	1	1	2011-07-28		1	drugs used in diabetes
27	Boceprevir	Victrelis	1	1	2011-07-29		1	antivirals for systemic
28								use
29	Boceprevir,	Victrelis Triple	1	1	2011-08-10		1	immunostimulants
30	peginterferon							
31	alfa-2b, ribavirin							
32	Telaprevir	Incivek	1	1	2011-08-16		1	antivirals for systemic
33								use
34	Colesevelam	Lodalis	1	1	2011-09-22		1	lipid modifying agents
35	Senapine	Saphris	1	1	2011-10-07		1	psycholeptics
36								
37								
38								
39								
40								
41								
42								
43								
44								
45								
46								
47								

1							
2							
3	Dienogest	Visanne	1	1	2011-10-12	1	sex hormones and
4							modulators of the genital
5							svstem
6	Indacaterol	Onbrez	1	1	2011-12-06	1	drugs for obstructive
7		breezhaler					airway diseases
8	Prucalopride	Resotran	1	1	2011-12-07	1	drugs for constipation
9	Plerixafor	Mozobil	1	1	2011-12-08	1	immunostimulants
10	Eribulin	Halaven	1	1	2011-12-14	1	antineoplastic agents
11	Apixaban	Eliquis	1	1	2011-12-16	1	antithrombotic agents
12	Vandetanib	Caprelsa	1	1	2012-01-12	1	antineoplastic agents
13	Ipilimumab	Yervoy	1	1	2012-02-01		1 antineoplastic agents
14	Fesoterodine	Toviaz	1	1	2012-02-09	1	urologicals
15	Fampridine	Fampyra	1	1	2012-02-10	1	other nervous system
16	Vemurafenib	Zelboraf	1	1	2012-02-15		antineoplastic agents
17	Azilsartan	Edarbi	1	1	2012-03-08	1	agents acting on the
18							renin-angiotensin system
19	Ofatumumab	Arzerra	1	1	2012-03-09		1 antineoplastic agents
20	Palonosetron	Aloxi	1	1	2012-03-14	1	antiemetics and
21							antinauseants
22	Crizotinib	Xalkori	1	1	1 2012-04-25	1	antineoplastic agents
23	Fidaxomicin	Dificid	1	1	2012-06-07	1	antidiarrheals, intestinal
24							antiinflammatory/antiinf
25							ective agents
26	Lurasidone	Latuda	1	1	2012-06-13	1	psycholeptics
27	Ruxolitinib	Jakavi	1	1	2012-06-19	1	antineoplastic agents
28	Collagenase	Xiaflex	1	1	2012-07-05		1 other drugs for disorders
29	clostridium						of the musculo-skeletal
30	histolviticum						svstem
31	Axitinib	Inlyta	1	1	2012-07-12	1	antineoplastic agents
32	Catridecacog	Tretten	1	1	2012-07-19		1 antihemorrhagics
33	Bendamustine	Treanda	1	1	2012-08-24	1	antineoplastic agents
34	Pirfenidone	Esbriet	1	1	2012-10-01		immunosuppressants
35							
36							
37							
38							
39							
40							
41							
42							
43							
44							
45							
46							
47							

1								
2								
3	Elvitegravir,	Stribild	1	1		2012-11-26	1	antivirals for systemic
4	emtricitabine,							use
5	tenofovir,							
6	cobicistat							
7								
8	Ivacaftor	Kalydeco	1			2012-11-26	1	other respiratory system
9								products
10	Stiripentol	Diacomit	1	1		2012-12-21	1	antiepileptics
11	Nebivolol	Bystolic	1	1		2012-12-21	1	beta blocking agents
12	Ingenol	Picato	1	1		2013-01-30	1	antibiotics and
13								chemotherapeutics for
14								dermatological use
15								antineoplastic agents
16	Brentuximab	Adcetris	1	1	1	2013-02-01	1	
17	Meningococcal	Nimenrix	1	1		2013-03-05	1	vaccines
18	polysaccharide							
19	groups A,C,W-							
20	135 & Y							
21	conjugate							
22	vaccine, Tetanus							
23	toxoid							
24	Mirabegron	Myrbetriq	1	1		2013-03-06	1	urologicals
25	Regorafenib	Stivarga	1		1	2013-03-11	1	antineoplastic agents
26	Rotigotine	Neupro	1	1		2013-03-21	1	anti-parkinson drugs
27	Dimethyl	Tecfidera	1	1		2013-04-03	1	other nervous system
28	Perampanel	Fycompa	1	1		2013-04-04	1	antiepileptics
29	Pertuzumab	Perjeta	1		1	2013-04-12	1	antineoplastic agents
30	Enzalutamide	Xtandi	1		1	2013-05-29	1	endocrine therapy
31	Ulipristal	Fibristal	1	1		2013-06-24	1	sex hormones and
32								modulators of the genital
33								system
34	Vismodegib	Erivedge	1	1		2013-07-12	1	antineoplastic agents
35	Dabrafenib	Tafinlar	1	1		2013-07-16	1	antineoplastic agents
36	Trametinib	Mekinist	1	1		2013-07-18	1	antineoplastic agents
37								
38								
39								
40								
41								
42								
43								
44								
45								
46								
47								

1							
2							
3	Fluticasone and vilatnerol	Breo ellipta	1	1	2013-07-23	1	drugs for obstructive airway diseases
4							
5	Aclidinium	Tudorza genuair	1	1	2013-07-29	1	drugs for obstructive airway diseases
6							
7	Rifaximin	Zaxine	1	1	2013-08-13	1	antidiarrheals, intestinal antiinflammatory/antiinf
8							
9							
10							
11	Ocriplasmin	Jetrea	1	1	2013-08-13	1	effective agents ophthalmologicals
12	Trastuzumab	Kadcyla	1	1	2013-09-11	1	antineoplastic agents
13	emtansine						
14	Galsulfase	Naglazyme	1	1	2013-09-16	1	other alimentary tract and metabolism products
15							
16							
17	Riociguat	Adempas	1	1	2013-09-19	1	antihypertensives
18	Pasireotide	Signifor	1	1	2013-09-23	1	pituitary and hypothalamic hormones
19							
20							
21	Efinaconazole	Jublia	1	1	2013-10-02	1	drugs used in diabetes
22	Romidepsin	Istodax	1	1	2013-10-16	1	antineoplastic agents
23	Dolutegravir	Tivicay	1	1	2013-10-31	1	antivirals for systemic use
24							
25	Afatinib	Giotrif	1	1	2013-11-01	1	antineoplastic agents
26	Macitentan	Opsumit	1	1	2013-11-06	1	antihypertensives
27	Aflibercept	Eylea	1	1	2013-11-08	1	antineoplastic agents
28	Teriflunomide	Aubagio	1	1	2013-11-14	1	immunosuppressants
29	Simeprevir	Galexos	1	1	2013-11-18	1	antivirals for systemic use
30							
31	Alogliptin	Nesina	1	1	2013-11-27	1	drugs used in diabetes
32							
33	Linacotide	Constella	1	1	2013-12-02	1	drugs for constipation
34							
35	Multicomponent meningococcal B vaccine	Bexsero	1	1	2013-12-06	1	vaccines
36							
37	Radium-223 dichloride	Xofigo	1	1	2013-12-12	1	therapeutic radiopharmaceuticals
38							
39							
40							
41							
42							
43							
44							
45							
46							
47							

1								
2								
3	Sofosbuvir	Sovaldi	1		1	2013-12-13	1	antivirals for systemic use
4								
5	Umeclidinium	Anoro ellipta		1	1	2013-12-23	1	drugs for obstructive airway diseases
6	and vilanterol							
7	Pomalidomide	Pomalyst	1		1	2014-01-20	1	immunosuppressants
8	Lomitapide	Juxtapid		1	1	2014-02-04	1	lipid modifying agents
9	Aflibercept	Zaltrap		1	1	2014-02-12		1 antineoplastic agents
10	Bosutinibs	Bosulif		1	1	1 2014-03-14	1	antineoplastic agents
11	Recombinant	Alprolix		1	1	2014-03-20		1 antihemorrhagics
12	human							
13	coagulation							
14	Factor IX, FC							
15	fusion protein							
16	Tofacitinib	Xeljanz		1	1	2014-04-17	1	immunosuppressants
17	Tesamorelin	Egrifta		1	1	2014-04-29	1	pituitary and hypothalamic hormones
18								
19	Canagliflozin	Invokana		1	1	2014-05-23	1	drugs used in diabetes
20	Taliglucerase	Elelyso		1	1	2014-05-29		1 other alimentary tract and metabolism products
21	Alfa							
22	Eslicarbazepine	Aptiom		1	1	2014-07-08	1	antiepileptics
23	Antihemophilic	Eloctate		1	1	2014-08-22		1 antihemorrhagics
24	factor, FC fusion							
25	protein							
26	Ledipasvir and	Harvoni		1	1	2014-10-15	1	antivirals for systemic use
27	sofosbuvir							
28	Vortioxetine	Trintellix		1	1	2014-10-22	1	psychoanaleptics
29	Simoctocog alfa	Nuwiq		1	1	2014-10-23		1 antihemorrhagics
30	Azelastine and	Dymista		1	1	2014-10-23	1	nasal preparations
31	fluticasone							
32	Conjugated	Duavive		1	1	2014-10-23	1	sex hormones and modulators of the genital system
33	estrogens and							
34	bazedoxifene							
35	acetate							
36								
37								
38								
39								
40								
41								
42								
43								
44								
45								
46								
47								

For peer review only

1										
2										
3	Apremilast	Otezla		1	1		2014-11-12	1	immunosuppressants	
4	Ibrutinib	Imbruvica	1			1	1	2014-11-17	1	antineoplastic agents
5	Obinutuzumab	Gazyva	1		1			2014-11-25	1	antineoplastic agents
6	Siltuximab	Sylvant		1		1		2014-12-03	1	immunosuppressants
7	Dapagliflozin	Forxiga		1	1			2014-12-12	1	drugs used in diabetes
8	Ritonavir,	Holkira Pak		1		1		2014-12-22	1	antivirals for systemic
9	paritaprevir,									use
10	ombitasvir,									
11	dasabuvir									
12	Sodium	Pheburane		1		1		2015-01-26	1	other alimentary tract
13	phenylbutyrate									and metabolism products
14										
15	Vedolizumab	Entyvio		1	1			2015-01-29	1	immunosuppressants
16	Human	Gardasil 9		1	1			2015-02-05	1	vaccines
17	papillomavirus 9									
18	valent vaccine,									
19	recombinant									
20	Deferiprone	Ferriprox		1	1			2015-02-13	1	all other therapeutic
21										products
22	Secukinumab	Cosentyx		1	1			2015-02-27	1	immunosuppressants
23	Tedizolid	Sivextro		1	1			2015-03-17	1	antibacterials for
24										systemic use
25	Idelalisib	Zydelig		1	1		1	2015-03-27	1	antineoplastic agents
26	Ceritinib	Zykadia		1	1		1	2015-03-27	1	antineoplastic agents
27	Ponatinib	Iclusig		1	1		1	2015-04-02	1	antineoplastic agents
28	Carglumic Acid	Carbaglu	1			1		2015-04-10	1	other alimentary tract
29										and metabolism products
30										
31	Ivermectin	Rosiver		1	1			2015-04-22	1	anthelmintics
32	Levomilnacipran	Fetzima		1	1			2015-05-08	1	psychoanaleptics
33	Pembrolizumab	Keytruda		1	1		1	2015-05-19	1	antineoplastic agents
34	Naloxegol	Movantik		1	1			2015-06-02	1	drugs for constipation
35	Nintedanib	Ofev		1	1			2015-06-25	1	antineoplastic agents
36										
37										
38										
39										
40										
41										
42										
43										
44										
45										
46										
47										

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

For peer review only

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 svstem
Daclatasvir	Daklinza		1	1		2015-08-13	1	1	antivirals for systemic use
Asfotase Alfa	Strensiq	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 Emrifiumate	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	Blinicyto		1	1		2015-12-22		1	antineoplastic agents
Carfilzomib	Kyprolis		1		1	2016-01-15	1		antineoplastic agents

1								
2								
3	Elbasvir,	Zepatier	1	1	2016-01-19	1		antivirals for systemic
4	Grazoprevir							use
5	Selexipag	Uptravi	1	1	2016-01-20	1		antithrombotic agents
6	Ivacaftor,	Orkambi	1	1	2016-01-26	1		other respiratory system
7	Lumacaftor							products
8	Sugammadex	Bridion	1	1	2016-02-05	1		all other therapeutic
9								products
10								antineoplastic agents
11	Cobimetinib	Cotellic	1	1	2016-02-22	1		antiepileptics
12	Brivaracetam	Brivlera	1	1	2016-03-09	1		antivirals for systemic
13	Asunaprevir	Sunvepra	1	1	2016-03-09	1		use
14								antineoplastic agents
15	Palbociclib	Ibrance	1	1	2016-03-16	1	1	lipid modifying agents
16	Alirocumab	Praluent	1	1	2016-04-11			antihistamines for
17	Bilastine	Blexten	1	1	2016-04-21	1		systemic use
18								all other therapeutic
19	Idarucizumab	Praxbind	1	1	2016-04-29		1	products
20								antineoplastic agents
21	Olaparib	Lynparza	1	1	2016-04-29	1		immunosuppressants
22	Ixekizumab	Taltz	1	1	2016-05-25		1	antineoplastic agents
23	Osimertinib	Tagrisso	1	1	2016-07-05	1		antivirals for systemic
24	Sofosbuvir +	Epclusa	1	1	2016-07-11	1		use
25	Velpatasvir							antineoplastic agents
26	Ixazomib	Ninlaro	1	1	2016-08-04	1		other alimentary tract
27	Nitisinone	MDK-Nitisinone	1	1	2016-09-20	1		and metabolism products
28								
29								
30	Venetoclax	Venclexta	1	1	2016-09-30	1		antineoplastic agents
31	Edoxaban	Lixiana	1	1	2016-11-04	1		antithrombotic agents
32	Nitisinone	Nitisinone	1	1	2016-11-04	1		other alimentary tract
33								and metabolism products
34								
35								
36								
37								
38	Daclizumab beta	Zinbryta	1	1	2016-12-08		1	immunosuppressants
39								
40								
41								
42								
43								
44								
45								
46								
47								

