Hormonal contraception approval in Canada, the United States and the United Kingdom

Troskie C[1,2], Goktepe O[2] MSc, Soon JA[1,2] RPharm, PhD, Norman WV[2,3 *] MD, MHSc

[1]Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, BC, V6T 1Z3.
[2]Contraception Access Research Team, Women's Health Research Institute, University of British Columbia.
[3]Dept of Family Practice, Faculty of Medicine, University of British Columbia

Abbreviated title: Regulatory approval of contraceptives in 3 countries

Key words: Contraception; Drug approval; Canada; United States; United Kingdom; Pregnancy, Unplanned

*Author to whom correspondence should be addressed:
Wendy V. Norman
Department of Family Practice, University of British Columbia
320-5950 University Boulevard,
Vancouver, British Columbia, Canada V6Z 1T3
wendy.norman@ubc.ca

Number of words (text): 2382

Number of words (abstract):250

Number of tables: 2

Number of figures:4

Funding: CT was supported throughout this study by a Graduate Student Scholarship award from the Canadian Institutes of Health Research–Public Health Agency of Canada Chair in Family Planning Public Health Research (Funding Reference Number: CPP 137903). Infrastructure support was provided to the Contraception Access Research Team by the Women's Health Research Institute of the BC Women's Hospital and Health Centre.

Authors' Contributions: WN conceived and designed the study with elements and revisions contributed by all authors. CT undertook data acquisition and initial analyses with assistance from JS and WN. OG provided statistical support for the analyses. CT wrote the initial draft and all authors contributed to revisions and accepted the final manuscript.

Declaration of Conflict of Interest: All authors declare we have no conflict of interest with respect to this research. WN and JS conduct an investigator-initiated randomized controlled trial to which Bayer Canada Inc. has donated contraceptive devices.

Abstract

OBJECTIVE: To determine discrepancies in contraception regulatory approval between Health Canada (HC), the United States (USA) Food and Drug Administration (FDA), and the United Kingdom (UK) Medicines and Healthcare Products Regulatory Agency (MHRA).

METHODS: We obtained hormonal contraceptive application submission and approval dates for HC, FDA and MHRA for methods approved from Jan 2000–Jan 2015, as well as data from other agencies for drugs approved by HC during this period, through public data sources and direct correspondence with the regulatory agencies.

RESULTS: During the study period 16 contraceptives were approved in Canada, compared to 25 in the USA and 12 in the UK. All applications were submitted to the UK or USA prior to Canada, where applications were submitted 733 (SD557, USA), and 949 (SD940, UK) days later. Mean days to approval in Canada was significantly longer (754, SD502) than in the USA (504, SD257, p=0.04) and UK (392, SD233, p=0.02). No contraceptive implants have been approved in Canada.

CONCLUSION: Between 2000 and 2015, applications for hormonal contraceptive approval were consistently submitted later to Canadian, than to USA or UK regulators. HC approved fewer contraceptives than the FDA, and took longer to do so than the USA or UK regulators. Transparency was poor, with no information available on unsuccessful applications. Canadian women wait longer and have fewer options, including no access to implants, one of the two most effective reversible contraceptives. Review

of Canadian federal regulatory policies and procedures has the potential to improve prevention of unintended pregnancy in Canada.

INTRODUCTION

The existence of differences in the availability of hormonal contraceptives between Canada and other western countries had been demonstrated in the 1990's, but no recent evaluation is available [1]. Azzarello et al. (2004) found that up until the year 2000, Canadian women had access to fewer hormonal contraceptive options compared to the United States (USA) and United Kingdom (UK). Downing et al. (2012) noted that the overall drug approval process through Health Canada (HC) required more time when compared to similar approval in the USA and UK [2]. Researchers have also compared the overall access of new drugs in Canada to access in the USA and European Union (EU). The delay in submission to the national drug regulatory agency by the pharmaceutical companies, when compared between Canada's HC, the Food and Drug Administration (FDA) of the USA and the European Medicines Agency (EMA) was greater than the delay due to the approval process [3], compounding the delayed access to pharmaceuticals for Canadians.

Hormonal contraceptives are an effective method of pregnancy prevention [4-7]. In particular, long acting reversible contraception (LARC), including both intrauterine methods and sub-dermal implant methods, are the most effective non-permanent methods to prevent unintended pregnancy and thus support women to time and space their pregnancies [4,8-11]. Currently, hormonal contraceptives are available to use via several routes of administration: oral, vaginal, transdermal, injection, dermal patch, intrauterine or sub-dermal implants [12]. Hormonal

contraceptives are available with varying amounts of estrogen, and with alternative types and amounts of progestin. Having a range of available contraceptive choices, including variations in both route of administration and hormonal mix and dosage, allows women to select methods that best fit their individual requirements [13–15]. Contraceptives that more closely align with individual needs are more likely to be used [16–18]. In particular “set and forget” LARC methods have been exceptionally effective in reducing the consequences of unintended pregnancy [4, 8–11].

In 2005, 31% of Canadian women completing their reproductive years had experienced at least one abortion [19]. Similarly 30% of American women have at least one abortion during their lives and only just over half of pregnancies among women in the UK are intended [20–21]. As unintended pregnancy is common, women benefit when timely access to suitable contraceptive methods is available [19,22]. Hormonal contraceptives are convenient and effective resources allowing women to plan and space pregnancies [15–17]. As such, the timely approval of a full range of hormonal contraceptive methods is important to assist women and their families to meet their reproductive goals.

