A Comparison of the Drug Review Process at Five International Regulatory Agencies

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Regulatory approval time is a key metric that is used to evaluate the performance of regulatory agencies. A new methodology has been developed to compare the regulatory review process across five regulatory agencies in the United States, Europe, Canada, Switzerland, and Australia. Four main stages (receipt of data, scientific assessment, sponsor response, and authorization of the product) that are common across all these agencies have been identified and "milestone" dates were collected for over 1,000 new active substance (NAS) applications. Data were collected by year of submission between 1997 and 2002, which allowed cohorts of compounds to be tracked prospectively to approval, rejection, or withdrawal and ensured that the products had been reviewed in the same regulatory environment. Analyses of the mean/median time intervals between milestones and the overall review times were carried out. Twenty-nine NASs that were submitted to, and approved by, all five agencies were also identified and studied in more depth. Overall median approval times ranged across agencies from 368 to 595 days. This study showed that, although the stages in the review process may be common for the different agencies, the time that an application spends in each stage can differ significantly. The order in which activities are undertaken in the review process also differs, for example, the timing of advisory committees or stages in the process carried out in parallel rather than sequentially. The data suggest that the differences in the way projects are managed in the review process has an impact on the review times.

INTRODUCTION

All agencies have the same objectives and obligations to safeguard public health when assessing the safety, quality, and efficacy of medicines before they are authorized for marketing. However, the structure, strategies, practices, processes, and regulatory and legal obligations in place at each agency in order to carry out a regulatory review and achieve these objectives vary considerably.

From the pharmaceutical industry's perspective, the regulatory review of new medicines is the culmination of a research-and-development process that has taken between 10 and 12 years (1), and the outcome spells success or failure for a project that represents an $802 million investment (2).

The classic study for comparing regulatory processes looks at overall approval times from the time of receipt of the marketing application to the date of approval or authorization of the product (3–8). This can produce information on trends and show the impact of significant changes to the regulatory process but gives little insight into the different factors that have an impact on approval times.

The unique benchmarking project that has been undertaken by CMR International extends beyond comparative data for overall review times and looks in depth at the individual stages in the different regulatory processes followed by different agencies. An understanding of how each process fits into the agency is important for a true comparison (9).

The objectives of the study were to

- Identify and quantitate the stages of the submission, review, and regulatory action for new drug marketing authorizations at five international regulatory agencies.
- Provide benchmarking data that can be used to define performance targets and focus on ongoing performance improvement initiatives.
- Encourage systematic measuring of the processes that occur during the review of new drug marketing authorizations.

The methodology that was developed for this study is based on the premise that, notwith-

TABLE 1

Participating Regulatory Agencies
United States: Center for Drug Evaluation and Research (CDER), Food and Drug Administration (FDA)
European Union: European Medicines Agency (EMEA)
Australia: Therapeutic Goods Administration (TGA)
Canada: Therapeutic Products Directorate (TPD) and Biologics and Genetic Therapies Directorate (BGTD), Health Canada
Switzerland: Swissmedic (in 2002, the Intercantonal Office for the Control of Medicines, IKS, and the Therapeutic Products Section of the Swiss Federal Office of Public Health merged to form Swissmedic)

standing the apparent differences between the regulatory processes of different agencies, the processes are made up of a set of basic stages sufficiently similar to allow meaningful comparisons (10). Work on the design of the study started in 1996 when CMR International and 10 major international regulatory agencies worked together to achieve an understanding of the different processes employed by individual agencies, highlighting the areas of the review that the authorities considered particularly important (11). The stages and the critical events or milestones in the regulatory approval process were identified and defined. The details of the methodology were agreed on by all prospective participants, and a pilot study was carried out with the five agencies (Table 1) for applications submitted January 1, 1997, to December 31, 1998, to test the methodology and to provide a baseline of data for comparisons to be made in future years. The study was then updated to include compounds submitted to the agencies from January 1, 1999, to December 31, 2002, with outcomes tracked to July 2003.

This article reports on a selection of these analyses as an illustration of the scope and potential of this benchmarking methodology.

METHODOLOGY

Data were collected on applications for new active substances (NASs; see Table 2) that had not previously been approved by the agency in question. The study covered applications received between January 1, 1997, and December 31, 2002, and the outcome of applications that had not been determined by the latter date were tracked to the end of July 2003.

Data were collected according to the year of submission of the application rather than by the year in which the review of the application was completed. Collection by year of submission allowed cohorts of compounds to be tracked prospectively to approval, rejection, or withdrawal and means that the compounds had been submitted and reviewed in the same regu-

TABLE 2

Definitions and Criteria
New active substance (NAS) meeting the criteria for the study include • Chemical, biological, and radiopharmaceutical substances not previously available for therapeutic use in humans to be used for the cure, alleviation, treatment, prevention, or in vivo diagnosis of diseases in humans • An isomer, mixture of isomers, a complex or derivative or salt of a chemical substance previously available as a medicinal product but differing in properties regarding safety and efficacy from that substance previously available • A biological substance previously available as a medicinal product but differing in molecular structure, nature of source material, or manufacturing process • A radiopharmaceutical substance that is a radionuclide or a ligand not previously available as a medicinal product; alternatively, the coupling mechanism linking the molecule and the radionuclide has not been previously available
Biotech product • A naturally occurring or modified polypeptide, protein, DNA, or RNA product (produced by recombinant DNA or hybridoma technology and expressed in cell lines, transgenic animals, or transgenic plants) for therapeutic, prophylactic, or in vivo diagnostic use in humans; the only types of vaccines included in the biotech category are recombinant vaccines
Biological • A substance isolated from animal tissues (eg, vaccines, hormones, and antigens) or plant alkaloids

latory environment, which is important when studying time-related trends and the impact of major regulatory changes.

The methodology was based on identifying time periods, review stages, and data points that could be compared across regulatory agencies, notwithstanding the considerable differences between the individual regulatory procedures.