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

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)**

For peer review only

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

1						
2						
3	Reviparin	Clivarine	1		1996-09-10	antithrombotic agents
4	Diphtheria, tetanus &	Infanrix		1	1996-12-17	vaccines
5	acellular pertussis					
6	vaccine					
7	Cisatracurium	Nimbex injectior	1		1996-12-18	muscle relaxants
8	Remifentanil	Ultiva injection	1		1996-12-24	anesthetics
9	Tiludronate	Skelid	1		1997-02-06	drugs for treatment of bone
10						disease
11	Tazarotene	Tazorac Gel	1		1997-02-25	antipsoriatics
12	Praziquantel	Biltricide	1		1997-03-07	anthelmintics
13	Molgramostim	Leucomax		1	1997-03-10	immunostimulants
14	Fosphenytoin	Cerebyx injectioi	1		1997-03-20	antiepileptics
15	Butenafine	Dr. Scholl's athle	1		1997-04-15	antifungals for dermatological
16						use
17	Troglitazone	Rezulin		1	1997-05-09	drugs used in diabetes
18	Trandolapril	Odrik	1		1997-05-15	agents acting on the renin-
19						angiotensin system
20	Follitropin alpha	Gonal-F	1		1997-06-06	sex hormones and modulators
21						of the genital system
22	Kit for preparation	Myoscint	1		1997-07-02	diagnostic radiopharmaceuticals
23	of indium in 111					
24	imciromab					
25	pentetate					
26	Cytomegalovirus	Cytogam	1		1997-08-01	immune sera and
27	immune globulin					immunoglobulins
28	Oxiconazole	Oxizole	1		1997-08-08	antifungals for dermatological
29						use
30	Respiratory	Respigam		1	1997-08-20	immune sera and
31	syncytial virus					immunoglobulins
32	immune globulin					
33	Arcitumomab	CEA-Scan	1		1997-09-16	diagnostic radiopharmaceuticals
34						
35						
36						
37						
38						
39						
40						
41						
42						
43						
44						
45						
46						
47						

1						
2						
3	Olopatadine	Patanol	1	1997-09-16		ophthalmologicals
4						
5	Pegaspargase	Oncaspar	1	1997-11-19		antineoplastic agents
6						
7	Anagrelide as hydrochloride	Agrylin	1	1997-11-19		antineoplastic agents
8						
9	Nadroparin	Fraxiparine	1	1997-11-27		antithrombotic agents
10	Bicisate	OncoScint	1	1998-01-16		diagnostic radiopharmaceuticals
11						
12	Gadolinium (III)	Gadolite	1	1998-04-08		contrast media
13	Lexidronam	Quadramet	1	1998-06-22		therapeutic radiopharmaceuticals
14						
15	Miglitol	Glyset	1	1998-07-22		drugs used in diabetes
16						
17	Lipoprotein-OspA antigen	Lymerix	1	1998-12-02		vaccines
18						
19	recombinant					
20	Toremifene	Fareston	1	1998-12-14		endocrine therapy
21						
22	Cefdinir	Omnicef	1	1999-02-05		antibacterials for systemic use
23						
24	Methacholine	Methacoline	1	1999-02-25		diagnostic agents
25						
26	Fosfomycin	Monurol	1	1999-04-12		antibacterials for systemic use
27						
28	Alitretinoin	Panretin	1	1999-06-11		other dermatological preparations
29						
30	Ioxilan	Oxilan	1	1999-10-05		contrast media
31						
32	Mangafodipir	Teslascan	1	2000-02-09	1	contrast media
33						
34	Sevelamer	Renagel	1	2000-02-24	1	all other therapeutic products
35						
36	Valrubicin	Valstar	1	2000-07-04	1	antineoplastic agents
37						
38	Ibutilide	Corvert injection	1	2000-07-14	1	cardiac therapy
39						
40	Fomepizole	Antizol	1	2000-11-30	1	all other therapeutic products
41						
42	Amlexanox	Apthera	1	2000-12-11	1	stomatological preparations
43						
44	Tegafur/uracil and leucovorin calcium	Orzel	1	2001-04-06	1	antineoplastic agents
45						
46	Argatroban	Argatroban	1	2001-06-04	1	antithrombotic agents
47						

1							
2							
3	Aminolevulinic acid	Levulan	1		2001-06-20	1	antineoplastic agents
4	Infliximab	Remicade		1	2001-09-27		1 immunosuppressants
5							
6	Levobupivacaine	Chirocaine	1		2002-03-20	1	anesthetics
7	Unoprostone	Rescula	1		2002-04-03	1	ophthalmologicals
8	isopropyl						
9	Thyrotropin	Thyrogen	1		2002-05-31		1 diagnostic agents
10	Anti-thymocyte	Thymoglobulin	1		2002-11-20		1 immunosuppressants
11	globulin						
12	Dextromethylpheni	Attenade	1		2003-08-12	1	psychoanaleptics
13	date						
14	Sulfur Hexafluoride	Sonovue	1		2004-02-12	1	contrast media
15	Yttrium-90	Yttrium-90		1	2004-12-02		1 therapeutic
16							radiopharmaceuticals
17	Choriogonadotropin	Ovidrel	1		2004-12-16		1 sex hormones and modulators
18	Alfa						of the genital system
19	Sulesomab	Leukoscan	1		2005-01-17		1 diagnostic radiopharmaceuticals
20							
21	Tositumomab	Bexxar		1	2005-08-18		1 therapeutic
22							radiopharmaceuticals
23	Nitric oxide	Inomax		1	2005-09-23	1	other respiratory system
24							products
25	F-	Cantrace		1	2006-07-27		1 diagnostic radiopharmaceuticals
26	Fluorodeoxyglucose						
27	Lumiracoxib	Prexige	1		2006-11-02	1	antiinflammatory and
28							antirheumatic products
29	Nelarabine	Atriance		1	2007-09-22	1	antineoplastic agents
30	Rotavirus vaccine	Rotarix	1		2007-10-09		1 vaccines
31							
32	Retapamulin	Altargo	1		2008-03-19	1	antibiotics and
33							chemotherapeutics for
34							dermatological use
35							
36							
37							
38							
39							
40							
41							
42							
43							
44							
45							
46							
47							

1							
2							
3	Methoxy	Mircera	1	2008-03-31		1	antianemic preparations
4	Polyethylene glycol-						
5	epoetin beta						
6	Telavancin	Vibativ	1	2009-09-29	1		antibacterials for systemic use
7	Human C1 esterase	Berinert	1	2010-05-31		1	other hematological agents
8	inhibitor						
9	Influenza vaccine	Flumist	1	2010-06-22		1	vaccines
10	Zucapsaicin	Civanex (Zuacta	1	2010-07-15	1		topical products for joint and
11							muscular pain
12							
13	Clevidipine	Cleviprex	1	2011-04-15	1		calcium channel blockers
14	Rubidium chloride rb	Ruby-fill		2011-09-20		1	diagnostic radiopharmaceuticals
15	82		1				
16	Doxycycline	Efracea	1	2011-11-14	1		antibacterials for systemic use
17	Ferumoxytol	Feraheme	1	2011-12-08	1		antianemic preparations
18	Remestemcel-L	Prochymal		2012-05-17		1	unassigned
19	Ezogabine	Potiga	1	2012-10-08	1		antiepileptics
20	Haemagglutinin-	Arepranrix H5N1	1	2013-02-13		1	vaccines
21	Strain A						
22	Olodaterol	Striverdi respim:	1	2013-06-11	1		drugs for obstructive airway
23							diseases
24	Difluprednate	Durezol	1	2013-11-04	1		corticosteroids, dermatological
25							preparations
26	Tafluprost	Saflutan	1	2014-05-26	1		ophthalmologicals
27	Elosulfase Alfa	Vimizim		2014-07-02		1	other alimentary tract and
28			1				metabolism products
29	Turoctocog alfa	Zonovate	1	2014-12-08		1	antihemorrhagics
30	Bromfenac	Prolensa	1	2015-03-26	1		ophthalmologicals
31	Albiglutide	Eperzan	1	2015-07-15		1	drugs used in diabetes
32	Vilazodone	Viibryd	1	2015-07-16	1		psychoanaleptics
33	Polidocanol	Varithena	1	2015-08-04	1		vasoprotectives
34	Peginterferon Beta-	Plegridy	1	2015-08-10		1	immunostimulants
35	1A						
36							
37							
38							
39							
40							
41							
42							
43							
44							
45							
46							
47							

1							
2							
3	Antihemophilic	Obizur	1		2015-10-14	1	antihemorrhagics
4	Factor						
5	(Recombinant)						
6	Porcine Sequence						
7	Lubiprostone	Amitiza	1		2015-10-14	1	drugs for constipation
8	Albutrepenonacog	Idelvion	1		2016-01-26	1	antihemorrhagics
9	Alfa						
10	Finafloxacin	Xtoro	1		2016-03-11	1	otologicals
11	Glycerol	Ravicti		1	2016-03-16	1	other alimentary tract and
12	Phenylbutyrate						metabolism products
13	Vorapaxar	Zontivity	1		2016-05-13	1	antithrombotic agents
14	Elotuzumab	Empliciti		1	2016-06-21	1	antineoplastic agents
15	Daratumumab	Darzalex		1	2016-06-29	1	antineoplastic agents
16	Rupatadine	Rupall	1		2016-07-20	1	antihistamines for systemic use
17							
18	Reslizumab	Cinqair	1		2016-07-20	1	drugs for obstructive airway
19							diseases
20	Bepotastine	Bepreve	1		2016-07-27	1	antihistamines for systemic use
21							
22	Alectinib	Alecensaro		1	2016-09-29	1	antineoplastic agents
23	Antihemophilic	Adynovate	1		2016-11-17	1	antihemorrhagics
24	Factor						
25	(Recombinant),						
26	PFGvlated						
27	Gadoterate	Dotarem	1		2016-11-25	1	contrast media
28	Meglumine						
29	Botulinium antitoxin	BAT	1		2016-12-08	1	immune sera and
30	serotypes A, B,C, D,						immunoglobulins
31	E, F and G						
32	Lonococog Alfa	Afstyla	1		2016-12-12	1	antihemorrhagics
33							
34							
35							
36							
37							
38							
39							
40							
41							
42							
43							
44							
45							
46							
47							

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	Title, 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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	Methods, pages 6, 7
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —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

1			(c) Explain how missing data were addressed	Not relevant
2			(d) <i>Cohort study</i> —If applicable, explain how loss to follow-	Not relevant
3			up was addressed	
4			<i>Case-control study</i> —If applicable, explain how matching of	
5			cases and controls was addressed	
6			<i>Cross-sectional study</i> —If applicable, describe analytical	
7			methods taking account of sampling strategy	
8			(e) Describe any sensitivity analyses	Not relevant
9				
10				
11				
12				
13	Results			
14	Participants	13*	(a) Report numbers of individuals at each stage of study—eg	Results, pages 10-12
15			numbers potentially eligible, examined for eligibility,	
16			confirmed eligible, included in the study, completing follow-	
17			up, and analysed	
18			(b) Give reasons for non-participation at each stage	
19			(c) Consider use of a flow diagram	Not relevant
20				
21	Descriptive data	14*	(a) Give characteristics of study participants (eg	Not relevant
22			demographic, clinical, social) and information on exposures	
23			and potential confounders	
24			(b) Indicate number of participants with missing data for	Results, page 13
25			each variable of interest	
26			(c) <i>Cohort study</i> —Summarise follow-up time (eg, average	Not relevant
27			and total amount)	
28				
29	Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or	Results, pages 11-15
30			summary measures over time	
31			<i>Case-control study</i> —Report numbers in each exposure	
32			category, or summary measures of exposure	
33			<i>Cross-sectional study</i> —Report numbers of outcome events	
34			or summary measures	
35				
36	Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-	
37			adjusted estimates and their precision (eg, 95% confidence	
38			interval). Make clear which confounders were adjusted for	
39			and why they were included	
40			(b) Report category boundaries when continuous variables	Not relevant
41			were categorized	
42			(c) If relevant, consider translating estimates of relative risk	Not relevant
43			into absolute risk for a meaningful time period	
44				
45	Other analyses	17	Report other analyses done—eg analyses of subgroups and	Not relevant
46			interactions, and sensitivity analyses	
47				
48				
49	Discussion			
50	Key results	18	Summarise key results with reference to study objectives	Discussion, page 16
51	Limitations	19	Discuss limitations of the study, taking into account sources of	Limitations, page 19
52			potential bias or imprecision. Discuss both direction and	
53			magnitude of any potential bias	
54				
55	Interpretation	20	Give a cautious overall interpretation of results considering	Conclusion, page 19
56			objectives, limitations, multiplicity of analyses, results from	
57			similar studies, and other relevant evidence	
58				
59				
60				

1			
2	Generalisability	21	Discuss the generalisability (external validity) of the study
3			results
4	<hr/>		

5 **Other information**

6	Funding	22	Give the source of funding and the role of the funders for the	Page 20
7			present study and, if applicable, for the original study on which	
8			the present article is based	

9

10 *Give information separately for cases and controls in case-control studies and, if applicable, for exposed and

11 unexposed groups in cohort and cross-sectional studies.

12

13

14 **Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and

15 published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely

16 available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at

17 <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is

18 available at www.strobe-statement.org.

19

20

21

22

23

24

25

26

27

28

29

30

31

32

33

34

35

36

37

38

39

40

41

42

43

44

45

46

47

48

49

50

51

52

53

54

55

56

57

58

59

60

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-023605.R2
Article Type:	Research
Date Submitted by the Author:	19-Jul-2018
Complete List of Authors:	Lexchin, Joel; York University, School of Health Policy & Management
Primary Subject Heading:	Health policy
Secondary Subject Heading:	Health services research, Pharmacology and therapeutics
Keywords:	Health policy < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, accelerated approvals, Health Canada, therapeutic evaluation, therapeutic groups

SCHOLARONE™
Manuscripts

Only

1
2
3 **1 Health Canada's use of expedited review pathways and therapeutic innovation, 1995-**
4
5 **2 2016: cross sectional analysis**
6

7
8 3 Joel Lexchin MSc, MD^{1,2,3}
9

10 4 ¹Professor Emeritus

11
12 5 School of Health Policy and Management

13
14 6 York University

15
16 7 ²Emergency Physician

17
18 8 University Health Network

19
20 9 ³Associate Professor

21
22 10 Faculty of Medicine

23
24 11 University of Toronto

25
26 12

27
28 13 Correspondence:

29
30 14 Joel Lexchin MD

31
32 15 School of Health Policy and Management

33
34 16 York University

35
36 17 4700 Keele St.