We explored the regulatory approval times of new hormonal contraceptives by HC since the year 2000, and compared these to similar approval times by the FDA in the USA, and the EMA in Europe. However, as the EMA has approved very few contraceptives we chose a single European country as a comparator, using data from submissions and approvals for the MHRA of the UK. In this

way we aimed to provide an updated analysis on the comparative submission and approval timelines for hormonal contraceptives in Canada, the USA and the UK.

MATERIALS AND METHODS

We collected data for this observational study from HC, the FDA, and MHRA. We included all available data related to any application to each of these agencies for any hormonal contraceptive medication that was approved between January 2000 and January 2015. We included all routes of delivery for hormonal contraception: oral tablets, dermal patches, intravaginal rings, intrauterine delivery systems, and subdermal implants (if any). We excluded approvals for generic versions of previously approved drugs. Two specific products were approved after January 2000 in Canada but received prior approval elsewhere. Thus we included relevant data dating from 1998 from the UK and USA on the submission and approval times of these two products.

The HC Drug Product Online Database [12] provided the dates for final approval in Canada, whereas the HC Notice of Compliance Online Database [23] and the HC Drugs, Health Products Patent Register [24] provided the application dates for contraceptives. We used the HC Health Products and Food Branch Performance Reports for 2004 [25], 2005 [26], 2006-07 [27] and the Drug Submission Performance Annual Reports for Therapeutic Products [28-9] to cross check application and approval dates when possible. Correspondence with the HC Office of Submissions and Intellectualal Property provided approval dates for applications

not available from the above-mentioned HC sources. We were not able to access any information related to applications for contraceptives that may have been submitted to HC but not approved.

For contraceptives approved in USA, we accessed application and approval dates through the FDA Approved Drug Products Database [30]. For some of the contraceptives available, the FDA Approved Drug Products Database did not list complete data including both application and approval dates. We corresponded with the FDA Division of Drug Information to complete the data.

Due to the different paths to drug approval in the European Union (EU), we searched several databases for contraceptive availability in Europe. Few contraceptives were approved through the European Medicines Agency (EMA) [31], while the majority of the contraceptives were approved through the MHRA [32]. Consequently, we focussed on the approval process in the UK. We found additional information in the Drug Information Handbook [33] on the drug approval process in the UK. On the MHRA website, we retrieved Patient Information Leaflet (PIL) and Summaries of Product Characteristics (SPC), for contraceptives available in the UK [34], as well as final approval dates for several contraceptives. Subsequently, some of these approval dates were confirmed through the MHRA Public Assessment Reports [35]. For information on contraceptives that were not available on the MHRA website, correspondence with the Information Management Division of MHRA provided the remaining application and approval dates.

Additional and confirmatory information on contraceptive availability in Canada, the USA, and the UK were acquired through the International Planned Parenthood Hormonal Contraceptives Directory [36]. Data published in the literature [1] was used to confirm contraceptives approved prior to 2002. The Lexicomp Drug Information Handbook provided an additional complete list of contraceptives available in Canada and the USA [37].

Analysis

Initial hormonal contraceptive application submission dates were compared using mean and standard deviation of the difference in days between the dates of submission of individual drugs to each successive national regulator.

Time to approval was defined as the number of days between submission date and approval date for each drug for Canada, USA and UK. Two drugs approved after 2000 in Canada had been approved prior to 2000 in the UK or the USA, thus for purposes of comparison, the approval dates in USA or UK prior to 2000 for these specific drugs was included. We examined the approval times for novel and non-novel pharmaceuticals both together and separately. We defined a hormonal contraceptive as novel when the product involved either a new active ingredient, such as a new type of progestin, or a new drug delivery system, such as an intravaginal ring. One-way Analysis of Variance (ANOVA) test was used to compare the means of drug approval times between USA, UK and Canada as well as to compare the means days between novel and non-novel drugs. All novel drugs were further reviewed between

countries and their approval years were examined. We stratified the years of approval dates into three intervals of 1998–2004, 2005–2010 and 2011–2015 to compare whether the approval times showed any differences between the three cohorts (early, mid and late) with the study period.

All statistical analyses were done in R version 3.1.2.

RESULTS

Between January 2000 and January 2015 we found that 16 contraceptives were approved in Canada, 12 were approved in the UK, and 25 were approved in the USA. Additionally, among the contraceptives approved in Canada after January 2000, an emergency contraceptive had been approved in the USA and UK in 1999, and a levonorgestrel intrauterine system had been approved in the UK in 1998, so that our submission and approval date calculations include 16 contraceptives in Canada comparing to 26 in the USA and 14 in the UK and encompass 29 distinct hormonal contraceptives in total.

The overall initial application submission dates were compared between Canada, USA and the UK for equivalent contraceptives. During this interval 16 drugs were submitted to at least two countries, although none of the applications in this period were submitted initially to Canada. In 12 out of 16 cases, applications were first submitted to the USA, and 3 were first submitted to the UK.

For the drugs submitted to the USA first, submission to Canada occurred an average of 733 days (N=12, SD 557, range= 83–

1552) later. For the drugs submitted to the UK first, submission to Canada was 949 days (N=4, SD 940, range=135-1977) later. When the UK and USA application dates were combined, submission to Canada occurred an average of 773 days later (N=16, SD 611, range=83-1977).