TIME PERIODS

Elapsed time during a review was categorized under the following headings:

Dossier Validation: The time between the date stamped on receipt of dossier and the date of sending the acceptance- (or refusal-) to-file letter.

Scientific Assessment Time: Amount of time spent actively reviewing the dossier or any additional information provided.

Sponsor Time: Time during which the "clock" is stopped during the review while the authority awaits additional data requested from the company.

Other Regulatory Authority Time: Any other time elapsing while the application is with the authority, including queuing to be picked up for assessment, administrative procedures, time for referral to and discussion by advisory committees, and so on.

Overall Approval Time: The time between the date stamped on receipt of dossier when received by authority and the date on the document (authorization/license) that allows legal marketing. Please note that for the European Medicines Agency (EMEA) this includes the time taken by the European Commission to issue an authorization.

REVIEW STAGES AND DATA POINTS

Four main stages were identified as common to all approval processes: receipt of data, scientific assessment, sponsor response, and authorization of the product. When an application is not approved, there is an additional stage terminating the procedure. Each of these stages is delineated by key dates or milestones as set out in Table 3.

DATA COLLECTED

The milestone dates set out as data points in Table 3 were collected for each application in the study insofar as they were applicable to the particular process. In addition, the following qualitative data were requested for each product:

- *Sponsor* (at time of application): anonymized for NASs that were not approved.
- *Generic Name*: anonymized for NASs that were not approved.
- *Trade Name:* anonymized for NASs that were not approved.
- *Compound Type*: Chemical entity, biotechnology product, biological, gene therapy product.
- *Type of Review*: Standard or expedited (also known as *accelerated approval* or *priority application* and applicable to products intended to treat serious or life-threatening conditions). Type also included *rolling review*, whether any data were reviewed by the agency prior to submission (procedure available only for Center for Drug Evaluation and Research [CDER] fast-track applications).
- *Presubmission Assistance*: Whether there was dialogue with the sponsor to give advice on scientific and administrative issues before the application was submitted. For the Therapeutic Goods Administration (TGA) and EMEA, the presubmission assistance that was included in this study was limited to scientific issues. For the other agencies, the scope of presubmission assistance included: formal communication, informal communication, Investigational New Drug (IND) application, teleconference, multiple communications.
- *Therapeutic Class*: A general classification of 14 headings was devised based on the World Health Organization (WHO) Anatomical Chemical and Therapeutic (ATC) coding system (12).

Data were collected from each agency using an electronic questionnaire supplied by CMR International. The exception was information on EMEA applications. Only approved applications were included, and the data were extracted by CMR International from the published European Public Assessment Reports. The regulatory framework in place at the time of the study did not allow for the information on ongoing applications, withdrawn applications, or applications with a negative opinion to be made public by the EMEA. The EMEA assisted by providing important milestone dates when these were missing.

TABLE 3

Key Milestones and Stages in the Review (For a Schematic Diagram, See Appendix)

Data Points: Dates of Key Milestones	Stage	Time Components	Notes
1 Receipt of dossier 2 Acceptance/refusal to file	Receipt of data	Validation and other regulatory time (queuing to be picked up)	a. *Receipt of Data*: The time from receiving the dossier to starting the scientific assessment includes validation and queuing. At Health Canada, there may be a clock stop for Screening Deficiency Notices during dossier validation, but this has not been captured in this study.
3 Start of scientific assessment 4 Completion of scientific assessment	Scientific assessment	Scientific assessment time; may include sponsor time/advisory committee review	b. *Scientific Assessment*: During the review of scientific data, TGA, Health Canada, Swissmedic, and CDER have procedures for requesting additional data, but only TGA and Swissmedic "stop the clock." This clock stop has been recorded by the agencies in this study. (For clock stops that occur outside the scientific assessment period, please refer to note e).
5 Date of advisory committee review		Other regulatory time	c. *Advisory Committees*: Reference to a committee of experts takes place after the scientific review in the Swissmedic and TGA procedures. The time for this step has been recorded separately as *other authority time*. For EMEA, this refers to the Committee for Medicinal Products for Human Use (CHMP), which gives the opinion rather than acting in an advisory capacity. In the United States, the advisory committee time is within the CDER scientific assessment time but could nonetheless be determined. Health Canada does not have a statutory advisory committee review process.
Multiple-cycle applications			d. *Multiple-Cycle Applications*: A review process is counted as *multicycle* if the outcome of the primary scientific assessment is a formal request for additional information that requires a further scientific assessment before it can be determined (ie, the application is deficient). The application can then cycle from point 7 through secondary, tertiary, and so on scientific assessments and requests for additional data (points 3i–7i, 3ii–7ii, etc) until the outcome at point 8 is either positive or negative. All five systems have provision for this, but

TABLE 3

Continued

Data Points: Dates of Key Milestones	Stage	Time Components	Notes
Multiple-cycle applications *continued*			all the EMEA applications in the study were recorded as multicycle as the procedure *routinely* included a step at which questions are sent to the applicant at the end of the first scientific assessment. At TGA, formal requests for information are sent out as part of a rolling review process within the normal evaluation time frame. However, one review cycle was considered complete only when a decision had been reached in principle.
6 Completion of all scientific assessments: deficiencies found, additional data requested 7 Receipt of response from sponsor (≡ point 1a)	Sponsor response	Sponsor time	e. *Sponsor Response*: In this period, known as *clock stop*, the regulatory activity pauses to wait for a response from the sponsor. This stage is triggered by a notice indicating that further information is needed before the application can be determined (point 6). Different terminology is used: EMEA, list of questions; CDER, approvable or nonapprovable letter; Health Canada, notice of deficiency or notice of noncompliance; Swissmedic, nonapprovable letter.
3i, ii Start of subsequent scientific assessment (second/third cycle)			f. *Start of Subsequent Scientific Assessment*: Any time lag between the receipt of the sponsor's response (point 7) and the start of the next assessment was counted as other regulatory time.
Successful applications			
8i Completion of all scientific assessments: positive outcome			g. *Completion of All Scientific Assessments*: Data point 8 is the date on which the scientific review is deemed complete, leading to a decision on the application. Applications that move from data points 4/5 directly to point 8 are counted as a single cycle.
9 Notification of intent to grant a marketing authorization 10 Issue of authorization/license or other document signifying legal marketing	Authorization of product	Other regulatory time; may include sponsor time (label negotiations)	h. *Legal Marketing*: Data point 10 marks the end of the approval time for a product and is the date when the public has access to the medicine. This is normally designated by the formal product license/authorization. For the EMEA, this refers to the date that the European Commission granted a marketing authorization.