37
38 18 Toronto, ON M3J 1P3

39
40 19 Tel: 416-964-7186

41
42 20 Email: jlexchin@yorku.ca

43
44 21 ORCID ID: 0000-0001-5120-8029

45
46 22 **Key words:**

47
48 23 expedited approvals, Health Canada, health policy, therapeutic evaluation, therapeutic group

49
50 24 **Word count:**

51
52 25 3077

1
2
3 26 **Structured summary**
4

5 27 **Objectives**
6
7

8 28 This study examines the use of expedited approval pathways by Health Canada over the
9
10 29 period 1995 to 2016 inclusive and the relationship between the use of these pathways and the
11
12 30 therapeutic gain offered by new products.
13
14

15 31 **Design**
16
17

18 32 Cross sectional study.
19
20
21

22 33 **Data sources**
23
24

25 34 Therapeutic Products Directorate, Biologics and Genetic Therapies Directorate, Notice of
26
27 35 Compliance database, Notice of Compliance with conditions web site, Patented Medicine
28
29 36 Prices Review Board, La revue Prescrire, World Health Organization (WHO) Anatomical
30
31 37 Therapeutic Chemical (ATC) classification system.
32
33
34

35 38 **Interventions**
36
37

38 39 None
39
40
41

42 40 **Primary and secondary outcomes**
43
44

45 41 Percent of new drugs evaluated by Health Canada that went through an expedited pathway
46
47 42 between 1995 and 2016 inclusive. Kappa values comparing the review status to assessments
48
49 43 of therapeutic value for individual drugs.
50
51

52 44 **Results**
53
54
55
56
57
58
59
60

1
2
3 45 Of 623 drugs approved by Health Canada between 1995 and 2016, 438 (70.3%) drugs went
4
5 46 through the standard pathway, 185 (29.7%) an expedited pathway. Therapeutic evaluations
6
7 47 were available for 509 drugs. Health Canada used an expedited approval pathway for 159 of
8
9 48 the 509 drugs whereas only 55 were judged to be therapeutically innovative. Forty-two of the
10
11 49 55 therapeutically innovative drugs received an expedited review and 13 received a standard
12
13 50 review. The Kappa value for the entire period for all 509 drugs was 0.276 (95% CI 0.194,
14
15 51 0.359) indicating “fair” agreement between Health Canada’s use of expedited pathways and
16
17 52 independent evaluations of therapeutic innovation.
18
19
20

21 **Conclusion**

22
23
24 54 Health Canada’s use of expedited approvals was stable over the entire time period. It was
25
26 55 unable to reliably predict which drugs will offer major therapeutic gains. The findings in this
27
28 56 study should provoke a discussion about whether Health Canada should continue to use these
29
30 57 pathways and if so how their use can be improved.
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58

1
2
3 59 **Article Summary**
4

5 60 *Strengths and limitations of this study*
6

- 7 61 • Cross sectional analysis of the use of expedited approval pathways by Health Canada
8
9 62 over an extended period of time.
10
11 63 • Comparison of use of expedited approval pathways to independent assessment of
12
13 64 therapeutic evaluation.
14
15 65 • Analysis of approvals and therapeutic value of therapeutic subgroups.
16
17
18 66 • Twenty percent of new drugs approved did not have therapeutic evaluations.
19

20 67
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 68 • **Acknowledgements**
4

5 69 • None
6

7 70 • **Competing Interests**
8

9 71 • In 2015-2017, Joel Lexchin received payment from two non-profit organizations for
10 being a consultant on a project looking at indication-based prescribing and a second
11 looking at which drugs should be distributed free of charge by general practitioners. In
12 2015, he received payment from a for-profit organization for being on a panel that
13 discussed expanding drug insurance in Canada. He is on the Foundation Board of Health
14 Action International.
15
16
17
18
19
20
21
22

23 77 • **Funding**

24 78 • This research received no specific grant from any funding agency in the public,
25 commercial or not-for profit sectors.
26
27
28

29 80 • **Data sharing statement**

30 81 • Extra data can be accessed via the Dryad data repository at <http://datadryad.org/> with the
31 doi: 10.5061/dryad.0bf6000
32
33
34
35

36 83 • **Contributorship statement**

37 84 • JL came up with the idea for this study, gathered and analyzed the data and wrote the
38 manuscript.
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

86 **Introduction**

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

94

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

105

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

110

1
2
3 111 This current study is a further and more detailed look at how Health Canada uses its
4
5 112 expedited review pathways, by extending previous work in a number of ways. First it covers
6
7 113 a wider time period – 1995 to 2016, inclusive. Second, it looks at the use of both of the
8
9 114 expedited review pathways over this entire time period for the entire sample of drugs as well
10
11 115 as subgroups – small molecule drugs, biologics, and therapies for serious diseases. Third, it
12
13 116 calculates the Kappa values for the entire sample of drugs as well as the subgroups listed
14
15 117 above. These subgroups were chosen because small molecules and biologics have
16
17 118 fundamentally different characteristics and these may influence a decision to use an
18
19 119 expedited review pathway and how accurately Health Canada can predict their therapeutic
20
21 120 value. Similarly, when the treatment is for serious medical conditions, Health Canada may be
22
23 121 more willing to use an expedited review pathway and may be more likely to believe that the
24
25 122 new product will provide a significant therapeutic benefit.
26
27
28
29
30

31 124 **Methods**

32 125 *Data sources*

33 126 All NAS approved from 1995 to 2016 inclusive were documented using the annual reports
34
35 127 from the Therapeutic Products and the Biologics and Genetic Therapies Directorates that are
36
37 128 in charge of reviewing applications for new small molecule drugs and biologics and vaccines,
38
39 129 respectively. (Reports are available by directly contacting the directorates at
40
41 130 publications@hc-sc.gc.ca.) A starting year of 1995 was selected as there are no annual
42
43 131 reports from Health Canada prior to that year. Generic and brand names along with the
44
45 132 specific approval pathway – standard, priority, NOC/c (only from 1998 onwards) – and
46
47 133 whether the product was a small molecule drug or biologic (information available only from
48
49 134 2000 onwards) were manually extracted from the annual reports by the author.
50
51
52
53
54
55
56
57
58
59
60

1
2
3 135 Not all of the drugs with a NOC/c are documented in the annual reports and they were
4
5 136 supplemented using four additional sources: articles by Lexchin⁶ and Law⁷, the Notice of
6
7 137 Compliance database (<http://webprod5.hc-sc.gc.ca/noc-ac/index-eng.jsp>) and the Notice of
8
9 138 Compliance with conditions web site ([http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-
10
11 139 avis/conditions/index-eng.php](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
12
13 140 can receive both a priority and NOC/c review and in this case they were only counted as
14
15 141 receiving a priority review.
16
17

18 142

19 143 *Assessment of therapeutic innovation*

20
21
22 144 The therapeutic value of drugs was assessed using the ratings from the annual reports of the
23
24 145 Canadian Patented Medicine Prices Review Board (PMPRB) ([54
55 159
56
57
58
59
60](http://www.pmprb-
25
26 146 <u>cepmb.gc.ca/english/View.asp?x=91</u>) and Prescrire International, the English language
27
28 147 translation of the French drug bulletin La revue Prescrire⁸. The processes that these two
29
30
31 148 organizations use in arriving at their decisions about therapeutic innovation have been
32
33 149 previously described⁵. For the purpose of this study, products that the PMPRB deemed
34
35 150 breakthrough and substantial improvement were termed “innovative” and products in other
36
37 151 categories were termed “not innovative” (category 3 = moderate, little or no improvement
38
39 152 over existing medicines prior to 2010; slight or no improvement, moderate improvement –
40
41 153 primary and moderate improvement – secondary from 2010 onward). Prescrire uses seven
42
43 154 categories to rate therapeutic innovation. The first two, bravo (major therapeutic innovation
44
45 155 in an area where previously no treatment was available); a real advance (important
46
47 156 therapeutic innovation but has limitations) were defined as a significant therapeutic
48
49
50 157 innovation and the other Prescrire categories (except judgment reserved) were defined as no
51
52 158 therapeutic advance.
53</p></div><div data-bbox=)

1
2
3 160 If both the PMPRB and Prescrire evaluated the drug and the ratings were discordant, i.e., one
4
5 161 said it was not innovative and one said it was, the drug was still considered innovative. Table
6
7 162 1 shows that there is substantial agreement among the definitions used by Health Canada, the
8
9 163 PMPRB and Prescrire in assessing therapeutic innovation. Ratings were current for PMPRB
10
11 164 as of December 31, 2016 (the annual report for 2017 was not available at the time of writing)
12
13 165 and for Prescrire as of February 20, 2018.

166 **Table 1: Criteria used by Health Canada in determination of priority review or Notice**
167 **of Compliance with conditions pathway and by Human Drug Advisory Panel and**
168 **Prescrire in determining innovation status**
169

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

170
171 Adapted from: ⁹
172 *Notice of Compliance with conditions
173

174 *Data analysis*

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

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

177

178 Kappa values were used to compare the review status from Health Canada to the assessments

179 for the same drug from the PMPRB and/or Prescrire for each year and for the 22-year period.

180 Drugs approved through the priority review and NOC/c pathways were analyzed together as a

181 single group. Kappa scores measure whether there is more or less agreement between

182 different evaluations than would be expected by chance. Levels of agreement were graded in

183 accordance with the recommendations of Landis and Koch where < 0 indicates no agreement,

184 $0 - 0.20$ slight agreement, $0.21 - 0.40$ fair agreement, $0.41 - 0.60$ moderate agreement, $0.61 -$

185 0.80 substantial agreement, and $0.81 - 1.0$ almost perfect agreement¹⁰.

186

187 *Subgroup analyses*

188 The number and percent of small molecule drugs and biologics approved through the

189 standard, priority and NOC/c pathways were calculated and compared using the Chi-square

190 statistic. Similarly, the Kappa values were calculated separately for small molecule drugs and

191 biologics.

192

193 All drugs were categorized using the second level of the World Health Organization (WHO)

194 Anatomical Therapeutic Chemical (ATC) classification system¹¹. Drugs in three therapeutic

195 groups – antineoplastic agents (L01), antivirals for systemic use (J05) and immunosuppressants

196 (L04) – were chosen for subgroup analyses because they are primarily used for serious, life-

197 threatening diseases and because there are sufficient numbers in each group to allow for

198 statistical analyses. The number and percent of each subgroup that received an expedited

199 review was calculated and the review status and therapeutic ratings were compared for each

200 drug in each of the subgroups including “all other therapeutic groups” and Kappa values were

201 calculated for each subgroup. Distribution of approval pathways in the subgroups individually

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

205

206 *Patient and public involvement*

207 No patients were involved in any aspect of this study.

208

209 *Ethics*

210 No patients were involved in this study and only publicly available data was gathered.

211 Therefore, ethics approval was not required.

212

213 **Results**

214 *Review status*

215 From January 1, 1995 to December 31, 2016 Health Canada approved a total of 623 NAS. Of
 216 these, 438 (70.3%) went through the standard pathway, 152 (24.4%) the priority pathway and
 217 33 (5.3%) received a NOC/c. Almost 30 percent (29.7%) went through the expedited review
 218 pathways over the entire period, varying from a low of 9.1% in 2010 to a high of 47.8% in
 219 2006 (Table 2). (Health Canada used both a priority and NOC/c approval for 11 drugs, data
 220 not shown.) Visual inspection of Figure 1 shows that there is no trend to using expedited
 221 review pathways more liberally or more conservatively over the time period. (Supplementary
 222 Tables 1 & 2, drugs with and without therapeutic evaluations, respectively, give all of the
 223 data extracted for the 623 drugs in question.)

224

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

226

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)

227

228 *Notice of Compliance with conditions

229 †Patented Medicine Prices Review Board

230

231 There were 126 biologics approved versus 323 small molecules (data only available from
 232 2000 onward). There was no difference in the distribution of the approval pathways ($p =$
 233 0.4867) (Table 3). There were 81 approvals for antineoplastic agents, 47 for antivirals for
 234 systemic use, 36 for immunosuppressants and 365 for drugs in the remaining 68 categories
 235 (“all other 68 therapeutic groups”) (Supplementary Table 1). The distribution of approval
 236 pathways was significantly different for the three subgroups ($p = 0.0018$) and for the three
 237 subgroups combined versus “all other therapeutic groups” ($p < 0.00001$) (Table 3).

238 **Table 3: Subgroup comparison of review pathways**

239

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

240

241 Small molecules vs. biologics: chi-square = 1.4402 (p = 0.4867)

242 Antineoplastics vs. antivirals vs. immunosuppressants: chi-square = 17.1978 (p = 0.0018)

243 Antineoplastics + antivirals + immunosuppressants vs. all other therapeutic groups: chi-square = 97.4874 (p < 0.00001)

244

245

246 *Therapeutic value*

247

248 Out of the 623 NAS, 509 (81.7%) were evaluated for their therapeutic innovation either by

249

250 the PMPRB and/or Prescrire. Health Canada used an expedited review pathway for 159 of the

251

252 509 drugs whereas only 55 were judged to be therapeutically innovative by one or both of the

253

254 independent reviews. Forty-two of the 55 drugs that were therapeutic innovations received an

255

256 expedited review, 13 received a standard review and 117 (159 – 42) that were not therapeutic

257

258 innovations also received an expedited review (Table 4). The Kappa value for the entire

259

260 period for all 509 drugs was 0.276 (95% CI 0.194, 0.359) or fair. Figure 2 presents the Kappa

261

262 values for each year which generally ranged from 0 (slight) to 0.4 (fair).

263

264

265

266

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

268

269

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

270

271

272

273

274

275

	Patented Medicine Prices Review Board and/or Prescribe		either Patented Medicine Prices Review Board and/or Prescribe	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

260

261 *New active substance

262 †Number of drugs rated as innovative as a percent of all drugs given an expedited approval
263 review by Health Canada264 ‡Number of drugs rated as not therapeutically innovative as a percent of all drugs given a
265 standard review by Health Canada

266

267 There were 286 and 99 small molecule drugs and biologics, respectively, with therapeutic
268 ratings. The Kappa values were 0.313 (95% CI 0.205, 0.420) (fair) and 0.233 (95% CI 0.061,
269 0.405) (fair), respectively. The overlapping 95% CIs indicate no difference in the Kappa
270 values between the two groups (Table 5).

271 **Table 5: Subgroup analyses: Kappa values**

272

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)

273

274 The 509 drugs were in 58 different second level ATC groups (drugs in 13 ATC groups did
 275 not have therapeutic evaluations): antineoplastic agents (71), antivirals for systemic use (46),
 276 immunosuppressants (35) and “all other therapeutic groups” (357) (Supplementary Table 1).
 277 Kappa values for the four groups were: 0.091 (95% CI 0.017, 0.200) (slight), 0.200), 0.122
 278 (95% CI 0.011, 0.233) (slight)), 0.376 (95% CI 0.075, 0.675) (fair) and 0.385 (95% CI 0.263,
 279 0.506) (fair), respectively. The 95% CIs for the Kappa values for the antineoplastic agents,
 280 antivirals for systemic use and immunosuppressants overlapped indicating no difference
 281 among the groups and the 95% CI for the immunosuppressants overlapped with the 95% CI
 282 for “all other therapeutic groups”. Drugs in the three therapeutic subgroups were much less
 283 likely to receive a standard review than were drugs in “all other therapeutic groups”, 43.7%
 284 versus 79.1% (data not shown).

285

286 Discussion

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

1
2
3 293 examined – antineoplastics, antivirals and immunosuppressants – were collectively more
4
5 294 likely to be assigned to an expedited review pathway (56%) compared to drugs in “all other
6
7 295 therapeutic groups” (20.9%), possibly because of the nature of the diseases that they treat.
8

9 296

10
11 297 Just over 80% of the NAS approved had been assessed by the PMPRB and/or Prescrire for
12
13 298 their therapeutic benefit. The Kappa value for the 509 drugs was 0.276 meaning that Health
14
15 299 Canada’s ability to predict major therapeutic gain from these drugs was only fair.