We defined "time to approval" as the number of days between initial application and final approval. Time to approval (Table 1)in Canada was significantly longer (754, SD 502) than in the USA (504, SD 257, p=0.04) and UK (392, SD 233, p=0.02). Canada's approval times (Figure 1) were significantly different than UK-USA combined (p=0.006). The distribution of time to approval is shown in Figure 2.

Eight of the twenty-nine drugs are novel drugs and their approval times were investigated separately. Table 2 shows each novel drug by country and time to approval. Canada's time to approval for novel drugs generally required a year and a half to two years (range 452 to 775 days) with the exception of over six years (1926 days) in the cases of one combined hormonal oral contraceptive. Sub-dermal etonorgestrel implant contraception (Implanon®) was associated with the largest difference in time to approval between UK (78 days) and USA (1021 days), and this method has not yet been approved in Canada. For levonorgestrel-releasing intrauterine contraception, Health Canada approval required substantially longer (709 days) compared to UK (58 days) and USA (310 days). In contrast, time to approval for new administration formats of approved agents (combined hormonal

contraceptive vaginal ring, patch and oral tablets packaged for three months of continuous use) were similar across each country.

As shown in Figure 3 and Table 1, novel drug approval times did not show any difference when compared to non-novel drugs (p=0.94).

Approval year cohorts examining three intervals, did not show any overall difference in the mean time to approval (p=0.90) between the early, mid or late cohorts of years within the study time frame. Canada demonstrates no improvement in time to approval across the three time cohorts (Figure 4). In contrast, contraceptive approvals in the UK have taken longer more recently, while approvals in the USA have occurred more rapidly.

DISCUSSION

Applications for approval of hormonal contraceptive methods were consistently submitted more than two years later to Canada for methods approved between 2000 and 2015, compared to submissions for approval of the same medication to either the UK or the USA. Once the application was submitted, Health Canada required 50% more time to approve contraceptives than the FDA in the USA, and nearly twice as long as did the MHRA in the UK. Health Canada approved 64% of the number of hormonal contraceptives approved by the FDA, and only just over half (55%) of all agents approved by any of the three jurisdictions during the study interval. The UK had fewer contraceptives approved in this interval than Canada (12 vs. 16), however sub-dermal etonorgestrel implant (one of only two types of highly effective

LARC method) was approved in both the UK and the USA, yet not in Canada. This is relevant as internationally contraceptive sub-dermal implants have been shown to have a significant positive effect on population health and the reduction of unintended pregnancy, abortion, and adverse neonatal outcomes particularly among vulnerable populations such as teenagers and low income families [4, 8-11, 16-18, 38-41]

We were unable to locate information on applications that may have been submitted to Health Canada but were not approved [12, 42]. Thus, it is not possible to understand whether any application for approval of a contraceptive sub-dermal implant has been made to Health Canada, or if an application had been assessed but not approved.

Due to the lack of publicly available data on the health product regulatory agency websites or in publications, direct correspondence with the agencies was required to collect data on all hormonal contraception applications. Thus, a potential for bias may be introduced through the reliance on agency employees to report the application and approval times. However, we consider that the details provided to our request to the regulatory agencies for information was approved by the agency prior to their response, and is thus accurate.

Comprehensive data presentation by health regulatory agency websites could improve transparency and provide better public information. As we utilized every source we were able to identify for each portion of the data, and established triangulation

between multiple sources for most data, we are confident that our data is reliable and represents all hormonal contraceptives approved during this period within Canada, the USA, and the UK.

Further research could determine facilitators and barriers for drug approval process timelines in Canada. In addition to the delay in approval of contraceptives in Canada, there is a significant delay in application submissions by pharmaceutical companies to Health Canada. Analyses to define the relevant factors should be undertaken. Proactive leadership to facilitate or invite application submissions for contraceptives with significant proven population health advantages could be considered by Canadian health regulators.

Canadian women have access to fewer contraceptive choices, and wait longer for access, due both to delay in submission of applications for contraceptives to Health Canada, and to current Canadian federal regulatory policies and procedures which require significantly more time than in other countries. No implantable contraceptives, one of only two classes of highly effective LARC methods, have been approved for use in Canada. Availability of a variety of hormonal contraception options, including both classes of LARC methods, can reduce the number of unintended pregnancies, abortions, and neonatal complications particularly among vulnerable populations. Canadian government health systems could improve population health through addressing the regulatory barriers associated with unmet need for contraception, including the current absence of an approved contraceptive implant method,

in order to reduce the adverse consequences of unintended pregnancy among Canadians.

REFERENCES

1. Azzarello D, Collins J. Canadian access to hormonal contraceptive drug choices. JOGC 2004; 26:489-500.

2. Downing NS, Aminawing JA, Shah ND, Braunstein JB, Krumholz HM, Ross JS. Regulatory review of novel therapeutics-comparison of three regulatory agencies. N Engl J Med 2012; 366 (24): 2284-2293.

3. Shajarizadeh A, Hollis A. Delays in the submission of new drugs in Canada. CMAJ 2015; 187(1): E46- E51.

4. Trussel J. Contraceptive failure in the United States. Contraception. 2011 May;83(5):397-404.

5. Bahamondes L, Valeria Bahamondes M, Shulman LP. Non-contraceptive benefits of hormonal and intrauterine reversible contraceptive methods. Hum Reprod Update. 2015 Sep;21(5):640-51. doi: 10.1093/humupd/dmv023.

6. Seidman DS. Non-contraceptive benefits of hormonal contraception: time for renewed awareness. Eur J Contracept Reprod Health Care. 2011 Dec;16(6):407-8.