TABLE 3

Continued

Data Points: Dates of Key Milestones		Stage	Time Components	Notes
Unsuccessful applications				i. *Unsuccessful Applications*: Applications can be rejected after a single scientific assessment, but multiple cycles are more common, before reaching completion of all scientific assessments at data point 8ii.
8ii	Completion of all scientific assessments: data inadequate			
11	Notification of intent to refuse a marketing authorization	Termination of procedure	Other regulatory time	j. *Termination of Procedure*: Before refusing an application, all authorities give notice of the intention to the applicant, and this may be followed by withdrawal of the application by the sponsor or a formal rejection (point 12). There may, however, be a successful appeal, leading to reentry at point 8i, or reentry may be earlier if the appeal is placed under review. In the United States, however, a formal rejection process is not used as, in law, a rejected product would become an illegal substance. Applications that cannot be approved remain unapprovable until they are withdrawn by the sponsor or resubmitted for a further review cycle with additional data.
12	Rejection of application/ withdrawal by sponsor			

CAVEATS

European Union: The EMEA data set only includes approved applications that were processed through the centralized procedure. NASs that were authorized in the European Union via the Mutual Recognition Procedure during the period of the study are also excluded.

Switzerland: The Swissmedic data include biological products but do not cover vaccines.

United States: Data were only collected from CDER and not from CBER (Center for Biologics Evaluation and Research) and therefore do not cover biologicals and some biotechnology products.

2002 Data: Applications made in 2002 were only tracked to July 31, 2003. The numbers of approved compounds resulting from applications submitted in 2002 were therefore underrepresented, and the data were excluded from some analyses.

STATISTICAL ANALYSES

The Kruskal-Wallis test was used to find whether there was a difference in the data across all agencies. The Mann-Whitney *U* test was used to compare two independent sets of data (eg, comparison of median approval times between 2 years within an authority). A linear regression model was used to determine whether there was a significant change to the number of NASs submitted and approved. All analyses were conducted using *SPSS 13.0* for Windows® with the two-tail *P* value set at 5%.

RESULTS

NUMBER OF APPLICATIONS IN THE STUDY

Data were collected on a total of 1,079 NAS applications submitted to the five regulatory au-

TABLE 4

Number and Type of Products Included in the Study and Outcome at July 31, 2003

	TGA	Health Canada	Swissmedic	CDER	EMEA*	Totals
Total submitted	301	223	210	208	137	1,079
Biotech products	75	42	48	7	49	
Biologicals	21	6	3	N/A†	5	
Chemical entities	200	171	154	201	83	
Nonbiotechs (unspecified)‡	5	4	5	0	0	
Approved	212	136	129	135	130	742
% Approved	70	61	61	65	N/A	
Rejected at validation	10	4	0	4	N/E	18
Rejected after review	15	11	5	N/A	N/E	31
Withdrawn by sponsor	34	29	34	11	N/E	108
Pending	30	43	42	58	7	180

N/A, not applicable; N/E, not evaluated.
*EMEA data included only applications that were approved.
†At the time of the study, CDER did not review biological products. In 2003, monoclonal antibodies, therapeutic proteins (eg, cytokines and enzymes), and immunomodulators were transferred from CBER to CDER.
‡The initial data collection distinguished between biotech and nonbiotech products, and subsequently the latter category was split into chemical and biological products. However, some products remained that could not be categorized, retrospectively.

thorities between January 1, 1997, and December 31, 2002 (Table 4). Of these applications, 942 were submitted to the TGA, Health Canada, Swissmedic, and CDER, and the final outcome was recorded for applications determined by July 31, 2003. The percentage of NASs approved during the time period was similar for the four agencies, ranging from 61% to 70%. Table 4 also shows the number of applications still pending at the end of the study.

For the European Union, the study was confined to the 137 products that were submitted and approved via the EU centralized procedure during the same time period of January 1, 1997, to July 31, 2003. Only approved applications were included, and therefore the number of NASs included in this study is lower than for the other agencies. It is also possible to submit an application in Europe through the Mutual Recognition Procedure, which is another possible reason for the lower number of submissions to the EMEA. The seven pending applications were those for which a positive opinion had been published by the EMEA, but the final authorization had not yet been issued.

TIME INTERVALS FOR THE DIFFERENT STAGES OF REVIEW AND APPROVAL

To provide a comparative overview of the timelines for the different regulatory procedures, the mean time interval was calculated for the main stages in the review process, counted in calendar days between the major milestones. The results are shown in Table 5 for TGA, Health Canada, Swissmedic, and CDER. This covered all applications regardless of outcome; therefore, EMEA data were not included.

These data highlighted the differences in the agencies' timelines that can be related to differences in review procedures. Examples are shown next. Statistical analyses indicated that the time taken at each interval was significantly different between some agencies ($P < .01$), as shown in Table 5.