16
17 300 Furthermore, almost 25% (13/55) of the drugs that were therapeutic innovations did not
18
19 301 receive an expedited review underscoring that Health Canada is not reliably able to predict
20
21 302 which drugs will offer major therapeutic gains. The relatively low Kappa value may relate to
22
23 303 when Health Canada makes its decision about what type of approval pathway to use. This
24
25 304 assignment is at the start of the review process when all of the data will not have been fully
26
27 305 assessed. In contrast, the PMPRB and Prescrire make their assessments after the drug has
28
29 306 been marketed when more information about efficacy and safety is available.
30
31

32
33 307

34
35 308 As was the case with the assignment of an expedited review pathway, there is no difference
36
37 309 in how accurately Health Canada predicts the therapeutic value of small molecule drugs and
38
39 310 biologics as measured by Kappa values. The Kappa value for drugs in “all other therapeutic
40
41 311 groups” is higher than the value for drugs in the antineoplastic, antiviral and
42
43 312 immunosuppressant groups. This difference may be because Health Canada is better able to
44
45 313 predict that these drugs are less likely to be therapeutic innovations than drugs in the
46
47 314 antineoplastic, antiviral and immunosuppressant groups. Out of the 357 drugs that had
48
49 315 therapeutic evaluations in the “all other therapeutic groups,” 79.3% received a standard
50
51 316 review compared to 43.7% of the 151 drugs in the three therapeutic subgroups.
52
53

54
55 317
56
57
58
59

1
2
3 318 How Health Canada uses its expedited review pathways is important for a number of reasons.
4
5 319 First, their use may explicitly create an impression among clinicians and patients that these
6
7 320 drugs are likely to deliver major new therapeutic benefits despite the fact that the likelihood
8
9 321 that they will is only “fair” as measured by the Kappa value. Second, the NOC/c pathway
10
11 322 requires companies to commit to conducting post-market studies to validate the efficacy of
12
13 323 the product, but many of these studies are delayed^{6,7}, leaving clinicians and patients
14
15 324 uncertain about the value of these products. In at least one case, Health Canada did not
16
17 325 suspend the sale of a drug and allowed it to stay on the market despite not fulfilling the
18
19 326 conditions required under its NOC/c. In December 2003, Iressa (gefitinib) was approved as a
20
21 327 third-line treatment for non-small cell lung cancer on the condition that the company submit a
22
23 328 study showing that it improved survival¹². When the study results were submitted to Health
24
25 329 Canada they showed no survival benefit for gefitinib compared to placebo¹³. Health Canada
26
27 330 recognized that the conditions had not been fulfilled, but rather than removing gefitinib from
28
29 331 the market, in February 2005 it elected to allow it to continue to be sold¹². In 2009, the drug
30
31 332 was deemed to have met its conditions after a new study showed non-inferiority, i.e., survival
32
33 333 after taking it was no worse compared to another chemotherapeutic agent¹⁴. Third, although
34
35 334 the priority and standard approval pathways are equivalent in terms of the amount of data
36
37 335 reviewed, the former is done in 180 days compared to 300 days for the latter, meaning that
38
39 336 the priority pathway is more resource intensive possibly drawing resources from other Health
40
41 337 Canada activities. Finally, drugs reviewed through both expedited review pathways are more
42
43 338 likely to receive safety warnings once they are on the market compared to drugs with a
44
45 339 standard approval^{2,15}.

50 340

51
52 341 As Figure 1 indicates, Health Canada is not using the expedited review pathways more
53
54 342 liberally (or more conservatively) over time, but as Figure 2 shows it has not improved its

1
2
3 343 ability to predict therapeutic innovation over the 22 years evaluated in this study. The
4
5 344 Introduction describes the criteria that Health Canada uses to assign a drug to either a priority
6
7 345 review or a NOC/c review but how those criteria are applied and whether Health Canada
8
9 346 periodically reviews its performance are not known.

10
11 347

12
13 348 Contrary to the situation in the United States (US) where the Food and Drug Administration
14
15 349 (FDA) has been using an increasing number of expedited development or review programs,
16
17 350 Health Canada's use of its programs has been relatively stable since 1995. Between 1987 and
18
19 351 2014, 43% received a priority review from the FDA and 19% were approved through the fast
20
21 352 track program which approximately corresponds to a NOC/c¹⁶. (Drugs could be associated
22
23 353 with both programs.) However, when it comes to approving oncology drugs through an
24
25 354 expedited pathway, Health Canada is only marginally better than the FDA. In the US, only 1
26
27 355 of 15 (6.7%) oncology drugs approved through an expedited program from January 1, 2008,
28
29 356 through December 31, 2012 had a proven survival benefit compared to the other 6 and 8 that
30
31 357 either had no overall survival benefit or an unknown benefit, respectively¹⁷. In this current
32
33 358 study, out of 42 antineoplastic agents that Health Canada gave an expedited review, only 6
34
35 359 (14.3%) were rated as therapeutically innovative. The accelerated assessment (AA) process
36
37 360 and the conditional approvals pathway used by the European Medicines Agency (EMA) are
38
39 361 roughly the equivalent of Health Canada's priority review and NOC/c pathway¹⁸. The EMA
40
41 362 used the former for 15.5% (23/148) of new drugs between 2012 and 2016^{19,20}, while the
42
43 363 latter was used for 10.1% (30/296) of new drugs between 2006 and 2016^{20,21}. In the same
44
45 364 time periods, Health Canada used a priority approval 21.6% (35/162) of the time and its
46
47 365 NOC/c pathway 9.1% (28/308) of the time.

48
49 366

50
51 367

1
2
3 368 *Limitations*

4
5 369 Almost 20% of new drugs approved by Health Canada were not evaluated for their
6
7 370 therapeutic innovation by either the PMPRB or La revue Prescrire. The absence of these
8
9 371 evaluations may have skewed the Kappa values in either a more positive or more negative
10
11 372 direction. The lack of the availability of reports from Health Canada reviewers means that the
12
13 373 reasons why drugs were assigned to a specific review pathway cannot be evaluated.
14

15
16 374

17
18 375 **Conclusion**

19
20 376 Health Canada continues to use expedited review pathways for about 30% of new drugs.
21
22 377 Other regulatory authorities such as the Australian Therapeutic Goods Administration and the
23
24 378 EMA are in the process of either implementing or expanding expedited review pathways²²⁻²⁴
25
26 379 and should study the example of what has happened in Canada. The rationale for using
27
28 380 expedited review pathways is to get important therapeutic advances to patients in a timely
29
30 381 manner, but Health Canada's ability to predict which of these drugs will fulfill this
31
32 382 expectation has not improved over a 22-year period and remains relatively low. Moreover,
33
34 383 use of these pathways comes with both health related and resource costs. The findings in this
35
36 384 study should provoke a discussion about whether Health Canada should continue to use these
37
38 385 pathways and if so how their use can be improved.
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 386 **Figure 1 legend**
4

5 387 Grey – Percent with Notice of Compliance with conditions

6 388

7 389 Orange – Percent with priority

8 390

9 391 Blue – Percent with standard

10 392

11
12 393 **Figure 2 legend**
13

14 394 Kappa values:

15
16 395 < 0 = no agreement

17 396

18 397 0 – 0.20 = slight agreement

19 398

20 399 0.21 – 0.40 = fair agreement

21 400

22 401 0.41 – 0.60 = moderate agreement

23 402

24 403 0.61 – 0.80 = substantial agreement

25 404

26 405 0.81 – 1.0 = almost perfect agreement

27 406

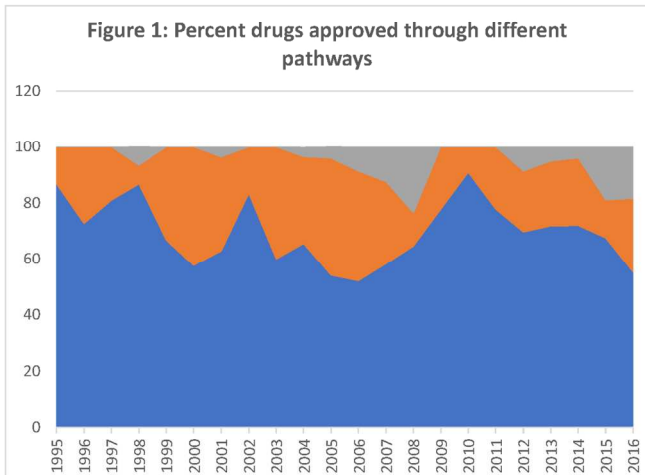
28
29 407
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

408 **References**

- 409 1. Health Products and Food Branch. Access to therapeutic products: the regulatory
410 process in Canada. Secondary Access to therapeutic products: the regulatory
411 process in Canada 2006.
412 http://publications.gc.ca/collections/collection_2007/hc-sc/H164-9-2006E.pdf.
- 413 2. Lexchin J. Post-market safety warnings for drugs approved in Canada under the
414 Notice of Compliance with conditions policy. *British Journal of Clinical
415 Pharmacology* 2015;**79**:847-59.
- 416 3. Health Canada: Health Products and Food Branch. Guidance for industry: priority
417 review of drug submissions. Ottawa, 2009.
- 418 4. Health Canada. Notice of compliance with conditions (NOC/c). Ottawa, 2002.
- 419 5. Lexchin J. Health Canada's use of its priority review process for new drugs: a cohort
420 study. *BMJ Open* 2015;**5**:e006816.
- 421 6. Lexchin J. Notice of compliance with conditions: a policy in limbo. *Healthcare Policy*
422 2007;**2**:114-22.
- 423 7. Law M. The characteristics and fulfillment of conditional prescription drug approvals
424 in Canada. *Health Policy* 2014;**116**:154-61.
- 425 8. Prescrire Editorial Staff. Prescrire's ratings system: gauge the usefulness of new
426 products at a glance. Secondary Prescrire's ratings system: gauge the usefulness
427 of new products at a glance 2011.
428 <http://english.prescrire.org/en/81/168/46800/0/NewsDetails.aspx>.
- 429 9. Lexchin J. Postmarket safety in Canada: are significant therapeutic advances and
430 biologics less safe than other drugs? A cohort study. *BMJ Open* 2014;**4**:e004289.
- 431 10. Landis JR, Koch GG. The measurement of observer agreement for categorical data.
432 *Biometrics* 1977;**33**:159-74.
- 433 11. WHO Collaborating Centre for Drug Statistics Methodology, Norwegian Institute of
434 Public Health. Structure and principles. Secondary Structure and principles
435 2011. http://www.whocc.no/atc/structure_and_principles/.
- 436 12. Health Canada. Clarification from Health Canada regarding the status of Iressa®
437 (gefitinib) in Canada. Secondary Clarification from Health Canada regarding the
438 status of Iressa® (gefitinib) in Canada 2005. http://www.hc-sc.gc.ca/dhp-mps/prodpharma/activit/fs-fi/fact_iressa-eng.php.
- 439 13. Thatcher N, Chang A, Parikh P, et al. Gefitinib plus best supportive care in previous
440 treated patients with refractory advanced non-small-cell lung cancer: results
441 from a randomised, placebo-controlled, multicentre study (Iressa Survival
442 Evaluation in Lung Cancer). *Lancet* 2005;**366**:1527-37.
- 443 14. Kim E, Hirsh V, Mok T, et al. Gefitinib versus docetaxel in previously treated non-
444 small-cell lung cancer (INTEREST): a randomised phase III trial. *Lancet*
445 2008;**372**:1809-18.
- 446 15. Lexchin J. New drugs and safety: what happened to new active substances approved
447 in Canada between 1995 and 2010? *Archives of Internal Medicine*
448 2012;**172**:1680-81.
- 449 16. Kesselheim A, Wang B, Franklin J, et al. Trends in utilization of FDA expedited drug
450 development and approval programs, 1987-2014: cohort study. *BMJ*
451 2015;**351**:h4633.
- 452 17. Kim C, Prasad V. Cancer drugs approved on the basis of a surrogate end point and
453 subsequent overall survival: an analysis of 5 years of US Food and Drug
454 Administration approvals. *JAMA Internal Medicine* 2015;**175**:1992-94.
- 455

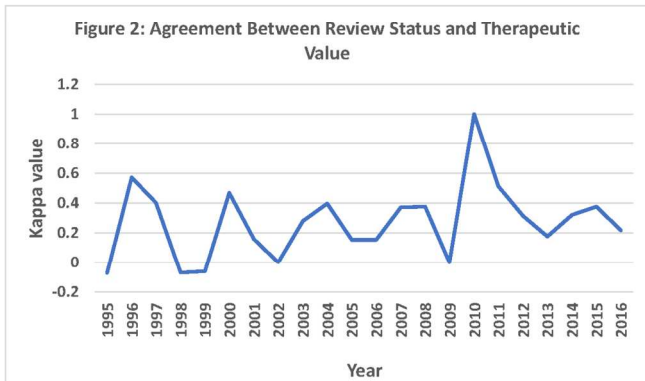
- 1
2
3 456 18. Baird L, Banken R, Eicher H-G, et al. Accelerated access to innovative medicines for
4 457 patients in need. *Clinical Pharmacology & Therapeutics* 2014;**96**:559-72.
5 458 19. European Medicines Agency. Accelerated assessment (AA): review of 10 months
6 459 experience with the new AA process. Secondary Accelerated assessment (AA):
7 460 review of 10 months experience with the new AA process 2018.
8 461 [http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2018](http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2018/01/WC500241575.pdf)
9 462 [/01/WC500241575.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2018/01/WC500241575.pdf).
10 463 20. Centre for Innovation in Regulatory Science. New drug approvals in six major
11 464 authorities 2007-2016: focus on the internationalisation of medicines. London,
12 465 2017.
13 466 21. European Medicines Agency. Conditional marketing authorisation: report on ten
14 467 years of experience at the European Medicines Agency. London, 2017.
15 468 22. European Medicines Agency. Final report on the adaptive pathways pilot. London,
16 469 2016.
17 470 23. Department of Health Therapeutic Goods Administration. Consultation: provisional
18 471 approval pathway for prescription medicines. Proposed registration process and
19 472 post-market requirements. Woden, ACT, 2017.
20 473 24. Department of Health Therapeutic Goods Administration. Consultation: expedited
21 474 pathways for prescription medicines. Eligibility criteria and designation process.
22 475 Woden, ACT, 2016.
23 476
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



148x209mm (300 x 300 DPI)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



148x209mm (300 x 300 DPI)

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 Standard Priority	Notice of compliance with conditions	Notice of compliance or notice of compliance with conditions date	Small molecule	Biologic	ATC group (second level)
Adapalene	Differin		1	1		1995-01-24			anti-acne preparation
Dexrazoxane	Zinocard	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		1	1		1995-04-24			psycholeptics
Zuclopenthixol	acuphase 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 svstemic use
Sevoflurane	Sevorane		1	1		1995-09-18			anesthetics

1						
2						
3	Losartan	Cozaar	1	1	1995-09-28	agents acting on the
4						renin-angiotensin system
5	Iotrolan	Osmovist 280	1	1	1995-10-04	contrast media
6	Bicalutamide	Casodex	1	1	1995-11-02	endocrine therapy
7	Acarbose	Prandase	1	1	1995-11-15	drugs used in diabetes
8	Mycophenolate	Cellcept	1	1	1995-11-15	immunosuppressants
9	Tacrolimus	Prograf	1	1	1995-12-06	immunosuppressants
10	Lamivudine	3TC	1	1	1995-12-08	antivirals for systemic
11						use
12	Alendronate	Fosamax	1	1	1995-12-20	drugs for treatment of
13						bone disease
14	Stavudine	Zerit	1	1	1996-03-26	antivirals for systemic
15						use
16	Acellular	Acel-P	1	1	1996-03-29	vaccines
17	pertussis vaccine					
18	adsorbed					
19						
20	Dorzolamide	Trusopt	1	1	1996-04-25	ophthalmologicals
21	Amifostine	Ethyol	1	1	1996-04-25	all other therapeutic
22						products
23	Valacyclovir	Valtrex	1	1	1996-05-01	antivirals for systemic
24						use
25	Quinagolide	Norprolac	1	1	1996-06-25	other gynecologicals
26	Meropenem	Merrem	1	1	1996-07-02	antibacterials for
27						systemic use
28	Abciximab	Reopro	1	1	1996-07-04	antithrombotic agents
29	Anastrozole	Arimidex	1	1	1996-08-01	endocrine therapy
30	Ritonavir	Norvir	1	1	1996-08-14	antivirals for systemic
31						use
32	Raltitrexed	Tomudex	1	1	1996-09-12	antineoplastic agents
33	Indinavir	Crixivan	1	1	1996-09-13	antivirals for systemic
34						use
35	Insulin lispro	Humalog	1	1	1996-10-08	drugs used in diabetes
36						
37						
38						
39						
40						
41						
42						
43						
44						
45						
46						
47						