7. Barr NG. Managing adverse effects of hormonal contraceptives. American Family Physician 2010; 82(12): 1499-1506.

8. Romero L, Pazol K, Warner L, Gavin L, Moskosky S, Besera G, Loyola Briceno AC, Jatlaoui T, Barfield W; Centers for Disease Control and Prevention (CDC). Vital signs: trends in use of long-acting reversible contraception among teens aged 15-19 years seeking contraceptive services—United States, 2005-2013. MMWR Morb Mortal Wkly Rep. 2015 Apr 10;64(13):363-9.

9. American College of Obstetricians and Gynecologists Committee on Gynecologic Practice; Long-Acting Reversible Contraception Working Group. ACOG Committee Opinion no. 450: Increasing use of contraceptive implants and intrauterine devices to reduce unintended pregnancy. Obstet Gynecol. 2009 Dec;114(6):1434-8. doi: 10.1097/AOG.0b013e3181c6f965

10. Ricketts S, Klingler G, Schwalberg R. Game change in Colorado: widespread use of long-acting reversible contraceptives and rapid decline in births among young, low-

income women. Perspect Sex Reprod Health. 2014 Sep;46(3):125-32. doi: 10.1363/46e1714.

11. Biggs MA, Rocca CH, Brindis CD, Hirsch H, Grossman D. Did increasing use of highly effective contraception contribute to declining abortions in Iowa? Contraception. 2015 Feb;91(2):167-73. doi: 10.1016/j.contraception.2014.10.009

12. Health Canada Drug Product Online Database. Ottawa (ON): Health Canada. Available at: http://webprod5.hc-sc.gc.ca/dpd-bdpp/start-debuter.do?lang=eng (Accessed 2014 Nov - 2015 Feb).

13. Marnach ML, Long ME, Casey PM. Current issues in contraception. Mayo Clin Proc. 2013 Mar;88(3):295-9.

14. Lamvu G, Steiner MJ, Condon S, et al. Consistency between most important reasons for using contraception and current method used: the influence of health care providers. Contraception. 2006;63(4):399-403.

15. Johnson S, Pion C, Jennings V. Current methods and attitudes of women towards contraception in Europe and America. Reprod Health. 2013 Feb 5;10:7. doi: 10.1186/1742-4755-10-7.

16. Hatcher RA, Trussel J, Nelson AL. Contraceptive Technology. 20th revised ed. New York, NY: Ardent Media, 2011.

17. Halpern V, Lopez L, Grimes DA, Stockton LL, Gallo MF. Strategies to improve adherence and acceptability of hormonal methods for contraception. Cochrane Database Syst Rev, 10 (2013).

18. Wellings K, Brima N, Sadler K, Copas AJ, McDaid L, Mercer CH, McManus S, Stephenson J, Glasier A. Stopping and switching contraceptive methods: findings from Contessa, a prospective longitudinal study of women of reproductive age in England. Contraception. 2015 Jan;91(1):57-66.

19. Norman WV. Induced abortion in Canada 1974-2005: trends over the first generation with legal access. Contraception 2012; 85:185-191.

20. Jones RK, Kavanaugh ML. Changes in abortion rates between 2000 and 2008 and lifetime incidence of abortion. Obstet Gynecol. 2011 Jun;117(6):1358-66. doi: 10.1097/AOG.0b013e31821c405e.

21. Wellings K, Jones KG, Mercer CH, Tanton C, Clifton S, Datta J, Copas AJ, Erens B, Gibson LJ, Macdowall W, Sonnenberg P, Phelps A, Johnson AM. The prevalence of unplanned pregnancy and associated factors in Britain: findings from the third National Survey of Sexual Attitudes and Lifestyles (Natsal-

3). Lancet. 2013 Nov 30;382(9907):1807-16. doi: 10.1016/S0140-6736(13)62071-1.

22. Black A, Yang Q, Wu Wen S, Lalonde AB, Guilbert E, Fisher W. Contraceptive use among Canadian women of reproductive age: results of a national survey. J Obstet Gynaecol Can. 2009 Jul;31(7):627-40

23. Health Canada Notice of Compliance Online Database. Ottawa (ON): Health Canada. Available at: http://webprod5.hc-sc.gc.ca/noc-ac/index-eng.jsp (Accessed 2014 Nov. - 2015 Feb.).

24. Health Canada Drugs and Health Products Patent Register. Ottawa (ON): Health Canada Available at: http://pr-rdb.hc-sc.gc.ca/pr-rdb/index-eng.jsp (Accessed 2014 Nov. - 2015 Feb.).

25. Health Canada Regulatory Review of Pharmaceuticals, Biologics, and Medical Devices. 2004 Annual Summary of Performance. Ottawa (ON): Health Canada.

26. Health Canada Regulatory Review of Pharmaceuticals, Biologics, and Medical Devices. 2005 Annual Summary of Performance. Ottawa (ON): Health Canada.

27. Health Canada Health Products and Food Products Performance Report 2006-07. Ottawa (ON): Health Canada.

28. Therapeutic Products Directorate. Drug Submission Performance Annual Report. Fiscal Year 2013-2014. Ottawa (ON): Health Canada.

29. Therapeutic Products Directorate. Drug Submission Performance Annual Report. Fiscal Year 2011-2012. Ottawa (ON): Health Canada.

30. FDA Approved Drug Products Database. Available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm (Accessed 2014 Nov 30).