- *Receipt of Data:* The time from receiving the dossier to starting the scientific assessment included validation and queuing and was achieved in a single day at CDER because validation (which must be completed in 60 days) is carried out in parallel with the start of the scientific assessment. By contrast, at the time of the study, Health Canada had a con-

TABLE 5

1997–2002: Mean Interval in Calendar Days to Complete Stages Between Major Milestones From Receipt of Dossier to Start of the Second Review Cycle for NAS Applications

Stage as Delineated by Major Milestones*	Mean Interval in Calendar Days† TGA (A)	Health Canada (B)	Swissmedic (C)	CDER (D)	Mann-Whitney *U* test ($P < .01$ for All Pairs Shown)
Receipt of dossier (1) to start of scientific assessment (3)	61 (288)	197 (211)	46 (208)	1 (204)	A vs B , A vs C, A vs D, B vs C, B vs D, C vs D
Start scientific assessment (3) to end of scientific assessment (4)	299 (258)	312 (184)	96 (207)	273‡ (182)	A vs C, B vs C, C vs D
End scientific assessment (4) to outcome letter 1 (6/9)	99‡ (245)	25 (178)	66‡ (205)	10 (182)	A vs B, A vs C, A vs D, B vs C, B vs D, C vs D
Outcome letter 1 (9) to license to market (first-cycle approvals only) (10)	67 (189)	0 (110)	178 (94)	0 (66)	A vs C
Receipt of dossier (1) to license to market (first-cycle approvals only) (10)	531 (188)	554 (110)	369 (94)	248 (66)	A vs C, A vs D, B vs C, B vs D, C vs D
Outcome letter 1 (6) to start of second scientific assessment (3i) for applications not approved in the first review cycle	55 (30)	107 (53)	197 (75)	208 (88)	A vs B, A vs C, A vs D, B vs C

*(n) = data point reference from Table 1.
†(n) = number of compounds with both milestones.
‡This interval includes the evaluation time by advisory committees.

siderable backlog of applications that were held in a queue after validation and before the assessment commenced. The problem has since been addressed for pharmaceuticals (13).

- *Scientific Assessment:* The times from start to finish of the primary scientific assessment were comparable for TGA, Health Canada, and CDER (the difference in time between CDER and Health Canada, CDER and TGA, Health Canada and TGA were not significant), but there was an additional step for TGA, adding an average of 99 days while the application was referred to an advisory committee. At CDER, the evaluation time by advisory committees is within the scientific assessment time. Advisory committees are not a standard part of Health Canada's review process, but when convened, the committee's evaluation time is included in the total scientific assessment time. Swissmedic achieved the fastest time from the start of the scientific review to issue of the first outcome letter (including reference to an advisory committee), but some technical issues were resolved at a later stage (see Authorization of Product).
- *Authorization of Product:* The differences in time from issuing letter 1 notifying intent to approve the product to the date of the license allowing legal operation reflect different procedures. In the United States and Canada, this is a one-step process with a single approval letter (United States) and notice of compliance (Canada) that permit immediate marketing.

In Switzerland, this stage was exceptionally long as negotiations on the detail of the product information (labeling) only occur after an "approvable" letter is issued and minor deficiencies relating to quality can also be resolved at this stage. In Australia, the delay was shorter but can be more than 2 months, during which the product information and standard provisions are verified, and the sponsor company responds to the final product approval notice and agrees to registration. This is followed by the issue of the Certificate of Registration.

Looking at the time taken from receipt of dossier to license to market for first-cycle approvals (fifth data row in Table 5), there was no significant difference between TGA and Health Canada.

- *Clock Stop for Sponsor Response:* For compounds that went to a second review, there were considerable differences in the times from notifying deficiencies until the data were received and a second review commenced. There appeared to be a correlation between these times and the limits set by agencies for the receipt of data. For TGA and Health Canada, the targets are 60 and 90 days, respectively, whereas CDER does not set time limits, and the interval before starting the second assessment was far longer. Swissmedic, for which the delay was similar to that for CDER, only introduced a time limit (4 months) in 2002; therefore, the majority of reviews in this study predated this limit. There were no significant differences between CDER and Health Canada and between CDER and Swissmedic for this interval.

SUBMISSION RATES

The numbers of applications received by year and the number approved are shown in Figure 1. The rate at which applications for NASs were submitted to the agencies over the period studied showed a significant decline for all agencies except Swissmedic ($P < .05$). For the TGA, the numbers submitted in 2001–2002 were 26% lower than for 1997–1998, and for Health Canada and CDER, the number was 39% lower. Year-on-year submissions showed a similar trend to the overall submission, with TGA averaging 50 per year and the averages for the other agencies similar at 37 per year for Health Canada and 35 per year for Swissmedic and CDER.

When the number of NASs approved was plotted against the year of submission, the pattern mirrored the decline in submissions, as may be expected, and the decline was significant for TGA, Health Canada, and CDER ($P < .05$). The ratios between the number of submissions per year and the number that were approved were generally constant across agencies. An exception was seen in 2001, when TGA showed a percentage approval of 79% compared with 53% for Swissmedic, 44% for Health Canada, and 33% for CDER.

APPROVAL TIMES

A comparison of the overall approval times for all approved applications in the study is shown in Figure 2. The median approval times and the 5th, 25th, 75th, and 95th percentiles for each agency were calculated by year of submission. The results showed a wide variation in approval times across agencies as well as within agencies.