1						
2						
3	Dirithromycin	Dynabac	1	1	1996-10-28	antibacterials for
4						systemic use
5	Olanzapine	Zyprexa	1	1	1996-10-28	psycholeptics
6	Nalmefene	Revex	1	1	1996-11-06	other nervous system
7	Zolpidem	Ambien	1	1	1996-11-20	psycholeptics
8	Desflurane	Suprane	1	1	1996-12-03	anesthetics
9	Gemcitabine	Gemzar	1	1	1996-12-23	antineoplastic agents
10	Ropivacaine	Naropin	1	1	1996-12-24	anesthetics
11		injections				
12	Imiglucerase	Cerezyme	1	1	1997-02-12	other alimentary tract
13						and metabolism products
14	Atorvastatin	Lipitor	1	1	1997-02-19	lipid modifying agents
15	Topiramate	Topamax	1	1	1997-03-06	antiepileptics
16	Formoterol	Foradil dry	1	1	1997-03-06	drugs for obstructive
17		powder				airway diseases
18		capsules				
19	Epoprostenol	Flolan	1	1	1997-03-06	antithrombotic agents
20	Coagulation	Benefix	1	1	1997-03-21	antihemorrhagics
21	factor IX					
22	Topotecan	Hycamtin	1	1	1997-04-15	antineoplastic agents
23	Dolasetron	Anzemet	1	1	1997-05-21	antiemetics and
24						antinauseants
25	Letrozole	Femara	1	1	1997-05-21	endocrine therapy
26	Fexofenadine	Allegra	1	1	1997-06-11	antihistamines for
27						systemic use
28	Latanoprost	Xalatan	1	1	1997-06-16	ophthalmologicals
29	Carbetocin	Duratocin	1	1	1997-06-24	pituitary and
30						hypothalamic hormones
31						and analogues
32	Follitropin beta	Puregon	1	1	1997-07-02	sex hormones and
33						modulators of the genital
34						svstem
35						
36						
37						
38						
39						
40						
41						
42						
43						
44						
45						
46						
47						

1						
2						
3	Irinotecan	Camptosar	1	1	1997-07-04	antineoplastic agents
4	Donepezil	Aricept	1	1	1997-08-12	psychoanaleptics
5	Ropinirole	Requip		1	1997-08-19	anti-parkinson drugs
6	Ibandronate	Bondronat		1	1997-08-27	drugs for treatment of
7						bone disease
8	Glatiramer	Copaxone for		1	1997-09-04	immunostimulants
9		injection				
10	Tolcapone	Tasmar		1	1997-10-08	anti-parkinson drugs
11	Zafirlukast	Accolate		1	1997-10-21	drugs for obstructive
12						airway diseases
13	Valsartan	Diovan		1	1997-11-03	agents acting on the
14						renin-angiotensin system
15						
16	Levofloxacin	Levaquin		1	1997-11-14	antibacterials for
17						systemic use
18	Brimonidine	Alphagan		1	1997-11-24	ophthalmologicals
19		ophthalmic				
20	Quetiapine	Seroquel		1	1997-12-02	psycholeptics
21	Pramipexole	Mirapex		1	1998-01-29	anti-parkinson drugs
22	Interferon Beta-	Rebif		1	1998-02-05	immunostimulants
23	Emedastine	Emadine		1	1998-02-16	ophthalmologicals
24		ophthalmic				
25	Cerivastatin	Baycol		1	1998-02-18	lipid modifying agents
26	Grepafloxacin	Raxar		1	1998-04-09	antibacterials for
27						systemic use
28	Naratriptan	Amerge		1	1998-04-28	analgesics
29	Bupropion	Wellbutrin SR		1	1998-04-28	psychoanaleptics
30	Irbesartan	Avapro		1	1998-06-01	agents acting on the
31						renin-angiotensin system
32						
33	Tamsulosin	Flomax		1	1998-06-01	urologicals
34	Montelukast	Singulair		1	1998-06-17	drugs for obstructive
35						airway diseases
36						
37						
38						
39						
40						
41						
42						
43						
44						
45						
46						
47						

1							
2							
3	Delavirdine	Rescriptor	1	1	1	1998-07-22	antivirals for systemic
4							use
5	Nelfinavir	Viracept	1		1	1998-08-11	antivirals for systemic
6							use
7	Zolmitriptan	Zomig	1	1		1998-08-24	analgesics
8	Capecitabine	Xeloda	1		1	1998-08-31	antineoplastic agents
9	Nevirapine	Viramune	1	1	1	1998-09-04	antivirals for systemic
10							use
11	Clopidogrel	Plavix	1	1		1998-10-07	antithrombotic agents
12	Brinzolamide	Azopt	1	1		1998-10-23	ophthalmologicals
13		ophthalmic					
14		suspension					
15	Raloxifene	Evista	1	1		1998-11-06	sex hormones and
16							modulators of the genital
17							svstem
18	Candesartan	Atacand	1	1		1998-11-20	agents acting on the
19							renin-angiotensin system
20							
21							
22							
23	Tolterodine	Detrol	1	1		1998-11-20	urologicals
24	Varicella vaccine	Varivax	1	1		1998-12-02	vaccines
25							
26	Alatrofloxacin	Trovan (IV)	1	1		1998-12-04	antibacterials for
27							systemic use
28	Trovafoxacin	Trovan (tablets)	1	1		1998-12-04	antibacterials for
29							systemic use
30	Becaplermin gel	Regranex	1	1		1998-12-30	preparations for wounds
31							and ulcers
32	Tizanidine	Zanaflex	1	1		1999-01-25	muscle relaxants
33	Penciclovir	Denavir	1	1		1999-02-02	antivirals for systemic
34							use
35	Citalopram	Celexa	1	1		1999-02-05	psychoanaleptics
36	Recombinant	Niastase	1		1	1999-02-12	antihemorrhagics
37	factor VIIa						
38	Modafinil	Alertec	1	1		1999-02-26	psychoanaleptics
39							
40							
41							
42							
43							
44							
45							
46							
47							

For peer review only

1							
2							
3	Sildenafil	Viagra	1	1		1999-03-08	urologicals
4	Recombinant-	Infergen		1	1	1999-03-11	immunostimulants
5	methionyl						
6	interferon						
7	consensus 1						
8	Efavirenz	Sustiva	1	1		1999-03-19	antivirals for systemic
9							use
10	Repaglinide	Gluconorm	1	1		1999-04-06	drugs used in diabetes
11	Celecoxib	Celebrex	1		1	1999-04-14	antiinflammatoary and
12							antirheumatic products
13	Triptorelin	Trelstar	1	1		1999-05-06	endocrine therapy
14	Ancestim	Stemgen	1	1		1999-05-20	immunostimulants
15	Orlistat	Xenical	1	1		1999-06-03	antiobesity preparations
16	Abacavir	Ziagen	1		1	1999-06-04	antivirals for systemic
17							use
18	Eptifibatide	Integrilin	1	1		1999-06-11	antithrombotic agents
19	Eprosartan	Teveten	1	1		1999-07-09	agents acting on the
20							renin-angiotensin system
21	Cidofovir	Vistide	1	1		1999-07-13	antivirals for systemic
22							use
23	Rizatriptan	Maxalt	1	1		1999-07-16	analgesics
24	Trastuzumab	Herceptin	1		1	1999-08-13	antineoplastic agents
25	Telmisartan	Micardis	1	1		1999-08-16	agents acting on the
26							renin-angiotensin system
27	Risedronate	Actonel	1	1		1999-08-18	drugs for treatment of
28							bone disease
29	Tirofiban	Aggrastat	1	1		1999-08-19	antithrombotic agents
30	Icodextrin	Extraneal	1	1		1999-09-17	blood substitutes and
31							perfusion solutions
32	Varicella zoster	Varilrix	1		1	1999-10-13	vaccines
33	vaccine						
34	Temozolomide	Temodal	1	1		1999-10-25	antineoplastic agents

1								
2								
3	Rofecoxib	Vioxx	1	1	1999-10-25			antiinflammaotory and
4								antirheumatic products
5	Zanamivir	Relenza	1	1	1	1999-11-02		antivirals for systemic
6								use
7	Melanoma	Melacine	1	1	1999-11-04			immunostimulants
8	theracine							
9	Gadobutrol	Gadovist	1	1	1999-11-08			contrast media
10	Dalfopristin	Synercid	1	1	1999-12-10			antibacterials for
11								systemic use
12	Oseltamivir	Tamiflu	1	1	1999-12-23			antivirals for systemic
13								use
14	Daclizumab	Zenaprax	1	1	2000-01-04		1	antineoplastic agents
15	Leflunomide	Arava	1	1	2000-03-16	1		immunosuppressants
16	Rituximab	Rituxan	1	1	2000-03-17		1	immunosuppressants
17	Rosiglitazone	Avandia	1	1	2000-03-21	1		drugs used in diabetes
18	Oxcarbazepine	Trileptal	1	1	2000-04-13	1		antiepileptics
19	Rivastigmine	Exelon	1	1	2000-04-13	1		psychoanaleptics
20	Zaleplon	Starnoc	1	1	2000-05-11	1		psycholeptics
21	Verteporfin	Visudyne	1	1	2000-05-31	1		ophthalmologicals
22	Cabergoline	Dostinex	1	1	2000-06-30	1		anti-parkinson drugs
23	Exemestane	Aromasin	1	1	2000-08-17	1		endocrine therapy
24	Pioglitazone	Actos	1	1	2000-08-17	1		drugs used in diabetes
25	Zoledronic acid	Zometa	1	1	2000-08-21	1		drugs for treatment of
26								bone disease
27	Riluzole	Rilutek	1	1	1	2000-08-30	1	other nervous system
28	Meloxicam	Mobic	1	1	2000-08-31	1		antiinflammaotory and
29								antirheumatic products
30	Basiliximab	Simulect	1	1	2000-09-01		1	immunosuppressants
31	Moxifloxacin	Avelox	1	1	2000-10-19	1		antibacterials for
32								systemic use
33	Peginterferon	Peg-intron	1	1	2000-10-20		1	immunostimulants
34	Alfa-2b							
35	Etanercept	Enbrel	1	1	2000-12-01		1	immunosuppressants
36								
37								
38								
39								
40								
41								
42								
43								
44								
45								
46								
47								

1							
2							
3	Gadoversetamid	Optimark	1	1		2000-12-11	1 contrast media
4	e						
5	Sibutramine	Meridia	1	1		2000-12-28	1 antiobesity preparations
6	Sirolimus	Rapamune	1	1		2001-01-05	1 immunosuppressants
7	Gatifloxacin	Tequin	1	1		2001-01-09	1 antibacterials for systemic use
8							
9							
10	Glucagon, rDNA origin	Glucagon	1		1	2001-01-11	1 pancreatic hormones
11							
12	Mequinol/tretinoin	Solage	1	1		2001-01-17	1 other dermatological preparations
13							
14	Amprenavir	Agenerase	1	1	1	2001-03-01	1 antivirals for systemic use
15							
16	Lopinavir/ritonavir	Kaletra	1		1	2001-03-09	1 antivirals for systemic use
17							
18	Linezolid	Zyvoxam	1	1		2001-04-02	1 antibacterials for systemic use
19							
20							
21	Iron	Venoferr	1		1	2001-04-17	1 antianemic preparations
22	Doxercalciferol	Hectorol	1	1		2001-04-30	1 calcium homeostasis
23	Rabeprazole	Pariet	1	1		2001-05-07	1 drugs for acid related disorders
24							
25	Entacapone	Comtan	1	1		2001-05-08	1 anti-parkinson drugs
26	Eflornithine	Vaniqa	1	1		2001-05-10	1 antiprotozoals
27	Mirtazapine	Remeron	1	1		2001-05-18	1 psychoanaleptics
28	Desloratadine	Aerius	1	1		2001-05-29	1 antihistamines for systemic use
29							
30							
31	Infliximab	Remicade	1	1		2001-06-06	1 immunosuppressants
32	Caspofungin	Cancidas	1		1	2001-07-29	1 antimycotics for systemic use
33							
34							
35	Galantamine	Reminyl	1	1		2001-07-31	1 psychoanaleptics
36	Esomeprazole	Nexium	1	1		2001-08-17	1 drugs for acid related disorders
37							
38	Imatinib	Gleevec			1	2001-09-20	1 antineoplastic agents
39	Tenecteplase	Tnkase	1	1		2001-10-17	1 antithrombotic agents
40	Travoprost	Travatan	1	1		2001-11-09	1 ophthalmologicals
41							
42							
43							
44							
45							
46							
47							

1							
2							
3	Bosentan	Tracleer	1	1	2001-11-30	1	antihypertensives
4	Meningococcal	Neisvac-C	1	1	2001-12-18	1	vaccines
5	group C						
6	polysaccharide,						
7	tetanus toxoid						
8	Glimepiride	Amaryl	1	1	2002-01-25	1	drugs used in diabetes
9	Nateglinide	Starlix	1	1	2002-02-13	1	drugs used in diabetes
10	Alfuzosin	Xatral	1	1	2002-02-21		urologicals
11	Tegaserod	Zelnorm	1	1	2002-03-12	1	drugs for constipation
12	Ganirelix	Orgalutran	1	1	2002-05-01	1	pituitary and
13							hypothalamic hormones
14	Valganciclovir	Valcyte	1	1	2002-05-03	1	antivirals for systemic
15							use
16	Palivizumab	Synagis	1	1	2002-05-15	1	immune sera and
17							immunoglobulins
18	Docosanol	Abreva	1	1	2002-05-24	1	antibiotics and
19							chemotherapeutics for
20							dermatological use
21	Bimatoprost	Lumigan	1	1	2002-05-24	1	ophthalmologicals
22	Anakinra	Kineret	1	1	2002-05-24	1	immunosuppressants
23	Moroctocog	Refacto	1	1	2002-05-28	1	antihemorrhagics
24	alpha						
25	Peginterferon	Pegetron	1	1	2002-05-31	1	immunostimulants
26	Alfa-2b ribavirin						
27	Fondaparinux	Arixtra	1	1	2002-06-13	1	antithrombotic agents
28	Hetastarch	Hextend	1	1	2002-07-08	1	blood substitutes and
29							perfusion solutions
30	Darbepoetin	Aranesp	1	1	2002-08-02	1	antianemic preparations
31	alpha						
32	Norelgestromin/	Evra	1	1	2002-08-20	1	sex hormones and
33	ethinyl estradiol						modulators of the genital
34							system
35	Treprostinil	Remodulin	1	1	2002-10-04	1	antithrombotic agents
36	Bivalirudin	Angiomax	1	1	2002-10-09	1	antithrombotic agents
37							
38							
39							
40							
41							
42							
43							
44							
45							
46							
47							

