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# Canadian, European and United States new drug approval times now relatively similar☆

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ABSTRACT

The objectives of this analysis were to assess whether consistency in Health Canada's (HC's) approval times identified in 2011 has been sustained and to compare HC's approval times with those of the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA). Between 2002 and 2016, 460 new drugs were approved by at least one of the agencies: 351 (76.3%), 319 (69.3%) and 392 (85.2%) by HC, the EMA and the FDA, respectively – all three approved 252 (54.8%). Overall medians and inter-quartile ranges of approval times for HC, the EMA and the FDA were 364 days (343–651), 371 days (322–434) and 304 days (209–455), respectively. The EMA's annual median approval time was consistent over the 15 years, while HC's and the FDA's median times were only consistent with each other and the EMA after 2005. Almost 80% of the drugs approved by all three agencies were submitted to HC later than to the other two agencies, which led to a median delay of a year between the agency first giving approval (FDA or EMA) and HC's approval. Rates of drugs withdrawn for safety reasons were 1.4% in Canada, 0.9% in Europe and 0.8% in the United States.

## 1. Introduction

The process of obtaining approval to market a new drug in Canada is similar to that in other industrialized countries (Paul, 2001). After successful completion of clinical trials, the manufacturer files a new drug submission with Health Canada (HC; the regulatory agency), which should provide sufficient information to evaluate the drug's efficacy, safety and suitability for marketing. HC's review examines the information in terms of quantity and quality to ensure that the medication meets regulatory requirements, the manufacturing methods and controls are satisfactory, and the proposed labeling is adequate. For acceptable submissions, HC issues a Notice of Compliance (NOC), which allows the marketing of the drug. In some cases, a Notice of Compliance with Conditions (NOC/C) is issued, which requires the manufacturer to undertake additional studies of the new drug before a full NOC can be issued; the review period is shorter for these drugs if advanced consideration for eligibility for a NOC/C is requested by the company before filing the submission.

HC's approval system for new drugs was investigated in several studies in the 1980s and early 1990s (Rawson, 2000), almost all of which concluded that it was inefficient and contained unnecessary delays. Long review times for new drugs continued in Canada into the mid-1990s, whereas the time taken to approve new drugs by the United States Food and Drug Administration (FDA) had already begun to decrease (Rawson et al., 1998). In the late 1990s, the Canadian median approval time shortened to around 18 months following the introduction of a cost-recovery fee structure and performance standards for new drug submission reviews, but remained longer than in Sweden, the United Kingdom and the United States (Rawson, 2000). A further evaluation of drugs approved between 1999 and 2001 in the same countries demonstrated that the Canadian median time increased to almost two years in 2001 (Rawson, 2003). Comparisons with individual European countries became impossible after 2001 as the European Medicines Agency (EMA) took over the review of most new drugs for countries in the European Union, but by 2006, the Canadian median approval time had decreased to around a year and was consistent with the median in the United States (Rawson, 2013), which continued to 2011.

The objectives of this analysis were to assess whether the consistency in Canadian approval times has been sustained, to compare HC's approval times with the EMA's and the FDA's, particularly for medications for unmet needs such as drugs for rare disorders (DRDs),

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and to assess the ranking of submissions to and approvals by HC relative to the other agencies.

## 2. Materials and methods

Information on new drugs approved by HC was obtained from the agency's annual performance reports (Government of Canada, 2018). The FDA's website was used to obtain data on new drugs approved in the United States (FDA, 2018), while the EMA's website provided information on new drugs approved through the centralized authorization procedure (EMA, 2018a). These resources have been utilized in other regulatory research (Downing et al., 2012; Shajarizadeh and Hollis, 2015).

The EMA's centralized procedure was gradually introduced in the late 1990s and early 2000s and is compulsory for medicines to treat HIV/AIDS, cancer, diabetes, neuro-degenerative disease, auto-immune dysfunctions and viral diseases, drugs derived from biotechnology processes, advanced medicines such as gene therapy, and DRDs (EMA, 2018b). For other medicines, the centralized procedure is optional, but the majority of new drugs pass through the procedure so that they can be marketed throughout the 34 countries in the European medicines regulatory network. Before a drug can be marketed, the EMA Committee for Medicinal Products for Human Use must issue a positive marketing authorization and, subsequently, the European Commission must formally adopt the Committee's opinion. Since adoption by the Commission is primarily an administrative action, the date of the Committee's positive assessment was taken as the EMA approval date.

A new drug was defined as any new therapeutic agent of chemical or biologic origin. This excluded new salts, esters and dosage forms of existing products, biosimilars, diagnostic products and vaccines. Drugs satisfying the definition were included if they were approved by one or more of the three agencies between January 2012 and December 2016. If a drug was approved by one or more of the other agencies outside this period, the relevant information was recorded.

Each drug's approval time was calculated as the difference in calendar days between the date that the regulatory agency received the submission and the approval date. Medians and inter-quartile ranges (IQRs) of approval times were used as summary statistics. Approval times were compared using the Kruskal-Wallis test with $p < 0.01$ as a marker of statistical significance to adjust for multiple comparisons.