As shown in Figure 2, the median overall approval time in ascending order of calendar days was as follows: CDER 368; Swissmedic 398; EMEA 496; TGA 533; Health Canada 595. When the medians were compared in pairs using the Mann-Whitney *U* test, there was no significant difference between Swissmedic and CDER. Of

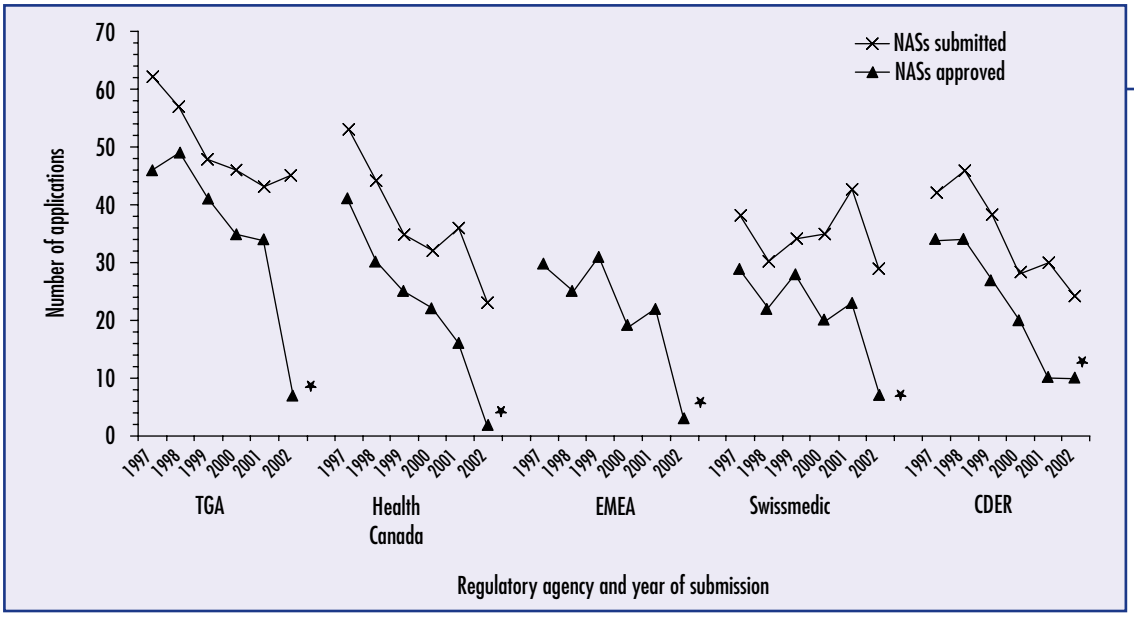
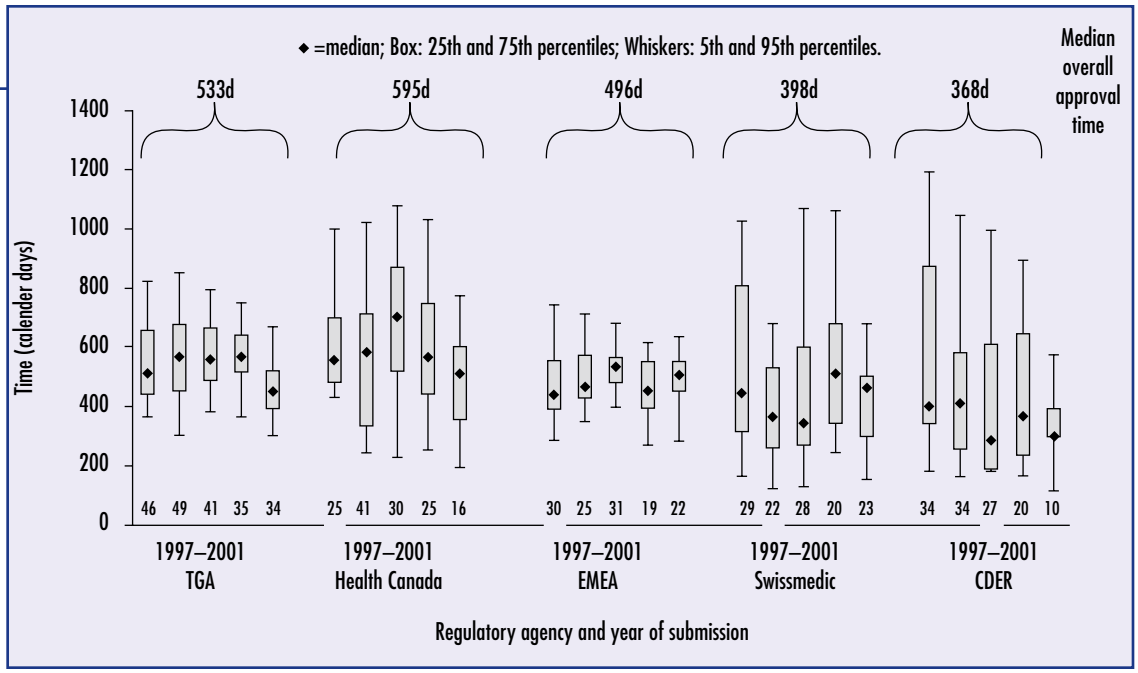


FIGURE 1

*Number of NASs submitted between 1997 and 2002 and the number approved by year of submission tracked through July 31, 2003. *2002 submissions have only been tracked through July 31, 2003; therefore, the numbers of approved compounds are underrepresented.*

FIGURE 2



Range of approval times by year of submission for NASs submitted between 1997 and 2001 that were approved by July 31, 2003. The n numbers are shown below each plot. The approval time for EMEA includes the Commission decision phase.

the other pairs, a significant difference was found between Health Canada and TGA ($P < .05$); in all other pairs, the significant differences were $P < .01$.

The results for EMEA showed the least variation when considering the 25th to 75th percentiles, followed by TGA. The wide difference between 25th and 75th percentiles for Health Canada, CDER, and Swissmedic can partly be explained by the fact that two populations were measured, namely, expedited reviews and standard reviews, which have markedly different review times at these agencies.

The data in Figure 2 included all types of compounds (chemical, biologic, and biotech). The overall median approval times for chemical entities alone were CDER 370; Swissmedic 381; EMEA 486; TGA 536; Health Canada 565 (data not shown). The median approval times were not significantly different for CDER and Swissmedic and for Health Canada and TGA; between other agencies, the difference was significant ($P < .05$ or $P < .01$).