1									
2									
3	Tiotropium	Spiriva		1	1		2002-11-20	1	drugs for obstructive
4									airway diseases
5	Valdecoxib	Betra		1	1		2002-12-11	1	antiinflammaotory and
6									antirheumatic products
7									antithrombotic agents
8	Drotrecogin Alfa	Xigris	1				2003-01-31		1
9	Rosuvastatin	Crestor		1	1		2003-02-18	1	lipid modifying agents
10	Recombinant cholera toxin B subunit	Dukoral		1	1		2003-02-21		1
11									vaccines
12	Levetiracetam	Keppra		1	1		2003-03-06	1	antiepileptics
13	Tenofovir	Viread		1		1	2003-03-18	1	antivirals for systemic use
14									other dermatological preparations
15	Pimecrolimus	Elidel		1	1		2003-03-19	1	antibacterials for systemic use
16									lipid modifying agents
17	Ertapenem	Invanz		1	1		2003-05-12	1	antibacterials for systemic use
18									lipid modifying agents
19	Ezetimibe	Ezetrol		1	1		2003-05-12	1	antibacterials for systemic use
20	Telithromycin	Ketek		1	1		2003-05-28	1	antibacterials for systemic use
21									antivirals for systemic use
22	Enfuvirtide	Fuzeon	1			1	2003-07-14	1	antivirals for systemic use
23									urologicals
24	Dutasteride	Avodart		1	1		2003-07-22	1	immunostimulants
25	Peginterferon Alfa-2a	Pegasys		1	1		2003-08-13		1
26	Cetrorelix	Cetrotide		1	1		2003-08-13	1	pituitary and hypothalamic hormones
27									antivirals for systemic use
28	Adefovir	Hepsera		1		1	2003-08-27	1	urologicals
29									agents acting on the renin-angiotensin system
30	Tadalafil	Cialis		1	1		2003-09-17	1	
31	Almotriptan	Axert		1	1		2003-10-01	1	
32									
33	Rasburicase	Fasturtec		1		1	2003-10-29		1
34									all other therapeutic products
35									
36									
37									
38									
39									
40									
41									
42									
43									
44									
45									
46									
47									

1									
2									
3	Atazanavir	Reyataz	1	1	2003-12-05	1		antivirals for systemic	
4								use	
5	Gefitinib	Iressa	1	1	1	2003-12-17	1	antineoplastic agents	
6	Agalsidase Beta	Fabrazyme	1	1		2004-01-23		1	other alimentary tract
7									and metabolism products
8									
9									
10	Agalsidase	Replagal	1	1	1	2004-02-06		1	other alimentary tract
11									and metabolism products
12									
13	Fulvestrant	Faslodex	1	1		2004-02-17	1		endocrine therapy
14	Gemifloxacin	Factive	1	1		2004-03-09	1		antibacterials for
15									systemic use
16	Pegfilgrastim	Neulasta	1	1		2004-03-12		1	immunostimulants
17	Vardenafil	Levitra	1	1		2004-03-17	1		urologicals
18	Gadobenate	Multihance	1	1		2004-03-31	1		contrast media
19	Miglustat	Zavesca	1	1		2004-03-31	1		other alimentary tract
20									and metabolism products
21									
22									
23	Botulinum Toxin	Myobloc	1	1		2004-04-16		1	muscle relaxants
24	Type B								
25	Peginterferon	Pegasys RBV	1	1		2004-05-10		1	immunostimulants
26	Alfa-2A Ribavirin								
27									
28									
29	Ethinyl	Nuvaring	1	1		2004-05-11	1		sex hormones and
30	estradiol/etonog								modulators of the genital
31	estrel								svstem
32	Pemetrexed	Alimta	1	1		2004-05-21	1		antineoplastic agents
33	Laronidase	Adlurazyme	1	1		2004-05-31		1	other alimentary tract
34									and metabolism products
35									
36	Teriparatide	Forteo	1	1		2004-06-03		1	calcium homeostasis
37	Cinacalcet	Sensipar	1	1		2004-08-04	1		calcium homeostasis
38	Eletriptan	Relpax	1	1		2004-08-05	1		analgesics
39									
40									
41									
42									
43									
44									
45									
46									
47									

1							
2							
3	Voriconazole	Vfend	1	1		2004-08-20	1 antimycotics for systemic
4							use
5	Frovatriptan	Frova	1	1		2004-09-03	1 analgesics
6	Adalimumab	Humira	1	1		2004-09-24	1 immunosuppressants
7	Alefacept	Amevive	1	1		2004-10-06	1 immunosuppressants
8	Omalizumab	Xolair	1	1		2004-11-18	1 drugs for obstructive
9							airway diseases
10	Memantine	Ebixa	1	1	1	2004-12-08	1 psychoanaleptics
11	Fosamprenavir	Telzir	1	1		2004-12-10	1 antivirals for systemic
12							use
13	Drospirenone/et	Yasmin 21/28	1	1		2004-12-10	1 sex hormones and
14	hinyI estradiol						modulators of the genital
15							svstem
16	Atomoxetine	Strattera	1	1		2004-12-24	1 psychoanaleptics
17	Escitalopram	Cipralax	1	1		2004-12-24	1 psychoanaleptics
18	Bortezomib	Velcade	1	1	1	2005-01-27	1 antineoplastic agents
19	Paricalcitol	Zemplar	1	1		2005-03-31	1 calcium homeostasis
20	Pantoprazole	Pantaloc M	1	1		2005-04-22	1 drugs for acid related
21							disorders
22	Pegaptanib	Macugen	1	1		2005-05-02	1 ophthalmologicals
23	Ibritumomab	Zevalin	1	1		2005-05-10	1 therapeutic
24							radiopharmaceuticals
25	Pregabalin	Lyrica	1	1		2005-06-03	1 antiepileptics
26	Lutropin Alfa	Luveris	1	1		2005-06-24	1 sex hormones and
27							modulators of the genital
28							svstem
29	Erlotinib	Tarceva	1	1		2005-07-07	1 antineoplastic agents
30	Tramadol	Tramacet	1	1		2005-07-20	1 analgesics
31	Sodium oxybate	Xyrem	1	1		2005-08-05	1 other nervous system
32	Perindopril	Coversyl	1	1		2005-08-23	1 agents acting on the
33							renin-angiotensin system
34	Bevacizumab	Avastin	1	1		2005-09-09	1 antineoplastic agents
35							
36							
37							
38							
39							
40							
41							
42							
43							
44							
45							
46							
47							

1								
2								
3	Cetuximab	Erbix	1		1	2005-09-09	1	antineoplastic agents
4	Insulin detemir	Levemir	1	1		2005-09-29	1	drugs used in diabetes
5	Pegvisomant	Somavert	1		1	2005-10-17	1	pituitary and
6								hypothalamic hormones
7								
8	Efalizumab	Raptiva	1	1		2005-10-24	1	immunosuppressants
9	Darifenacin	Enablex	1	1		2005-11-14	1	urologicals
10	Emtricitabine	Emtriva	1	1		2005-11-21	1	antivirals for systemic
11								use
12								
13	Tipranavir	Aptivus	1		1	2005-11-21	1	antivirals for systemic
14								use
15	Alemtuzumab	Mabcampath	1	1		2005-11-30	1	immunosuppressants
16	Palifermin	Kepivance	1		1	2005-12-09	1	all other therapeutic
17								products
18	Trospium	Trosec	1	1		2006-01-10	1	urologicals
19	Solifenacin	Vesicare	1	1		2006-02-20	1	urologicals
20	Histrelin	Vantas	1	1		2006-03-10	1	endocrine therapy
21	Insulin glulisine	Apidra	1	1		2006-04-12	1	drugs used in diabetes
22	Sunitinib	Sutent	1		1	2006-05-26	1	antineoplastic agents
23	Entecavir	Baraclude	1		1	2006-06-16	1	pituitary and
24								hypothalamic hormones
25								and analogues
26								
27	Abatacept	Orencia	1		1	2006-06-29	1	immunosuppressants
28	Recombinant	Gardasil	1		1	2006-07-10	1	vaccines
29	human							
30	papillomavirus							
31	Lanreotide	Somatuline	1	1		2006-07-17	1	antivirals for systemic
32		autogel						use
33	Sorafenib	Nexavar	1	1		2006-07-28	1	antineoplastic agents
34	Darunavir	Prezista	1	1	1	2006-07-28	1	antivirals for systemic
35								use
36	Rotaviruses	Rotateq	1	1		2006-08-01	1	vaccines
37								
38								
39								
40								
41								
42								
43								
44								
45								
46								
47								

1									
2									
3	Alglucosidase	Myozyme	1		1		2006-08-14	1	other alimentary tract
4	Alfa								and metabolism products
5									
6	Rasagiline	Azilect		1	1		2006-08-17	1	anti-parkinson drugs
7	Ciclesonide	Alvesco		1	1		2006-09-11	1	drugs for obstructive
8									airway diseases
9	Tigecycline	Tygacil		1	1		2006-09-14	1	antibacterials for
10									systemic use
11	Natalizumab	Tysabri		1	1		2006-09-28		immunosuppressants
12	Lanthanum	Fosrenol		1	1		2006-10-17	1	all other therapeutic
13									products
14	Deferasirox	Exjade		1	1	1	2006-10-18	1	all other therapeutic
15									products
16	Gadofosveset	Vasovist		1	1		2006-10-31	1	contrast media
17	Telbivudine	Sebivo		1	1		2006-11-28	1	antivirals for systemic
18									use
19	Varenicline	Champix		1	1		2007-01-24	1	other nervous system
20	Acamprosate	Campral		1	1		2007-03-16	1	other nervous system
21	Dasatinib	Sprycell	1		1	1	2007-03-26	1	antineoplastic agents
22	Posaconazole	Spriafil	1			1	2007-03-26	1	antimycotics for systemic
23		(Posanol)							use
24	Micafungin	Mycamine		1	1		2007-05-22	1	antimycotics for systemic
25									use
26	Sitaxentan	Thelin		1	1		2007-05-30	1	antihypertensives
27	Idursulfase	Elaprase		1		1	2007-06-13	1	other alimentary tract
28									and metabolism products
29									
30	Oxaliplatin	Eloxatin		1	1		2007-06-15	1	antineoplastic agents
31	Ranibizumab	Lucentis	1			1	2007-06-26		ophthalmologicals
32	Fluticasone	Avamys		1	1		2007-08-14	1	drugs for obstructive
33									airway diseases
34	Aprepitant	Emend		1	1		2007-08-24	1	antiemetics and
35									antinauseants
36									
37									
38									
39									
40									
41									
42									
43									
44									
45									
46									
47									

1								
2								
3	Maraviroc	Celsentri	1	1	2007-09-21	1		antivirals for systemic
4								use
5	Daptomycin	Cubicin	1	1	2007-09-24	1		antibacterials for
6								systemic use
7	Paliperidone	Invega	1	1	2007-09-26	1		psycholeptics
8	Duloxetine	Cymbalta	1	1	2007-11-01	1		psychoanaesthetics
9	Nesiritide	Natrecor	1	1	2007-11-08		1	cardiac therapy
10	Aliskiren	Rasilez	1	1	2007-11-14	1		agents acting on the
11								renin-angiotensin system
12								
13								
14	Anidulafungin	Eraxis	1	1	2007-11-14	1		antimycotics for systemic
15								use
16	Raltegravir	Isentress	1	1	2007-11-27	1	1	antivirals for systemic
17								use
18	Rivastigmine	Exelon patch	1	1	2007-11-29	1		psychoanaesthetics
19	Sitagliptin	Januvia	1	1	2007-12-14	1		drugs used in diabetes
20	Temsirolimus	Torisel	1	1	2007-12-21	1		antineoplastic agents
21	Lenalidomide	Revlimid	1	1	2008-01-17	1	1	immunosuppressants
22	Ambrisentan	Volibris	1	1	2008-03-20	1		antihypertensives
23	Etravirine	Intelence	1	1	2008-03-27	1		antivirals for systemic
24								use
25	Methylnaltrexon	Relistor	1	1	2008-03-28	1		drugs for constipation
26	e							
27	Panitumumab	Vectibix	1	1	2008-04-03		1	antineoplastic agents
28	Nepafenac	Nevanac	1	1	2008-04-17	1		ophthalmologicals
29	Dabigatran	Pradaxa	1	1	2008-06-10	1		antithrombotic agents
30	Ceftobiprole	Zeftera	1	1	2008-06-26	1		antibacterials for
31								systemic use
32	Idebenone	Catena	1	1	2008-07-23	1		psychoanaesthetics
33	Nilotinib	Tasigna	1	1	2008-09-09	1		antineoplastic agents
34	Rivaroxaban	Xarelto	1	1	2008-09-15	1		antithrombotic agents
35								
36								
37								
38								
39								
40								
41								
42								
43								
44								
45								
46								
47								

1								
2								
3	Olmesartan	Olmotec	1	1		2008-10-28	1	agents acting on the
4								renin-angiotensin system
5								
6	Capsular	Synflorix	1	1		2008-12-11		1 vaccines
7	polysaccharide							
8	Ustekinumab	Stelara	1	1		2008-12-12		1 immunosuppressants
9	Loteprednol	Alrex	1	1		2008-12-23	1	ophthalmologicals
10	Eculizumab	Soliris	1		1	2009-01-28		1 immunosuppressants
11	Desvenlafaxine	Pristiq	1	1		2009-02-04	1	psychoanaleptics
12	Lisdexamfetami	Vyvanse	1	1		2009-02-19	1	psychoanaleptics
13	ne							
14	Romiplostim	Nplate	1		1	2009-02-19		1 antihemorrhagics
15	Methyl	Metvix	1	1		2009-02-26	1	antineoplastic agents
16	aminolevulinate							
17	Eplerenone	Inspra	1	1		2009-02-26	1	diuretics
18	Fosaprepitant	Emend IV	1	1		2009-04-01	1	antivirals for systemic
19								use
20	Golimumab	Simponi	1	1		2009-04-07		1 immunosuppressants
21	Lapatinib	Tykerb	1	1		2009-05-15	1	antineoplastic agents
22	Vorinostat	Zolinza	1	1		2009-06-11	1	antineoplastic agents
23	Aripiprazole	Abilify	1	1		2009-07-09	1	psycholeptics
24	Clofarabine	Clolar	1	1		2009-07-16	1	antineoplastic agents
25	Dronedarone	Multaq	1		1	2009-08-11	1	cardiac therapy
26	Certolizumab	Cimzia	1	1		2009-08-12		1 immunosuppressants
27	Doripenem	Doribax	1	1		2009-09-02	1	antibacterials for
28								systemic use
29	Aztreonam	Cayston	1		1	2009-09-11	1	antibacterials for
30								systemic use
31	Saxagliptin	Onglyza	1	1		2009-09-14	1	drugs used in diabetes
32	Besifloxacin	Besivance	1	1		2009-10-23	1	ophthalmologicals
33	Azacitidine	Vidaza	1		1	2009-10-23	1	antineoplastic agents
34								
35								
36								
37								
38								
39								
40								
41								
42								
43								
44								
45								
46								
47								