31. European Medicines Agency. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/includes/medicines/medicines_landing_page.jsp&mid=. (Accessed 2015 Feb 30)

32. Medicines and Healthcare Regulatory Agency. Available at: https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency (Accessed 2015 Feb 30)

33. Bonnie Snow. Drug Information: A guide to current resources. 3rd ed. New York: Neal-Schuman Publishers Inc; 2008.

34. MHRA Patient Information Leaflet (PIL) and Summaries of Product Characteristics (SPC). Available at:

http://www.mhra.gov.uk/Safetyinformation/Medicinesinformation/SPCandPILs/index.htm (Accessed 2014 Dec. – 2015 March).

35. MHRA Public Assessment Reports. Available at: http://www.mhra.gov.uk/Publications/PublicAssessmentReports/index.htm (Accessed 2014 Dec. – 2015 March).

36. Directory of Hormonal Contraceptives. International Planned Parenthood Federation. Available at: http://contraceptive.ippf.org/search (Accessed on 2014 Dec 16)

37. Drug Information Handbook. 23rd Edition. American Pharmacists Association. Lexicomp Drug Reference Handbooks. 2014.

38. Secura GM, Madden T, McNicholas C, Mullersman J, Buckel CM, Zhao Q, Peipert JF. Provision of no-cost, long-acting contraception and teenage pregnancy. N Engl J Med. 2014 Oct 2;371(14):1316-23. doi: 10.1056/NEJMoa1400506.

39. Goldthwaite LM, Duca L, Johnson RK, Ostendorf D, Sheeder J. Adverse Birth Outcomes in Colorado: Assessing the Impact of a Statewide Initiative to Prevent Unintended Pregnancy. Am J Public Health. 2015 Sep;105(9):e60-6. doi: 10.2105/AJPH.2015.302711.

40. Connolly A, Pietri G, Yu J, Humphreys S Association between long-acting reversible contraceptive use, teenage pregnancy, and abortion rates in England. Int J Womens Health. 2014 Nov 21;6:961-74. doi: 10.2147/IJWH.S64431.

41. Hathaway M, Torres L, Vollett-Krech J, Wohltjen H. Increasing LARC utilization: any woman, any place, any time. Clin Obstet Gynecol. 2014 Dec;57(4):718-30. doi: 10.1097/GRF.0000000000000071.

42. How Are Drugs Reviewed in Canada: Health Canada. Available at: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/activit/fs-fi/reviewfs_examenfd-eng.php (Accessed 2015 Aug 30).

Table 1: Analysis of Variance (ANOVA) results comparing approval times of different groups.

Comparison Groups: time to approval	**F-value(df)**	**p-value**
Comparing Canada, UK and USA	F(2, 53) = 4.63	0.01
Canada vs. UK only	F(1,28)=6.12	0.02
Canada vs. USA only	F(1,40)=4.57	0.04
Canada vs. [UK and USA combined]	F(1,54)=8.27	0.006
Novel Drugs vs. other drugs	F(1,54) = 0.006	0.94
Approval Year Intervals (98-04 vs. 05-10 vs. 11-15)	F(2,53) = 0.11	0.90

Table 2: Novel drug approval times stratified by country.

Contraceptive Method	Country	Days to Approval	Approval Days Stratified	Date of Approval
Ella® (ulipristal acetate- for emergency oral contraception)	Canada	452	401-600	2015-01-23
	UK	715	600+	2010-05-15
	USA	306	0-310	2010-08-16
Implanon® (etonorgestrel sub-dermal contraceptive implant)	Canada	Not Yet Approved	-	-
	UK	78	0-310	2009-02-06
	USA	1021	600+	2006-07-17
Mirena® (levonorgestrel-releasing intrauterine system)	Canada	709	600+	2000-11-24
	UK	58	0-310	1998-09-30
	USA	310	0-310	2000-12-06
Natazia® (combined hormonal oral contraceptive)	Canada	775	600+	2012-01-30
	UK	361	311-400	2008-12-08
	USA	308	0-310	2010-05-06
Nuvaring® (combined hormonal contraceptive vaginal ring)	Canada	554	401-600	2004-05-11
	UK	465	401-600	2008-06-05
	USA	645	600+	2001-10-03
Ortho-Evra® (combined hormonal contraceptive patch)	Canada	505	401-600	2002-08-20
	UK	528	401-600	2002-08-22
	USA	334	311-400	2001-11-20
Seasonale® (combined hormonal oral contraceptive- continuous three month package)	Canada	561	401-600	2007-07-04
	USA	396	311-400	2003-09-05
Yasmin® (combined hormonal oral contraceptive)	Canada	1926	600+	2004-12-10
	UK	212	0-310	2000-11-23
	USA	728	600+	2001-05-11

Figure 1. Time to approval of hormonal contraception applications in Canada, the USA and the UK.