AGENCY AND SPONSOR TIMES

The overall approval times were broken down further into agency and sponsor times. The regulatory component could be further broken down to differentiate between the time that the application is under active review (scientific assessment time) and the time spent in validation or queuing for the next stage in the procedure. For the sake of simplicity, however, this differentiation is not shown in Figure 3. The agency time and the corresponding sponsor time are given as mean values.

Taking the mean for each agency over the period of the study, the percentages of clock stop (sponsor) time were Swissmedic 45%; TGA 44%; EMEA 26% (40% if the European Commission decision time is not included in the approval time); CDER 24%; and Health Canada 3%.

Within an agency, there were significant changes to the percentage of sponsor time as a proportion of total approval time. At TGA, there was a significant decrease in the percentage of sponsor time in 1999 and 2000 in comparison to 1997 ($P < .05$). Swissmedic showed a significant decline in the percentage of sponsor time in 1999 when taking the percentage in 1997 as a baseline. At EMEA, there was a significant increase in the percentage of sponsor time in 1999 when comparing with the figure for 1997 ($P < .05$). There were no significant differences in sponsor time at Health Canada and CDER. The 2001 data were not

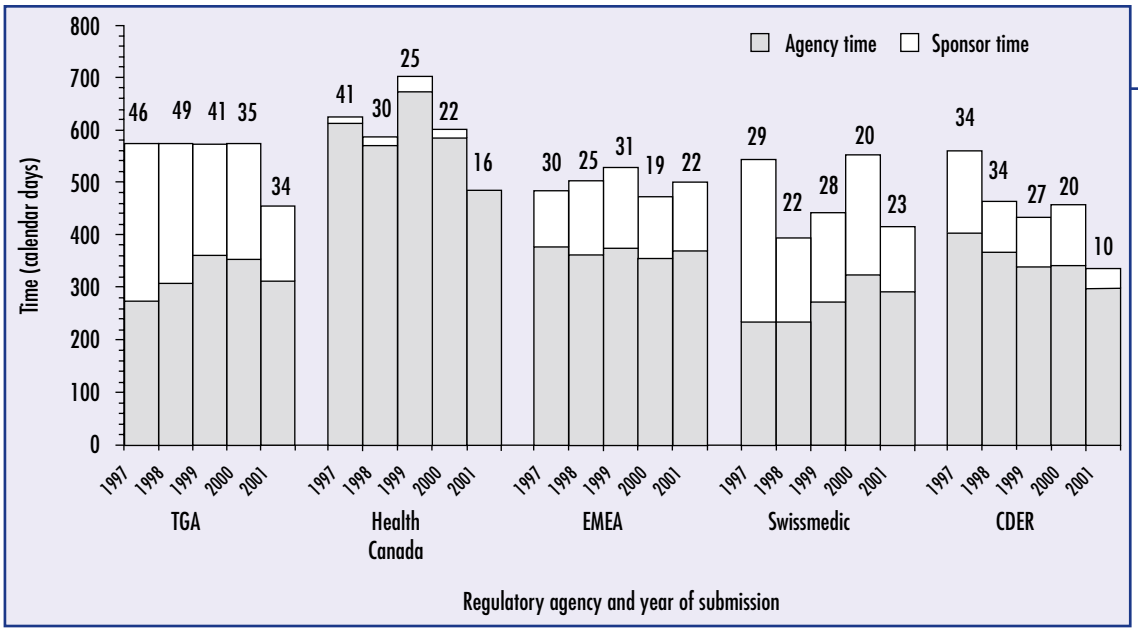


FIGURE 3

Mean approval time separated into agency and sponsor time by year of submission for NASs submitted between 1997 and 2001. The approval time for EMEA includes the Commission decision phase. The n numbers are shown above each bar.

analyzed as there were some applications that were still ongoing.

To make a valid comparison between these figures, however, the differences in review practices and procedures need to be taken into account. Both TGA and Swissmedic were able to calculate time taken for sponsors to respond to questions during the scientific review, as well as between reviews in multicycle applications; EMEA and CDER only calculated clock stops between reviews. The small percentage of sponsor time at Health Canada is potentially misleading as they seek sponsor responses during the review (in the form of "clarifaxes"), but no stoppage time is recorded.

IMPACT OF EXPEDITED REVIEW

The impact of expedited review procedures on timelines was investigated further as shown in Figure 4, which gave median approval times for both standard and expedited reviews by year of submission.

Although all agencies are able to designate applications for expedited review, the extent to which this procedure was used in the period of the study varied considerably; the percentage of approved applications that were designated as expedited review were CDER 45%; Health Canada 31%; TGA 20%; and Swissmedic 19%. Data on expedited reviews were not included for EMEA because there were no such reviews between 1997 and 1999 and only 1 or 2 expedited reviews in each of the subsequent years.