1								
2								
3	Japanese	Ixiaro	1	1	2009-10-29		1	vaccines
4	encephalitis							
5	vaccine							
6	Alitretinoin	Toctino	1	1	2009-11-13		1	antineoplastic agents
7	Degarelix	Firmagon	1	1	2009-11-16		1	endocrine therapy
8	Dexmedetomidine	Precedex	1	1	2009-12-09		1	psycholeptics
9								
10	Everolimus	Afinitor	1	1	2009-12-14	1	1	antineoplastic agents
11	Thrombin alfa	Recothrom	1	1	2009-12-15		1	antihemorrhagics
12	Pneumococcal conjugate	Prevnar	1		2009-12-21	1	1	vaccines
13	Gadoxetate	Primovist	1	1	2010-01-14		1	contrast media
14	Recombinant human papillomavirus	Cervarix	1	1	2010-02-03		1	vaccines
15	Canakinumab	Ilaris			2010-02-26		1	immunosuppressants
16	Prasugrel	Effient	1	1	2010-04-16		1	antithrombotic agents
17	Tocilizumab	Actemra	1	1	2010-04-30		1	immunosuppressants
18	Sapropterin	Kuvan	1		2010-04-30	1	1	other alimentary tract and metabolism products
19								
20	Trabectedin	Yondelis	1	1	2010-05-13		1	antineoplastic agents
21	Liraglutide	Victoza - 1.2 mg pen-injector	1	1	2010-05-21		1	drugs used in diabetes
22	Meningococcal oligosaccharides conjugated	Menveo	1	1	2010-05-21		1	vaccines
23	Pazopanib	Votrient	1	1	2010-05-27		1	antineoplastic agents
24	Paliperidone	Invega sustenna	1	1	2010-06-30		1	psycholeptics
25	Sevelamer	Renvela	1	1	2010-07-07		1	all other therapeutic products
26	Dexlansoprazole	Dexilant	1	1	2010-07-22		1	drugs for acid related disorders
27								
28								
29								
30								
31								
32								
33								
34								
35								
36								
37								
38								
39								
40								
41								
42								
43								
44								
45								
46								
47								

1							
2							
3	Denosumab	Prolia	1	1	2010-08-06	1	drugs for treatment of
4							bone disease
5	Febuxostat	Uloric	1	1	2010-09-22	1	antigout preparations
6	Lacosamide	Vimpat	1	1	2010-09-30	1	antiepileptics
7	Velaglucerase alf.	VPRIV	1	1	2010-10-01	1	other alimentary tract
8							and metabolism products
9							
10							
11	Roflumilast	Daxas	1	1	2010-11-23	1	drugs for obstructive
12							airway diseases
13	Tapentadol	Nucynta CR	1	1	2010-12-02	1	analgesics
14	Silodosin	Rapaflo	1	1	2011-01-11	1	urologicals
15	Eltrombopag	Revolade	1	1	2011-01-12	1	antihemorrhagics
16	Exenatide	Byetta	1	1	2011-01-13	1	drugs used in diabetes
17	Fingolimod	Gilenya	1	1	2011-03-09	1	immunosuppressants
18	Ticagrelor	Brilinta	1	1	2011-05-30	1	antithrombotic agents
19	Cabazitaxel	Jevtana	1	1	2011-06-16	1	antineoplastic agents
20	Rufinamide	Banzel	1	1	2011-06-22	1	antiepileptics
21	Belimumab	Benlysta	1	1	2011-07-06	1	immunosuppressants
22	Rilpivirine	Edurant	1	1	2011-07-21	1	antivirals for systemic
23							use
24	Tolvaptan	Samsca	1	1	2011-07-25	1	diuretics
25	Abiraterone	Zytiga	1	1	2011-07-27	1	endocrine therapy
26	Linagliptin	Trajenta	1	1	2011-07-28	1	drugs used in diabetes
27	Boceprevir	Victralis	1	1	2011-07-29	1	antivirals for systemic
28							use
29	Boceprevir,	Victralis Triple	1	1	2011-08-10	1	immunostimulants
30	peginterferon						
31	alfa-2b, ribavirin						
32	Telaprevir	Incivek	1	1	2011-08-16	1	antivirals for systemic
33							use
34	Colesevelam	Lodalis	1	1	2011-09-22	1	lipid modifying agents
35	Senapine	Saphris	1	1	2011-10-07	1	psycholeptics
36							
37							
38							
39							
40							
41							
42							
43							
44							
45							
46							
47							

1							
2							
3	Dienogest	Visanne	1	1	2011-10-12	1	sex hormones and
4							modulators of the genital
5							svstem
6	Indacaterol	Onbrez	1	1	2011-12-06	1	drugs for obstructive
7		breezhaler					airway diseases
8	Prucalopride	Resotran	1	1	2011-12-07	1	drugs for constipation
9	Plerixafor	Mozobil	1	1	2011-12-08	1	immunostimulants
10	Eribulin	Halaven	1	1	2011-12-14	1	antineoplastic agents
11	Apixaban	Eliquis	1	1	2011-12-16	1	antithrombotic agents
12	Vandetanib	Caprelsa	1	1	2012-01-12	1	antineoplastic agents
13	Ipilimumab	Yervoy	1	1	2012-02-01		1 antineoplastic agents
14	Fesoterodine	Toviaz	1	1	2012-02-09	1	urologicals
15	Fampridine	Fampyra	1	1	2012-02-10	1	other nervous system
16	Vemurafenib	Zelboraf	1	1	2012-02-15		antineoplastic agents
17	Azilsartan	Edarbi	1	1	2012-03-08	1	agents acting on the
18							renin-angiotensin system
19	Ofatumumab	Arzerra	1	1	2012-03-09		1 antineoplastic agents
20	Palonosetron	Aloxi	1	1	2012-03-14	1	antiemetics and
21							antinauseants
22	Crizotinib	Xalkori	1	1	1 2012-04-25	1	antineoplastic agents
23	Fidaxomicin	Dificid	1	1	2012-06-07	1	antidiarrheals, intestinal
24							antiinflammatory/antiinf
25							ective agents
26	Lurasidone	Latuda	1	1	2012-06-13	1	psycholeptics
27	Ruxolitinib	Jakavi	1	1	2012-06-19	1	antineoplastic agents
28	Collagenase	Xiaflex	1	1	2012-07-05		1 other drugs for disorders
29	clostridium						of the musculo-skeletal
30	histolviticum						svstem
31	Axitinib	Inlyta	1	1	2012-07-12	1	antineoplastic agents
32	Catridecacog	Tretten	1	1	2012-07-19		1 antihemorrhagics
33	Bendamustine	Treanda	1	1	2012-08-24	1	antineoplastic agents
34	Pirfenidone	Esbriet	1	1	2012-10-01		immunosuppressants
35							
36							
37							
38							
39							
40							
41							
42							
43							
44							
45							
46							
47							

1								
2								
3	Elvitegravir,	Stribild	1	1		2012-11-26	1	antivirals for systemic
4	emtricitabine,							use
5	tenofovir,							
6	cobicistat							
7								
8	Ivacaftor	Kalydeco	1	1		2012-11-26	1	other respiratory system
9								products
10	Stiripentol	Diacomit	1	1		2012-12-21	1	antiepileptics
11	Nebivolol	Bystolic	1	1		2012-12-21	1	beta blocking agents
12	Ingenol	Picato	1	1		2013-01-30	1	antibiotics and
13								chemotherapeutics for
14								dermatological use
15								antineoplastic agents
16	Brentuximab	Adcetris	1	1	1	2013-02-01	1	
17	Meningococcal	Nimenrix	1	1		2013-03-05	1	vaccines
18	polysaccharide							
19	groups A,C,W-							
20	135 & Y							
21	conjugate							
22	vaccine, Tetanus							
23	toxoid							
24	Mirabegron	Myrbetriq	1	1		2013-03-06	1	urologicals
25	Regorafenib	Stivarga	1	1		2013-03-11	1	antineoplastic agents
26	Rotigotine	Neupro	1	1		2013-03-21	1	anti-parkinson drugs
27	Dimethyl	Tecfidera	1	1		2013-04-03	1	other nervous system
28	Perampanel	Fycompa	1	1		2013-04-04	1	antiepileptics
29	Pertuzumab	Perjeta	1	1		2013-04-12	1	antineoplastic agents
30	Enzalutamide	Xtandi	1	1		2013-05-29	1	endocrine therapy
31	Ulipristal	Fibristal	1	1		2013-06-24	1	sex hormones and
32								modulators of the genital
33								system
34	Vismodegib	Erivedge	1	1		2013-07-12	1	antineoplastic agents
35	Dabrafenib	Tafinlar	1	1		2013-07-16	1	antineoplastic agents
36	Trametinib	Mekinist	1	1		2013-07-18	1	antineoplastic agents
37								
38								
39								
40								
41								
42								
43								
44								
45								
46								
47								

1								
2								
3	Fluticasone and vilatnerol	Breo ellipta		1	1	2013-07-23	1	drugs for obstructive airway diseases
4								
5	Aclidinium	Tudorza genuair		1	1	2013-07-29	1	drugs for obstructive airway diseases
6								
7	Rifaximin	Zaxine		1	1	2013-08-13	1	antidiarrheals, intestinal antiinflammatory/antiinf
8								
9								
10								
11	Ocriplasmin	Jetrea	1			2013-08-13	1	effective agents ophthalmologicals
12	Trastuzumab	Kadcyla		1	1	2013-09-11	1	antineoplastic agents
13	emtansine							
14	Galsulfase	Naglazyme	1		1	2013-09-16	1	other alimentary tract and metabolism products
15								
16								
17	Riociguat	Adempas		1	1	2013-09-19	1	antihypertensives
18	Pasireotide	Signifor	1		1	2013-09-23	1	pituitary and hypothalamic hormones
19								
20								
21	Efinaconazole	Jublia		1	1	2013-10-02	1	drugs used in diabetes
22	Romidepsin	Istodax		1	1	2013-10-16	1	antineoplastic agents
23	Dolutegravir	Tivicay		1	1	2013-10-31	1	antivirals for systemic use
24								
25	Afatinib	Giotrif		1	1	2013-11-01	1	antineoplastic agents
26	Macitentan	Opsumit		1	1	2013-11-06	1	antihypertensives
27	Aflibercept	Eylea		1	1	2013-11-08	1	antineoplastic agents
28	Teriflunomide	Aubagio		1	1	2013-11-14	1	immunosuppressants
29	Simeprevir	Galexos		1	1	2013-11-18	1	antivirals for systemic use
30								
31	Alogliptin	Nesina		1	1	2013-11-27	1	drugs used in diabetes
32	Linacotide	Constella		1	1	2013-12-02	1	drugs for constipation
33	Multicomponent meningococcal B vaccine	Bexsero	1		1	2013-12-06	1	vaccines
34								
35	Radium-223 dichloride	Xofigo		1	1	2013-12-12	1	therapeutic radiopharmaceuticals
36								
37								
38								
39								
40								
41								
42								
43								
44								
45								
46								
47								

1								
2								
3	Sofosbuvir	Sovaldi	1		1	2013-12-13	1	antivirals for systemic
4								use
5	Umeclidinium	Anoro ellipta		1	1	2013-12-23	1	drugs for obstructive
6	and vilanterol							airway diseases
7	Pomalidomide	Pomalyst	1		1	2014-01-20	1	immunosuppressants
8	Lomitapide	Juxtapid		1	1	2014-02-04	1	lipid modifying agents
9	Aflibercept	Zaltrap		1	1	2014-02-12		1 antineoplastic agents
10	Bosutinibs	Bosulif		1	1	1 2014-03-14	1	antineoplastic agents
11	Recombinant	Alprolix		1	1	2014-03-20		1 antihemorrhagics
12	human							
13	coagulation							
14	Factor IX, FC							
15	fusion protein							
16	Tofacitinib	Xeljanz		1	1	2014-04-17	1	immunosuppressants
17	Tesamorelin	Egrifta		1	1	2014-04-29	1	pituitary and
18								hypothalamic hormones
19	Canagliflozin	Invokana		1	1	2014-05-23	1	drugs used in diabetes
20	Taliglucerase	Elelyso		1	1	2014-05-29		1 other alimentary tract
21	Alfa							and metabolism products
22	Eslicarbazepine	Aptiom		1	1	2014-07-08	1	antiepileptics
23	Antihemophilic	Eloctate		1	1	2014-08-22		1 antihemorrhagics
24	factor, FC fusion							
25	protein							
26	Ledipasvir and	Harvoni		1	1	2014-10-15	1	antivirals for systemic
27	sofosbuvir							use
28	Vortioxetine	Trintellix		1	1	2014-10-22	1	psychoanaleptics
29	Simoctocog alfa	Nuwiq		1	1	2014-10-23		1 antihemorrhagics
30	Azelastine and	Dymista		1	1	2014-10-23	1	nasal preparations
31	fluticasone							
32	Conjugated	Duavive		1	1	2014-10-23	1	sex hormones and
33	estrogens and							modulators of the genital
34	bazedoxifene							system
35	acetate							
36								
37								
38								
39								
40								
41								
42								
43								
44								
45								
46								
47								

1										
2										
3	Apremilast	Otezla		1	1			2014-11-12	1	immunosuppressants
4	Ibrutinib	Imbruvica	1			1	1	2014-11-17	1	antineoplastic agents
5	Obinutuzumab	Gazyva	1		1			2014-11-25		1 antineoplastic agents
6	Siltuximab	Sylvant		1		1		2014-12-03		1 immunosuppressants
7	Dapagliflozin	Forxiga		1	1			2014-12-12	1	drugs used in diabetes
8	Ritonavir,	Holkira Pak		1		1		2014-12-22	1	antivirals for systemic
9	paritaprevir,									use
10	ombitasvir,									
11	dasabuvir									
12	Sodium	Pheburane		1		1		2015-01-26	1	other alimentary tract
13	phenylbutyrate									and metabolism products
14	Vedolizumab	Entyvio		1	1			2015-01-29		1 immunosuppressants
15	Human	Gardasil 9		1	1			2015-02-05		1 vaccines
16	papillomavirus 9									
17	valent vaccine,									
18	recombinant									
19	Deferiprone	Ferriprox		1	1			2015-02-13	1	all other therapeutic
20										products
21	Secukinumab	Cosentyx		1	1			2015-02-27		1 immunosuppressants
22	Tedizolid	Sivextro		1	1			2015-03-17	1	antibacterials for
23										systemic use
24	Idelalisib	Zydelig		1	1		1	2015-03-27	1	antineoplastic agents
25	Ceritinib	Zykadia		1	1		1	2015-03-27	1	antineoplastic agents
26	Ponatinib	Iclusig		1	1		1	2015-04-02	1	antineoplastic agents
27	Carglumic Acid	Carbaglu	1			1		2015-04-10	1	other alimentary tract
28										and metabolism products
29	Ivermectin	Rosiver		1	1			2015-04-22	1	anthelmintics
30	Levomilnacipran	Fetzima		1	1			2015-05-08	1	psychoanaleptics
31	Pembrolizumab	Keytruda		1	1		1	2015-05-19		1 antineoplastic agents
32	Naloxegol	Movantik		1	1			2015-06-02	1	drugs for constipation
33	Nintedanib	Ofev		1	1			2015-06-25	1	antineoplastic agents
34										
35										
36										
37										
38										
39										
40										
41										
42										
43										
44										
45										
46										
47										