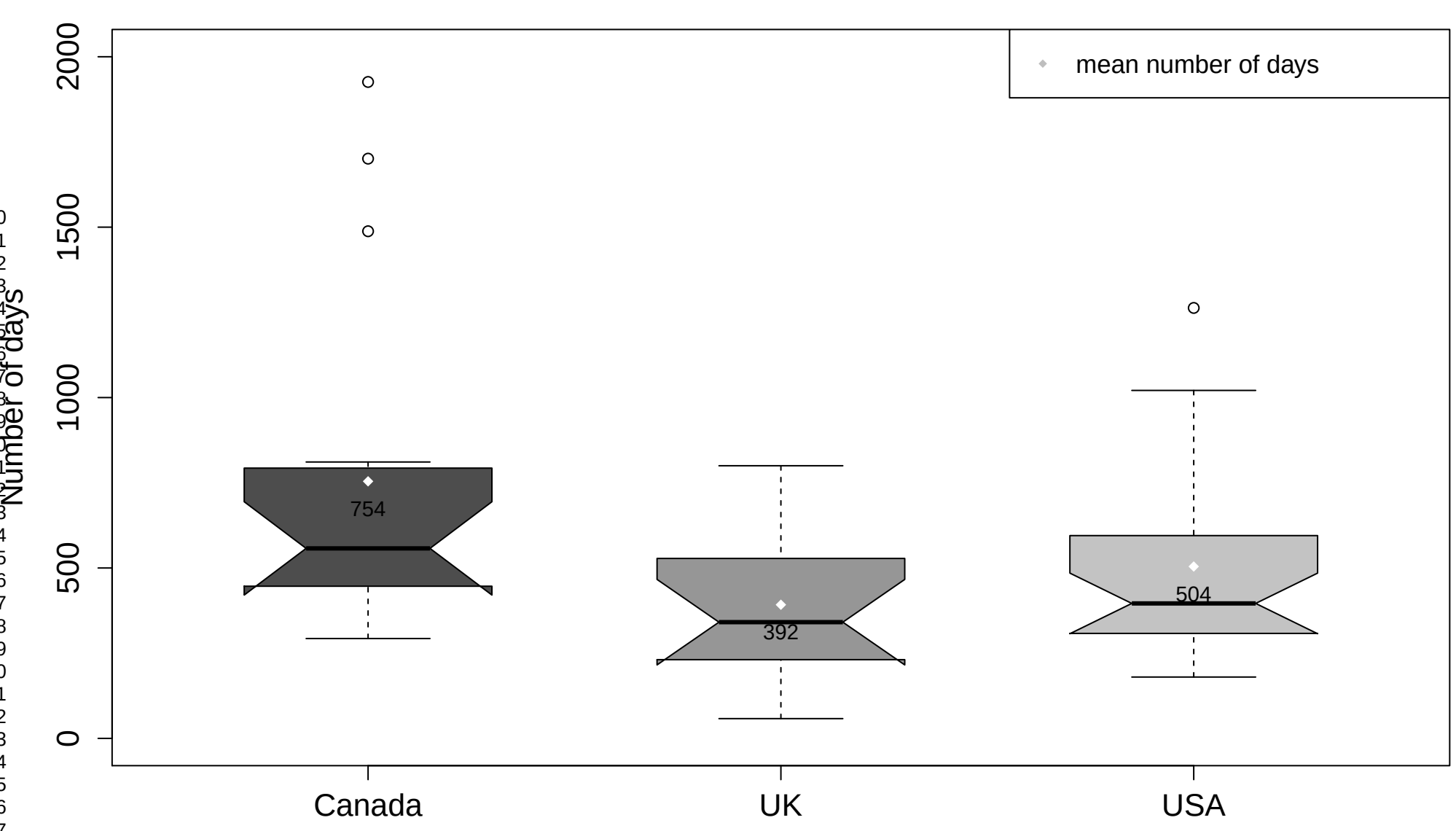
The red dots represent the mean number of days from submission to approval for Canada, UK and USA. For each boxplot the bottom of each box is the 25th percentile, the top is the 75th percentile, and the line in the middle is the 50th percentile (median). The whiskers from the lower and upper hinges show the minimum and maximum values. The data points outside of the min and max values are the outliers.

