Time required for approval of new drugs in Canada, Australia, Sweden, the United Kingdom and the United States in 1996–1998

Research

Recherche

Nigel S.B. Rawson

Dr. Rawson is Professor of Pharmacoepidemiology, Division of Community Health, Faculty of Medicine, and School of Pharmacy, Memorial University of Newfoundland, St. John's, Nfld.

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Abstract

Background: The timeliness with which national regulatory agencies approve new drugs for marketing affects health care professionals and patients. An unnecessarily long approval process delays access to new medications that may improve patients' health status. The author compared drug approval times in Canada, Australia, Sweden, the United Kingdom and the United States.

Methods: Application and approval dates of new chemical or biological substances (excluding diagnostic products, and new salts, esters, dosage forms and combinations of previously approved substances) approved for marketing in the 5 countries from January 1996 to December 1998 were requested from the relevant pharmaceutical companies. Data on new drug approvals during the study period were also obtained from the national drug regulatory agencies in Canada, Australia and Sweden and from publications of the US Food and Drug Administration.

Results: A total of 219 new drugs were identified as being approved in at least one of the countries during the study period: 23 (10.5%) in all 5 countries, 23 (10.5%) in 4, 27 (12.3%) in 3, 42 (19.2%) in 2, and 104 (47.5%) in 1 country. By individual nation, 97 drugs were identified as being approved in Canada, 94 in Australia, 107 in Sweden, 55 in the UK and 123 in the US. Approval times in Canada and Australia were similar (medians 518 and 526 days respectively), but both countries had significantly longer approval times than Sweden (median 371 days), the UK (median 308 days) and the US (median 369 days). This pattern was consistent across all 3 years and for the 23 new drugs approved in all 5 countries during the 3-year period. Median approval times in Canada were similar in all of the reviewing divisions of Health Canada's Therapeutic Product Program (539–574 days) except the Central Nervous System Division (428 days) and the Bureau of Biologics and Radiopharmaceuticals (698 days).

Interpretation: Median drug approval times during 1996–1998 decreased by varying amounts from the 1995 values in all 5 countries. However, the median approval time in Canada continues to be significantly longer than the times achieved in Sweden, the UK and the US, and it remains considerably longer than Canada's own target of 355 days for all new drugs.

The timeliness with which national regulatory agencies approve new drugs for marketing affects health care professionals and patients. An unnecessarily long approval process delays access to new medications that may improve patients' health status. Variation in the availability of drugs in different countries has been studied since the early 1970s,[1] and some marked differences have been found. However, drug regulatory agencies have recognized the importance of timeliness in their work and are endeavouring to reduce the time required for review and approval of new drug applications, several having established performance standards.[2]

The median time taken to approve new drugs in Canada has, for many years, been significantly longer than that in countries such as the United Kingdom and Sweden and has been criticized in several independent reviews of the drug approval system[3–8] and by patient advocacy groups.[9–12] The United States was relatively slow

in approving new drugs until the early 1990s, so that the timing of drug availability in the US and Canada was reasonably similar.[13] However, changes following the Prescription Drug User Fee Act in 1992[14] led to earlier availability of new drugs in the US[15] and reduced the median approval time in 1992–1994 to 655 days, as compared with 1057 days in Canada.[16] In 1995, following a substantial reduction in the backlog of new drug submissions to the Therapeutic Products Program (TPP) of Health Canada, the median approval time decreased to 650 days, which was closer to that in the US (464 days), and in Australia, Sweden and the UK (562, 444 and 439 days respectively).[16]

A single year with reduced approval times does not indicate a trend. Therefore, a study was undertaken to compare approval times in Canada, Australia, Sweden, the UK and the US for new drugs approved from January 1996 to December 1998.

Methods

The definition of "new drug" included new chemical or biological substances except diagnostic products. New salts, esters, dosage forms and combinations of previously approved substances were excluded.

Information on application and approval dates was obtained directly from the Canadian subsidiaries of the relevant pharmaceutical companies using a standardized questionnaire. The questionnaires were prepared and distributed by Canada's Research-Based Pharmaceutical Companies. For each product in each country, the company was asked to provide application and approval dates so that the approval time could be calculated as the number of calendar days between the 2 dates. The company was also asked to supply the time (in calendar days) taken to respond to questions asked by the agency during the review process ("company time") and the time that the agency spent reviewing the application ("agency time").

To ensure that all approved new drugs were identified in Canada, Australia and Sweden, their drug regulatory agencies were approached with a request for the same data on new drugs approved in their country during the study period. All 3 agencies supplied data on application and approval dates, and the Australian agency also provided agency and company times in "working days." For the US, information on the application and approval dates was extracted from publications on new drug approvals issued by the US Food and Drug Administration. The UK Medicines Control Agency does not release information on application dates, and therefore it was necessary to rely solely on pharmaceutical companies for information for that country.

Data supplied by companies and the regulatory agencies in Canada, Australia, Sweden and the US were cross-checked; company information was used if discrepancies occurred. If no information was received from a company, data from the agency were used. The reviewing division of the TPP was recorded for drugs approved in Canada; for products not approved in Canada, the division that most likely would have reviewed the drug was used.