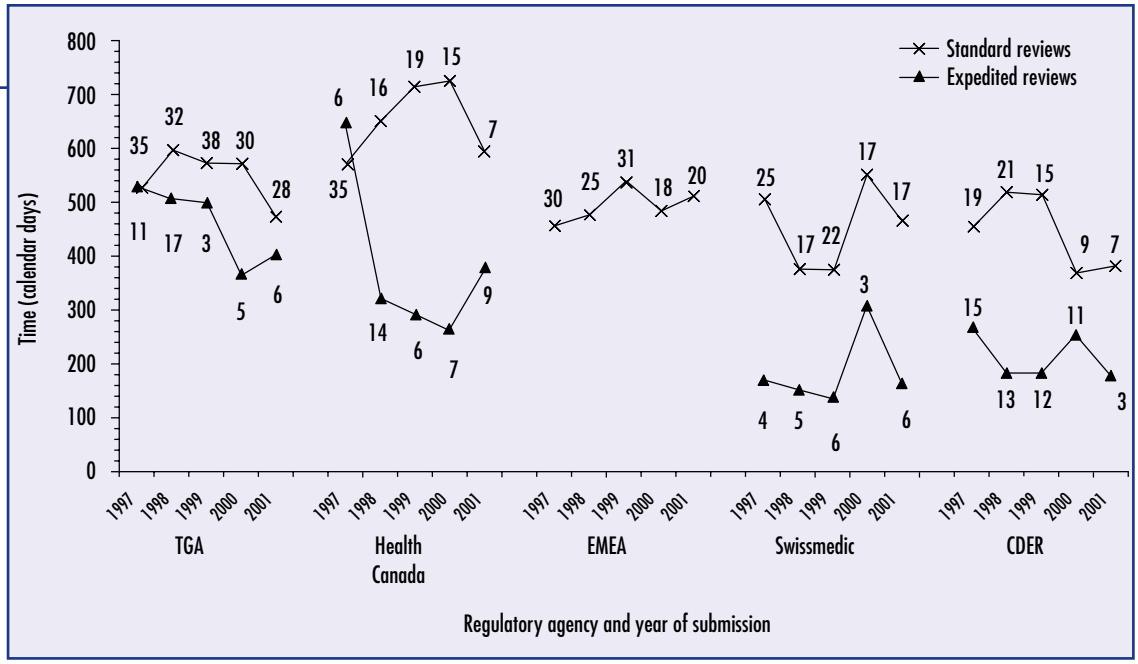
The median approval times for expedited review in 2000 at TGA, 1998 and 2000 at Health Canada, and 1999 at Swissmedic were significantly shorter than the median approval times for standard reviews ($P < .01$). At CDER, there was a significant difference in the median approval times between the standard and expedited reviews in all years with the exception of 2000 ($P < .01$ for 1997–1999). The 2001 data were not analyzed because there were some applications that were still ongoing. The percentage differences between the approval times for standard and expedited (calculated from the median approval times) were CDER 62%; Swissmedic 51%; Health Canada 51%; and TGA 9%. For both CDER and Swissmedic, the pattern of decreasing and increasing times for standard reviews in different years was mirrored in the times for expedited reviews. Health Canada, by contrast, showed a steeper decrease in expedited review times, but the standard review times increased over the period of the study.

IMPACT OF PRESUBMISSION ASSISTANCE

All agencies offer presubmission advice, but with the exception of CDER, this does not occur with all applications. The comparison of median

FIGURE 4

Comparison of median approval times for standard and expedited reviews for NASs submitted between 1997 and 2001 by year of submission. The approval time for EMEA includes the Commission decision phase. The n numbers are shown adjacent to the data points on the graph. Data shown for n = 3.

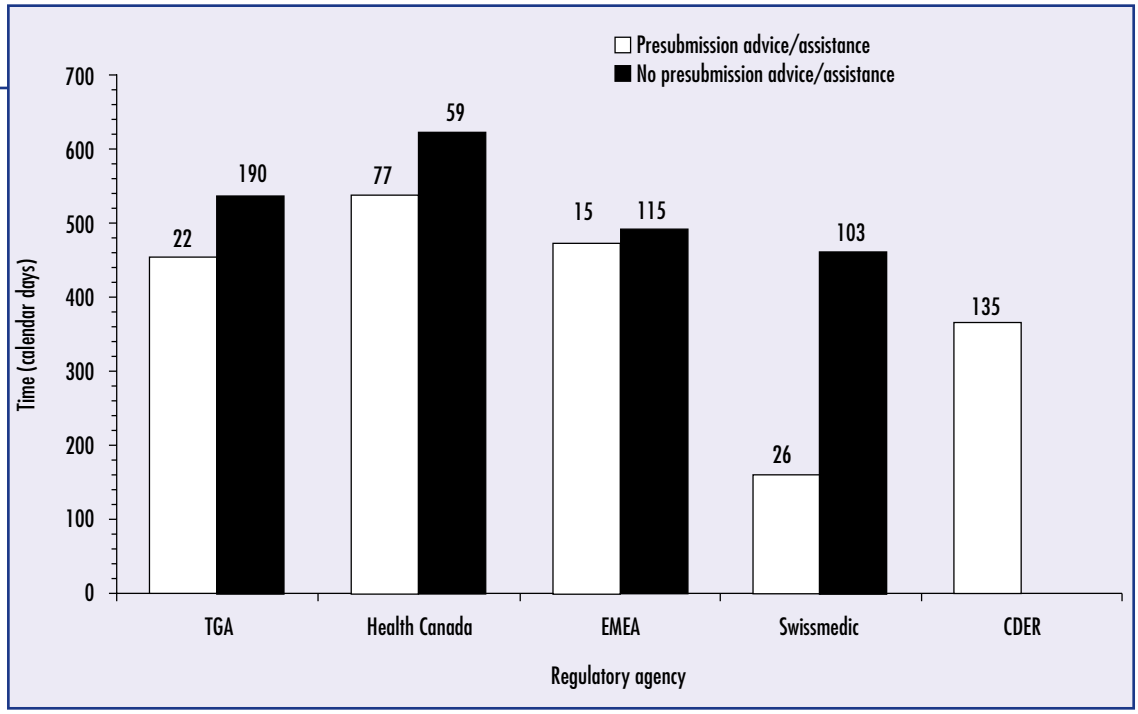


approval times for applications with and without presubmission advice, shown in Figure 5, appears to support the hypothesis that such advice will reduce the review time.

In the case of applications to Swissmedic, 100% of the applications with presubmission advice were destined for an expedited review. For TGA, 36% of the applications with presubmission advice were subject to expedited reviews compared with 18% of the applications without advice, but it should be noted that presubmission advice has only been tracked since 2000. The figures for Health Canada were 39% and 22%, respectively, but the comparison is

FIGURE 5

Median approval time for NASs submitted between 1997 and 2002, with and without presubmission advice/assistance. The approval time for EMEA includes the Commission decision phase. The n numbers are shown above each bar.



not possible for CDER because the procedures are such that all applications are subject to presubmission advice.