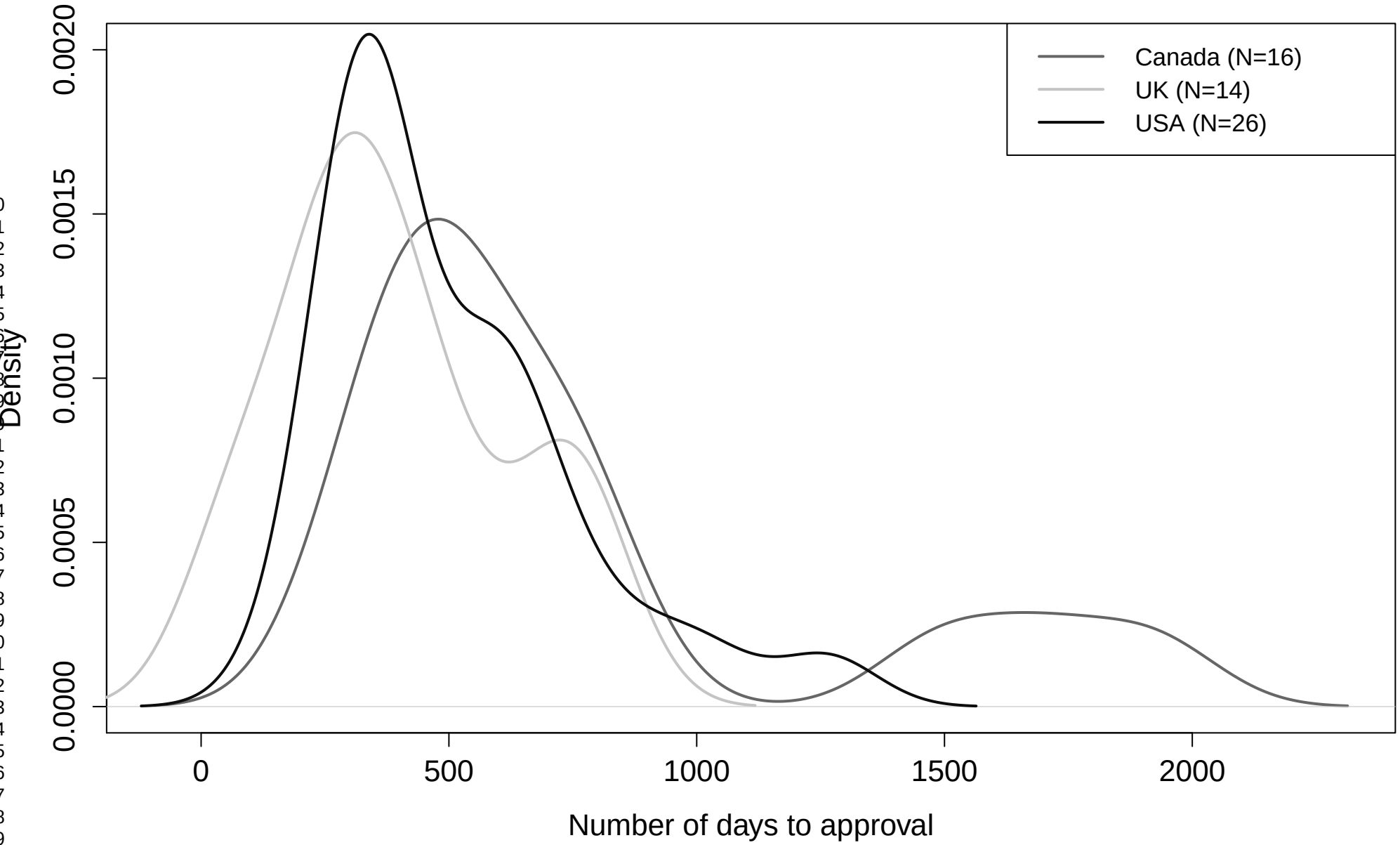
Figure 2: Distribution of time to approval: Number of days between submission and approval for hormonal contraceptives approved in Canada, UK, USA, 1998 – 2015.

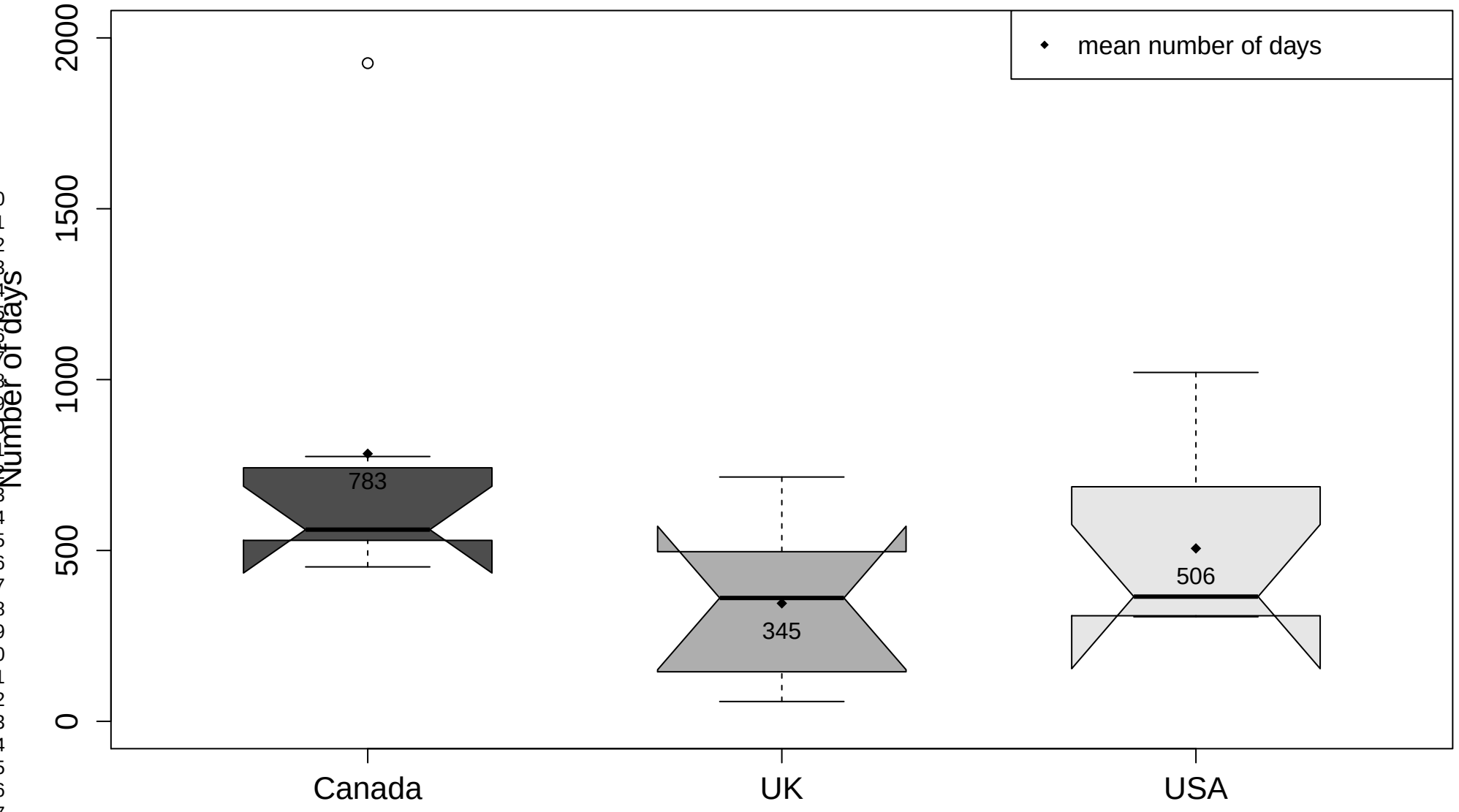
Figure 3: Novel drugs only: Time to approval (days) for Canada, UK and USA.