The median and range of the approval times were used as the principal summary statistics in the analyses because of the nonsymmetrical nature of the majority of distributions of approval times, although mean times are also presented to facilitate comparisons with other reports. Approval times were compared using the Kruskal–Wallis multiple comparison test[17] with an adjustment for post hoc comparisons. Comparisons between the countries were performed for the overall 3-year period, on an annual basis, by TPP reviewing division, and on drugs approved in all 5 countries in the 3 years.

Results

A total of 219 new drugs were identified as being approved in at least one of the countries during the 3-year study period: 23 (10.5%) in all 5 countries, 23 (10.5%) in 4, 27 (12.3%) in 3, 42 (19.2%) in 2 and 104 (47.5%) in 1 country. By individual nation, 97 drugs were identified as being approved in Canada, 94 in Australia, 107 in Sweden, 55 in the UK and 123 in the US.

Information on application and approval dates was received from pharmaceutical companies for 74 (76.3%), 51 (54.3%), 51 (47.7%) and 69 (56.1%) of the new drugs reported by the regulatory agencies of Canada, Australia, Sweden and the US. For several drugs, the application or the approval date, or both, supplied by the companies differed from those recorded in the agencies' data by 1–7 days, most likely representing the time taken by the passage of communications. The numbers of new drugs for which either date disagreed with the agency information by more than a week in the Canadian, Australian, Swedish and US data were 4 (4.1%), 10 (10.6%), 16 (15.0%) and 5 (4.1%) respectively.

Median and mean approval times and ranges for all drugs approved in each country are shown in Table 1. The overall median times in Canada and Australia did not differ significantly, but they were at least 5 months longer than those in Sweden, the UK and the US ($p < 0.01$). More than 85% of the approval times in Australia and Canada were over 1 year, as compared with 38%–53% in Sweden, the UK and the US (Fig. 1).

Table 2 shows the median and mean approval times in each of the 3 years of the study period. The Canadian median approval time fell from 562 days in 1996 to 490 days in 1997 but increased to 514 days in 1998. A similar trend occurred in Australia, Sweden and the UK (although extreme in the UK), whereas median approval times in the US decreased steadily by about 1 month each year. Canadian approval times were significantly longer than those of Sweden and the UK in 1996 and 1997 ($p < 0.01$), and those

Table 1: Approval times in 5 countries for new drugs approved from January 1996 to December 1998

Country	No. of new drugs approved	Approval time (in calendar days)		
		Median	Mean	Range
Canada	97	518	608	108–2454
Australia	94	526	538	141–1130
Sweden	107	371	360	88–892
United Kingdom	55	308	344	80–1119
United States	123	369	496	42–3053

of Sweden ($p < 0.01$), the UK ($p < 0.05$) and the US ($p < 0.01$) in 1998.

The median approval times by TPP reviewing division appear online (see Appendix 1 at www.cma.ca/cmaj/vol-162/issue-4/0501app1.htm). Median approval times in Canada ranged from 428 days in the Central Nervous System Division to 698 days in the Bureau of Biologics and Radiopharmaceuticals. Canada had the longest median time for biological products, and AIDS and antiviral drugs, and the second longest for drugs reviewed in the cardiovascular; endocrine, metabolism and arthritis; gastrointestinal, hematology and oncology; and infection and immunology divisions.

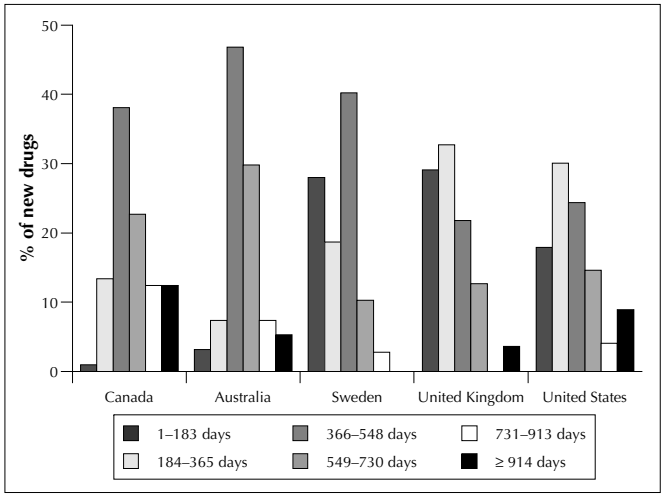

Fig. 1: Distribution of approval times for new drugs approved from January 1996 to December 1998, by country.