Some new drugs are intended for the treatment of life-threatening or disabling conditions for which there are few or no therapies. To accelerate patient access to drugs that address these unmet needs, some regulatory agencies have developed processes to select drugs for a priority review, which means that they receive the same evaluation, but the performance target for completion of the review is significantly shorter (Rawson, 2015). To qualify for a priority review in Canada, a drug must be intended for patients suffering from a serious, life-threatening or severely debilitating disease and indicated to treat or prevent a serious symptom or manifestation of the condition (Government of Canada, 2012). Manufacturers seeking priority status must submit a written request that describes the disease to be treated and how the drug will improve disease management by either satisfying an unmet need or improving the benefit-risk profile over existing therapies.

The FDA makes decisions regarding priority status from a preliminary review of the entire new drug submission. To qualify for priority review status, a drug must treat a serious condition, which is one “associated with morbidity that has substantial impact on day-to-day functioning” and must provide a significant improvement in safety or effectiveness (FDA, 2014). “Significant improvement” may be increased effectiveness in the treatment, prevention or diagnosis of a condition, elimination or substantial reduction of a treatment-limiting adverse reaction, enhanced patient compliance expected to lead to improvement in serious outcomes, or safety and effectiveness evidence in a new subpopulation. The FDA also has three other mechanisms to facilitate the development of treatments for serious and life-threatening conditions, one of which is accelerated assessment of all or part of the review.

Drugs may receive an accelerated assessment from the EMA within its centralized procedure (EMA, 2018c). Applications for this type of assessment need to demonstrate that the drug is expected to be of major public health interest, particularly from the point of view of therapeutic innovation. In addition, the EMA has a conditional marketing authorization process to expedite drugs for unmet needs (EMA, 2018d). The processes of HC, the EMA and the FDA for expedited reviews are not exactly the same, but their objectives to expedite patient access to drugs for unmet needs are. For this analysis, expedited review drugs were HC priority status and NOC/C drugs, EMA accelerated assessment and conditional authorization drugs and FDA priority status and accelerated assessment drugs.

Another way to expedite patients’ access to innovative drugs for life-threatening or disabling disorders are the orphan drug policies in place in Europe and the United States. The EMA defines an orphan drug as one for life-threatening or chronically debilitating disorders with a prevalence of less than 5 per 10,000 for which there is no existing treatment or the drug has a significant benefit over any current therapy (EMA, 2018e). Manufacturers of medications that achieve orphan status receive incentives such as market exclusivity for 10 years and fee reductions. At the FDA, orphan drugs are those for disorders that affect less than 200,000 individuals in the United States (a prevalence of 6.2 per 10,000), although drugs for disorders that affect more than 200,000 persons that are not expected to recover the costs of their development and marketing may also receive orphan status (FDA, 2017). The incentives for the development of orphan drugs in the United States are market exclusivity for seven years, waiver of submission fees and tax credits for clinical testing. HC does not have an orphan drug policy (Gupta, 2012); the previous Conservative government announced an Orphan Drug Regulatory Framework in 2012 which the current Liberal government deleted from its website in October 2017 without notice or consultation (Forrest, 2017).

Sub-analyses were performed to evaluate approval times by drug category, review type, orphan status, company size based on annual dollar sales (Informa, 2018), and DRDs for conditions with a prevalence of 1 per 10,000 or less based on Orphanet data (Orphanet, 2018). Separate analyses of the ranking of submissions and approvals of drugs approved by all three agencies were also performed.

## 3. Results

A total of 460 new drugs satisfying the study criteria were approved by one or more of the three regulatory agencies between 2002 and 2016: 351 (76.3%), 319 (69.3%) and 392 (85.2%) by HC, the EMA and the FDA, respectively. All three agencies approved 252 (54.8%) drugs during the observation period. Thirty-nine (8.5%) drugs were approved solely by HC, while the corresponding figures for the EMA and FDA were 18 (3.9%) and 53 (11.5%), respectively. Twenty-seven (69.2%) of the 39 drugs given approval by HC alone and three (16.7%) of the 18 approved only by the EMA were approved by the FDA before 2002. Just over half (30; 56.6%) of the drugs given approval solely by the FDA were approved between 2012 and 2016 and 11 of these received orphan status.

The overall medians and IQRs of the time required to approve drugs by HC, the EMA and the FDA were 364 days (343–651), 371 days (322–434) and 304 days (209–455), respectively ($p < 0.0001$). Fig. 1 shows that the EMA's median approval time by year was consistent over the 15-year period, while HC's and the FDA's median times were consistent with each other and those of the EMA only after 2005. In 2016, the median approval time was almost the same for each regulatory agency: HC 351 days (306–393), EMA 353 days (301–413), FDA 349 days (243–437).

The numbers of drugs approved and median approval times in three five-year periods are shown in Table 1, which demonstrate that HC has