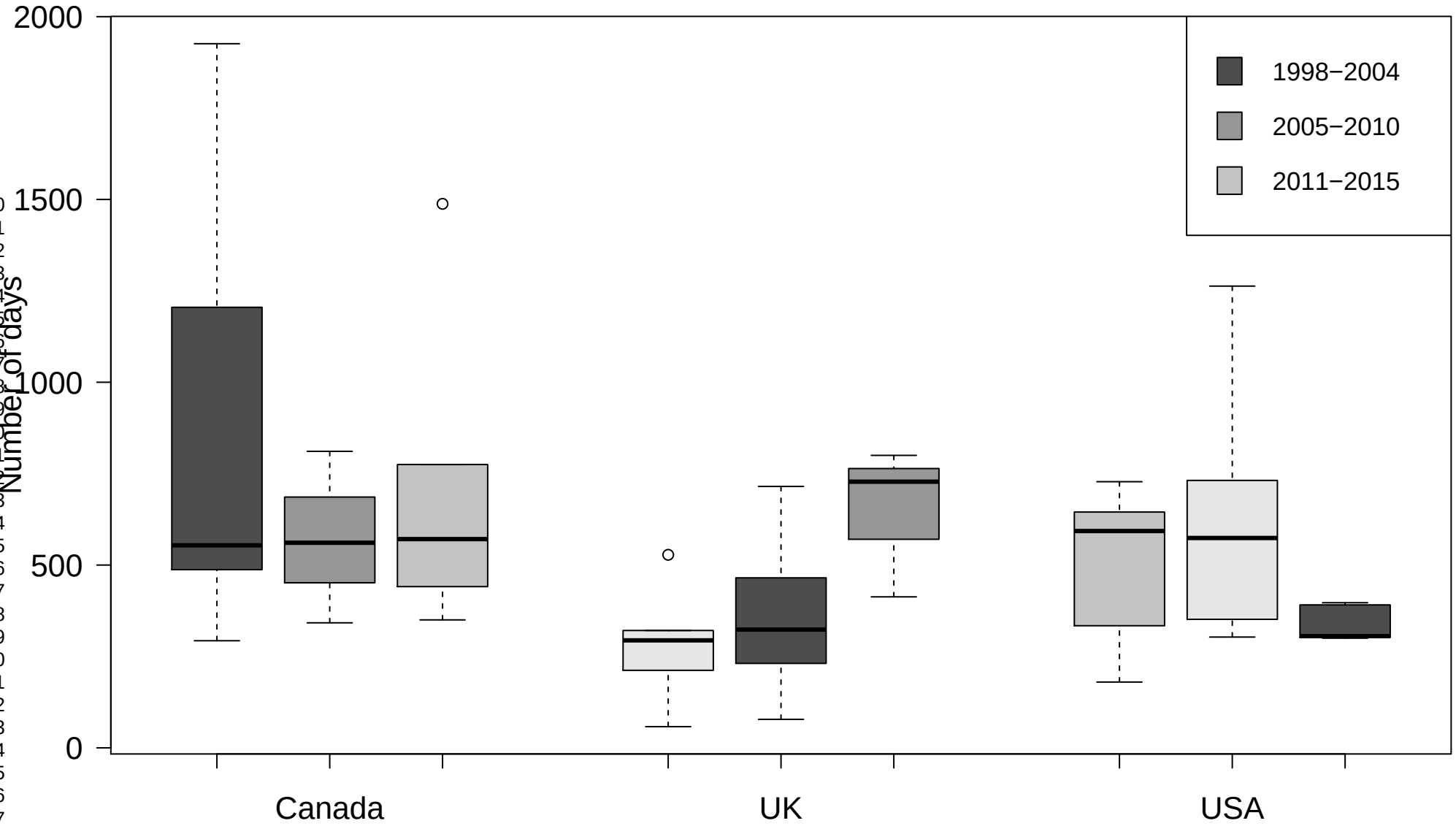
The red dots represent the mean number of days from submission to approval for Canada, UK and USA. For each boxplot the bottom of each box is the 25th percentile, the top is the 75th percentile, and the line in the middle is the 50th percentile (median). The whiskers from the lower and upper hinges show the minimum and maximum values. The data points outside of the min and max values are the outliers.

Figure 4: Mean time to approval (days) for Canada, UK and USA for three cohorts of approval years (1998–2004, 2005–2010, and 2011–2015).


mean number of days
Number of days
0
500
1000
1500
2000
754
392
504
Canada
UK
USA


Canada (N=16)
UK (N=14)
USA (N=26)
Density
0.0000
0.0005
0.0010
0.0015
0.0020
0
500
1000
1500
2000
Number of days to approval


mean number of days
Number of days
0
500
1000
1500
2000
783
345
506
Canada
UK
USA


2000
1500
1000
500
0
Number of days
1998−2004
2005−2010
2011−2015
Canada
UK
USA