Table 2: Approval times for new drugs, by year

Country/year	No. of new drugs approved	Approval time (in calendar days) Median	Mean	Range
Canada				
1996	32	562	584	108–1937
1997	39	490	660	227–2454
1998	26	514	560	301–1048
Australia				
1996	27	535	514	177–964
1997	33	518	533	141–916
1998	34	528	562	314–1130
Sweden				
1996	40	376	383	112–798
1997	34	332	340	88–698
1998	33	350	352	112–892
United Kingdom				
1996	21	308	348	149–679
1997	20	166	285	80–1119
1998	14	433	422	137–1078
United States				
1996	47	436	578	42–3053
1997	42	406	528	78–2971
1998	34	361	344	98–774

Information concerning the 23 new drugs approved in all 5 countries during the study period was also examined (Table 3). The Canadian and Australian approval times again did not differ significantly, but both were significantly longer than those in Sweden, the UK and the US ($p < 0.01$). When approval times for each of the 23 drugs were ranked from shortest to longest, the median ranks were 1, 2, 3, 4 and 4 for Sweden, the UK, the US, Canada and Australia, respectively.

Company and agency times were available from the companies or the regulatory agencies (after estimating calendar days from "working days" in the Australian data) for 64%, 100%, 20%, 45% and 25% of the new drugs approved in Canada, Australia, Sweden, the UK and the US respectively. The Canadian median approval time of 502 days for products with both company and agency times was similar to the overall median of 518 days, but the median agency time in Canada was significantly longer than the corresponding time in Australia (466 v. 269 days; $p < 0.001$).

Interpretation

This study shows that approval times for new drugs in Canada are comparable with those in Australia, but both of

Table 3: Approval times for the 23 new drugs* approved in all 5 countries in 1996–1998

Country	Approval time (in calendar days) Median	Mean	Range
Canada	488	495	190–922
Australia	518	500	141–1051
Sweden	153	254	88–634
United Kingdom	247	304	88–679
United States	364	344	42–714

*Atorvastatin, candesartan, clopidogrel, dolasetron, donepezil, follitropin beta, hepatitis A vaccine, indinavir, irbesartan, letrozole, motelukast, naratriptan, nevirapine, olanzapine, raloxifene, remifentanil, ritonavir, ropinirole, tolcapone, topotecan, trovafloxacin, valsartan, zolmitriptan.

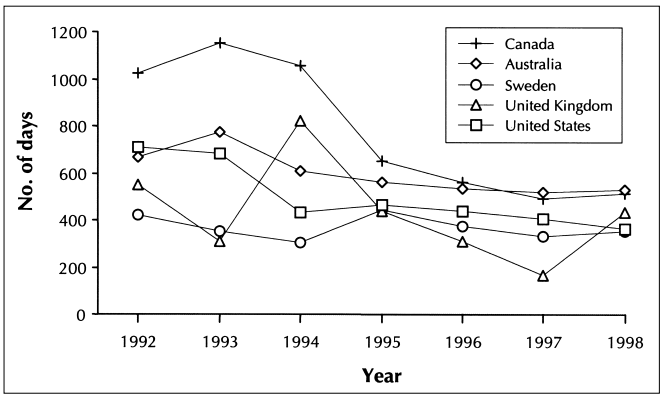

Fig. 2: Median approval times from 1992 to 1998, by year of approval and country. [Data for 1992–1995 are from Rawson et al.[16]]

these countries have significantly longer approval times than Sweden, the UK and the US. This pattern was broadly consistent across all 3 study years. The time spent by agencies reviewing applications was significantly longer in Canada than in Australia.

A study of the same 5 countries in 1992–1995 showed that median approval times in Canada fell from well over 1000 days in the early 1990s to 650 days in 1995.[16] The present study shows that further reductions occurred in 1996 and 1997 with a slight increase in 1998.

The proportion of new drugs reported by the national drug regulatory agencies for which data were also supplied by the pharmaceutical companies in Canada, Australia, Sweden and the US was highest in Canada (> 76%) and about 50% in the other 3 countries. One may assume from these figures that more new drugs were approved in the UK than were included in this study. If only 50% of the UK approvals were identified, this would mean that the actual number was 110, similar to the 123 drugs approved in the US, the other major market in the study. This limitation should be remembered when considering the results of this study and may contribute to the year-to-year variability in the UK median approval times.

The length of the approval process in a country may be affected by numerous factors, such as the availability of alternative therapies for similar indications, national regulations, the regulatory agency's access to data from other national agencies, and the agency's policies, procedures and resources. Although they have a similar number of new drugs to review, countries with smaller populations may have fewer resources with which to do their work. Participation in a centralized system of drug review, as exists in the European Union, is another factor that influences drug approval times in Sweden and the UK. Nevertheless, approval times for new drugs should be reasonably similar in countries with comparable scientific approaches to drug approval, such as those considered here.

Physicians want to be able to prescribe the most effective drugs for their patients, and patients want access to these drugs to get well quickly. Recent modifications to the Canadian approval process have led to a significant reduction in approval times since the early 1990s. However, Canadian approval times continue to be significantly longer than those in Sweden, the UK and the US, and Canada's own performance target of 355 days.[18]

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The opinions and conclusions expressed in this article are my own and do not necessarily represent those of the companies and agencies from which data were obtained, the respective national governments or Rx&D.

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Reprint requests to: *Dr. Nigel S.B. Rawson, Division of Community Health, Memorial University of Newfoundland, Health Sciences Centre, St. John's NF A1B 3V6; fax 709 737-7382; nrawson@morgan.ucs.mun.ca*