1								
2								
3	Ramucirumab	Cyramza	1	1		2015-07-16		1 antineoplastic agents
4	Empagliflozin	Jardiance	1	1		2015-07-23	1	drugs used in diabetes
5	Mifepristone	Mifegymiso	1	1		2015-07-29	1	sex hormones and
6	and Misoprostol							modulators of the genital
7								svstem
8	Daclatasvir	Daklinza	1	1		2015-08-13	1	antivirals for systemic
9								use
10	Asfotase Alfa	Strensiq	1	1		2015-08-14		1 other alimentary tract
11								and metabolism products
12								
13								
14	Teduglutide	Revestive	1	1		2015-09-04		1 other alimentary tract
15								and metabolism products
16								
17	Evolocumab	Repatha	1	1		2015-09-10		1 lipid modifying agents
18	Nivolumab	Opdivo	1	1		2015-09-25		1 antineoplastic agents
19	Ceftolozane	Zerbaxa	1	1		2015-09-30	1	antibacterials for
20	Sulfate and							systemic use
21	Tazobactam							
22	Sodium							
23	Sacubitril,	Entresto	1	1		2015-10-02	1	agents acting on the
24	Valsartan							renin-angiotensin system
25								
26	Dulaglutide	Trulicity	1	1		2015-11-10		1 drugs used in diabetes
27	Elvitegravir,	Genvoya	1	1		2015-11-27	1	antivirals for systemic
28	Cobicistat,							use
29	Emtricitabine,							
30	Tenofovir							
31	Alafenamide							
32	Humifumate							
33	Mepolizumab	Nucala	1	1		2015-12-03		1 drugs for obstructive
34								airway diseases
35	Lenvatinib	Lenvima	1	1		2015-12-22	1	antineoplastic agents
36	Blinatumomab	Blincyto	1	1		2015-12-22		1 antineoplastic agents
37	Carfilzomib	Kyprolis	1	1		2016-01-15	1	antineoplastic agents
38								
39								
40								
41								
42								
43								
44								
45								
46								
47								

1								
2								
3	Elbasvir,	Zepatier	1	1	2016-01-19	1		antivirals for systemic
4	Grazoprevir							use
5	Selexipag	Uptravi	1	1	2016-01-20	1		antithrombotic agents
6	Ivacaftor,	Orkambi	1	1	2016-01-26	1		other respiratory system
7	Lumacaftor							products
8	Sugammadex	Bridion	1	1	2016-02-05	1		all other therapeutic
9								products
10								antineoplastic agents
11	Cobimetinib	Cotellic	1	1	2016-02-22	1		antiepileptics
12	Brivaracetam	Brivlera	1	1	2016-03-09	1		antivirals for systemic
13	Asunaprevir	Sunvepra	1	1	2016-03-09	1		use
14								antineoplastic agents
15	Palbociclib	Ibrance	1	1	2016-03-16	1		lipid modifying agents
16	Alirocumab	Praluent	1	1	2016-04-11		1	antihistamines for
17	Bilastine	Blexten	1	1	2016-04-21	1		systemic use
18								all other therapeutic
19	Idarucizumab	Praxbind	1	1	2016-04-29		1	products
20								antineoplastic agents
21	Olaparib	Lynparza	1	1	2016-04-29	1		immunosuppressants
22	Ixekizumab	Taltz	1	1	2016-05-25		1	antineoplastic agents
23	Osimertinib	Tagrisso	1	1	2016-07-05	1		antivirals for systemic
24	Sofosbuvir +	Epclusa	1	1	2016-07-11	1		use
25	Velpatasvir							antineoplastic agents
26	Ixazomib	Ninlaro	1	1	2016-08-04	1		other alimentary tract
27	Nitisinone	MDK-Nitisinone	1	1	2016-09-20	1		and metabolism products
28								
29								
30								
31								
32								
33	Venetoclax	Venclexta	1	1	2016-09-30	1		antineoplastic agents
34	Edoxaban	Lixiana	1	1	2016-11-04	1		antithrombotic agents
35	Nitisinone	Nitisinone	1	1	2016-11-04	1		other alimentary tract
36								and metabolism products
37								
38								
39	Daclizumab beta	Zinbryta	1	1	2016-12-08		1	immunosuppressants
40								
41								
42								
43								
44								
45								
46								
47								

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

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)**

For peer review only

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

1						
2						
3	Reviparin	Clivarine	1		1996-09-10	antithrombotic agents
4	Diphtheria, tetanus &	Infanrix		1	1996-12-17	vaccines
5	acellular pertussis					
6	vaccine					
7	Cisatracurium	Nimbex injectior	1		1996-12-18	muscle relaxants
8	Remifentanil	Ultiva injection	1		1996-12-24	anesthetics
9	Tiludronate	Skelid	1		1997-02-06	drugs for treatment of bone
10						disease
11	Tazarotene	Tazorac Gel	1		1997-02-25	antipsoriatics
12	Praziquantel	Biltricide	1		1997-03-07	anthelmintics
13	Molgramostim	Leucomax		1	1997-03-10	immunostimulants
14	Fosphenytoin	Cerebyx injectioi	1		1997-03-20	antiepileptics
15	Butenafine	Dr. Scholl's athle	1		1997-04-15	antifungals for dermatological
16						use
17	Troglitazone	Rezulin		1	1997-05-09	drugs used in diabetes
18	Trandolapril	Odrik	1		1997-05-15	agents acting on the renin-
19						angiotensin system
20	Follitropin alpha	Gonal-F	1		1997-06-06	sex hormones and modulators
21						of the genital system
22	Kit for preparation	Myoscint	1		1997-07-02	diagnostic radiopharmaceuticals
23	of indium in 111					
24	imciromab					
25	pentetate					
26	Cytomegalovirus	Cytogam	1		1997-08-01	immune sera and
27	immune globulin					immunoglobulins
28	Oxiconazole	Oxizole	1		1997-08-08	antifungals for dermatological
29						use
30	Respiratory	Respigam		1	1997-08-20	immune sera and
31	syncytial virus					immunoglobulins
32	immune globulin					
33	Arcitumomab	CEA-Scan	1		1997-09-16	diagnostic radiopharmaceuticals
34						
35						
36						
37						
38						
39						
40						
41						
42						
43						
44						
45						
46						
47						

1						
2						
3	Olopatadine	Patanol	1	1997-09-16		ophthalmologicals
4						
5	Pegaspargase	Oncaspar	1	1997-11-19		antineoplastic agents
6						
7	Anagrelide as hydrochloride	Agrylin	1	1997-11-19		antineoplastic agents
8						
9	Nadroparin	Fraxiparine	1	1997-11-27		antithrombotic agents
10	Bicisate	OncoScint	1	1998-01-16		diagnostic radiopharmaceuticals
11						
12	Gadolinium (III)	Gadolite	1	1998-04-08		contrast media
13	Lexidronam	Quadramet	1	1998-06-22		therapeutic radiopharmaceuticals
14						
15	Miglitol	Glyset	1	1998-07-22		drugs used in diabetes
16						
17	Lipoprotein-OspA antigen	Lymerix	1	1998-12-02		vaccines
18						
19	recombinant					
20	Toremifene	Fareston	1	1998-12-14		endocrine therapy
21	Cefdinir	Omnicef	1	1999-02-05		antibacterials for systemic use
22						
23	Methacholine	Methacoline	1	1999-02-25		diagnostic agents
24						
25	Fosfomycin	Monurol	1	1999-04-12		antibacterials for systemic use
26						
27	Alitretinoin	Panretin	1	1999-06-11		other dermatological preparations
28						
29	Ioxilan	Oxilan	1	1999-10-05		contrast media
30	Mangafodipir	Teslascan	1	2000-02-09	1	contrast media
31						
32	Sevelamer	Renagel	1	2000-02-24	1	all other therapeutic products
33						
34	Valrubicin	Valstar	1	2000-07-04	1	antineoplastic agents
35	Ibutilide	Corvert injection	1	2000-07-14	1	cardiac therapy
36	Fomepizole	Antizol	1	2000-11-30	1	all other therapeutic products
37	Amlexanox	Apthera	1	2000-12-11	1	stomatological preparations
38						
39	Tegafur/uracil and leucovorin calcium	Orzel	1	2001-04-06	1	antineoplastic agents
40						
41	Argatroban	Argatroban	1	2001-06-04	1	antithrombotic agents
42						
43						
44						
45						
46						
47						

1							
2							
3	Aminolevulinic acid	Levulan	1		2001-06-20	1	antineoplastic agents
4	Infliximab	Remicade		1	2001-09-27		1 immunosuppressants
5							
6	Levobupivacaine	Chirocaine	1		2002-03-20	1	anesthetics
7	Unoprostone	Rescula	1		2002-04-03	1	ophthalmologicals
8	isopropyl						
9	Thyrotropin	Thyrogen	1		2002-05-31		1 diagnostic agents
10	Anti-thymocyte	Thymoglobulin	1		2002-11-20		1 immunosuppressants
11	globulin						
12	Dextromethylpheni	Attenade	1		2003-08-12	1	psychoanaleptics
13	date						
14	Sulfur Hexafluoride	Sonovue	1		2004-02-12	1	contrast media
15	Yttrium-90	Yttrium-90		1	2004-12-02		1 therapeutic
16							radiopharmaceuticals
17	Choriogonadotropin	Ovidrel	1		2004-12-16		1 sex hormones and modulators
18	Alfa						of the genital system
19	Sulesomab	Leukoscan	1		2005-01-17		1 diagnostic radiopharmaceuticals
20							
21	Tositumomab	Bexxar		1	2005-08-18		1 therapeutic
22							radiopharmaceuticals
23	Nitric oxide	Inomax		1	2005-09-23	1	other respiratory system
24							products
25	F-	Cantrace		1	2006-07-27		1 diagnostic radiopharmaceuticals
26	Fluorodeoxyglucose						
27	Lumiracoxib	Prexige	1		2006-11-02	1	antiinflammatory and
28							antirheumatic products
29	Nelarabine	Atriance		1	2007-09-22	1	antineoplastic agents
30	Rotavirus vaccine	Rotarix	1		2007-10-09		1 vaccines
31							
32	Retapamulin	Altargo	1		2008-03-19	1	antibiotics and
33							chemotherapeutics for
34							dermatological use
35							
36							
37							
38							
39							
40							
41							
42							
43							
44							
45							
46							
47							

1							
2							
3	Methoxy	Mircera	1	2008-03-31		1	antianemic preparations
4	Polyethylene glycol-						
5	epoetin beta						
6	Telavancin	Vibativ	1	2009-09-29	1		antibacterials for systemic use
7	Human C1 esterase	Berinert	1	2010-05-31		1	other hematological agents
8	inhibitor						
9	Influenza vaccine	Flumist	1	2010-06-22		1	vaccines
10	Zucapsaicin	Civanex (Zuacta	1	2010-07-15	1		topical products for joint and
11							muscular pain
12							
13	Clevidipine	Cleviprex	1	2011-04-15	1		calcium channel blockers
14	Rubidium chloride rb	Ruby-fill		2011-09-20		1	diagnostic radiopharmaceuticals
15	82		1				
16	Doxycycline	Efracea	1	2011-11-14	1		antibacterials for systemic use
17	Ferumoxytol	Feraheme	1	2011-12-08	1		antianemic preparations
18	Remestemcel-L	Prochymal		2012-05-17		1	unassigned
19	Ezogabine	Potiga	1	2012-10-08	1		antiepileptics
20	Haemagglutinin-	Arepranrix H5N1	1	2013-02-13		1	vaccines
21	Strain A						
22	Olodaterol	Striverdi respim:	1	2013-06-11	1		drugs for obstructive airway
23							diseases
24	Difluprednate	Durezol	1	2013-11-04	1		corticosteroids, dermatological
25							preparations
26	Tafluprost	Saflutan	1	2014-05-26	1		ophthalmologicals
27	Elosulfase Alfa	Vimizim		2014-07-02		1	other alimentary tract and
28			1				metabolism products
29	Turoctocog alfa	Zonovate	1	2014-12-08		1	antihemorrhagics
30	Bromfenac	Prolensa	1	2015-03-26	1		ophthalmologicals
31	Albiglutide	Eperzan	1	2015-07-15		1	drugs used in diabetes
32	Vilazodone	Viibryd	1	2015-07-16	1		psychoanaleptics
33	Polidocanol	Varithena	1	2015-08-04	1		vasoprotectives
34	Peginterferon Beta-	Plegrixy	1	2015-08-10		1	immunostimulants
35	1A						
36							
37							
38							
39							
40							
41							
42							
43							
44							
45							
46							
47							

1							
2							
3	Antihemophilic	Obizur	1	2015-10-14		1	antihemorrhagics
4	Factor						
5	(Recombinant)						
6	Porcine Sequence						
7	Lubiprostone	Amitiza	1	2015-10-14	1		drugs for constipation
8	Albutrepenonacog	Idelvion	1	2016-01-26		1	antihemorrhagics
9	Alfa						
10	Finafloxacin	Xtoro	1	2016-03-11		1	otologicals
11	Glycerol	Ravicti	1	2016-03-16		1	other alimentary tract and
12	Phenylbutyrate						metabolism products
13	Vorapaxar	Zontivity	1	2016-05-13		1	antithrombotic agents
14	Elotuzumab	Empliciti	1	2016-06-21		1	antineoplastic agents
15	Daratumumab	Darzalex	1	2016-06-29		1	antineoplastic agents
16	Rupatadine	Rupall	1	2016-07-20		1	antihistamines for systemic use
17							
18	Reslizumab	Cinqair	1	2016-07-20		1	drugs for obstructive airway
19							diseases
20	Bepotastine	Bepreve	1	2016-07-27		1	antihistamines for systemic use
21							
22	Alectinib	Alecensaro	1	2016-09-29		1	antineoplastic agents
23	Antihemophilic	Adynovate	1	2016-11-17		1	antihemorrhagics
24	Factor						
25	(Recombinant),						
26	PFGvlated						
27	Gadoterate	Dotarem	1	2016-11-25		1	contrast media
28	Meglumine						
29	Botulinium antitoxin	BAT	1	2016-12-08		1	immune sera and
30	serotypes A, B,C, D,						immunoglobulins
31	E, F and G						
32	Lonococog Alfa	Afstyla	1	2016-12-12		1	antihemorrhagics
33							
34							
35							
36							
37							
38							
39							
40							
41							
42							
43							
44							
45							
46							
47							

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	Title, 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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	Methods, pages 6, 7
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed	Not relevant
		<i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed	
		<i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	
		(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) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	Not relevant
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	Results, pages 11-15
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	
		<i>Cross-sectional study</i> —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

1
2 Generalisability 21 Discuss the generalisability (external validity) of the study Not relevant
3 results

4 **Other information**

5 Funding 22 Give the source of funding and the role of the funders for the Page 20
6 present study and, if applicable, for the original study on which
7 the present article is based
8

9
10 *Give information separately for cases and controls in case-control studies and, if applicable, for exposed and
11 unexposed groups in cohort and cross-sectional studies.
12

13
14 **Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and
15 published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely
16 available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at
17 <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is
18 available at www.strobe-statement.org.
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60