All applications submitted to EMEA were subject to a presubmission dialogue to discuss administrative/legal matters, but these consultations were not included in Figure 5. The data for EMEA were based on the reports of Scientific Advice included in the European Public Assessment Report and should be regarded with caution as use of the Scientific Advice procedure may not have been reported routinely in the past.

APPLICATIONS SUBMITTED TO ALL AGENCIES

Of the 742 applications approved within the time frame of the study (Table 4), 477 were submitted to two or more of the five agencies. These applications related to 144 different NASs. Of these, only 29 substances were submitted to all five agencies (145 applications), and these were the subject of more detailed investigations and analyses. Some of the findings are reported in Table 6 and Figure 6.

The data on approval times and differential times between agencies in Table 6 indicated that the United States was the country of first submission for the majority of applications (second row of data in the CDER column). EMEA was the next agency, with a median differential time of 5 days; the time lag from first submission to submission at TGA, Health Canada, and Swissmedic was 86, 90, and 57 days, respectively. A similar pattern was seen regarding the time difference between the granting of a marketing authorization in the first country and the other agencies.

Looking at the approval times for these 29 compounds (Table 6 and Figure 6), there were significant differences between all agencies ($P < .05$) with the exception of Health Canada compared to TGA and EMEA and between TGA and EMEA. The median approval times at

TABLE 6

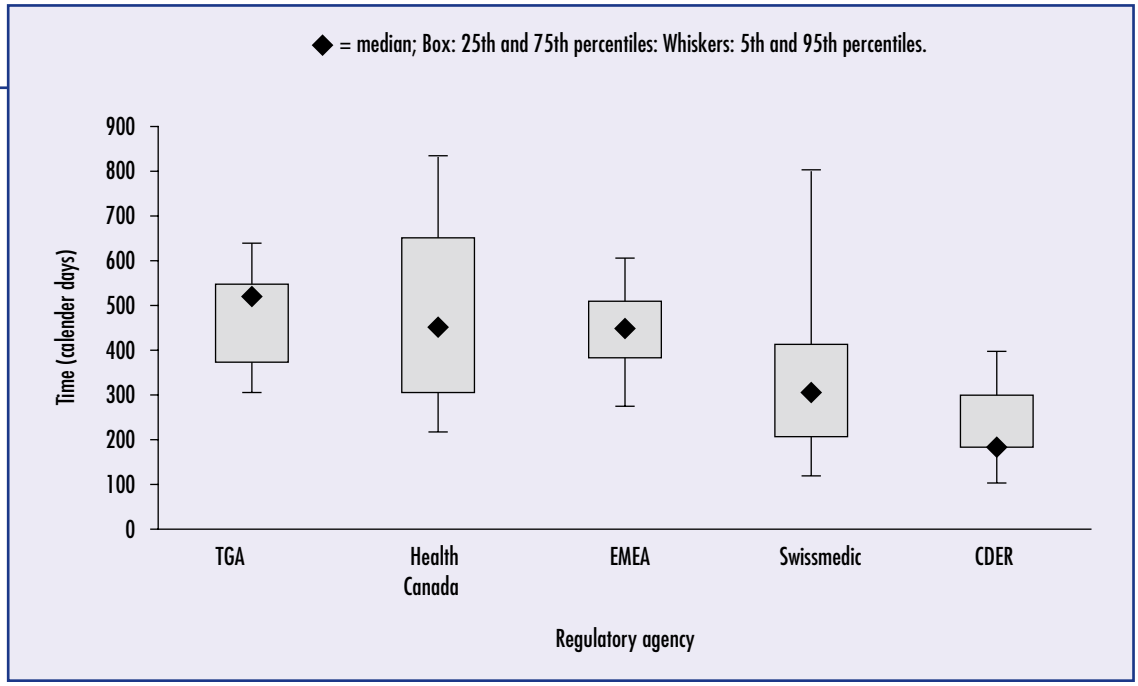
NASs (29) Submitted to All Agencies 1997–2002 and Approved by End of July 2003

	TGA (A)	Health Canada (B)	Swissmedic (C)	CDER (D)	EMEA* (E)	Mann-Whitney *U* test
Mean/median approval time (days)	490/517	503/467	368/311	254/182	451/452	A vs C‡, A vs D‡, B vs C‡, B vs D‡, C vs D†*, C vs E‡, D vs E‡
Mean/median time between first submission to any authority and submission to this authority (days)	168/86	132/90	118/57	30/0	90/5	—
Mean/median time difference between marketing authorization granted by the first and this authority (days)	407/358	384/324	234/127	33/0	289/238	—
Mean/median approval time and number (n) for expedited reviews (days)	372/364 (9)	334/281 (14)	174/152 (9)	186/181 (21)	266/266 (2)	A vs C‡, A vs D‡, B vs C‡, B vs D‡
Mean/median approval time and number (n) for standard reviews (days)	543/541 (20)	661/651 (15)	455/366 (20)	434/391 (8)	464/461 (27)	A vs C†, A vs E†, B vs C‡, B vs D‡, B vs E‡

—No analyses were conducted.
*The approval time for EMEA includes the Commission decision phase.
†$P < .05$.
‡$P < .01$.

FIGURE 6

Range of approval times for the 29 NASs submitted to all agencies 1997–2002 and approved by July 31, 2003.



Swissmedic and CDER were significantly shorter than for the other agencies.

As shown in Table 6, comparisons of approval times need to take account of whether applications were subject to standard or expedited reviews. However, the picture was complicated because not all authorities designated the same compounds for expedited review, and there was a considerable disparity between the 21 compounds expedited by CDER and the two expedited by EMEA.

For the median approval times for expedited reviews, CDER and Swissmedic were significantly shorter compared to Health Canada and TGA ($P < .01$). There was no significant difference between CDER and Swissmedic.

Comparison of the median approval times for standard reviews showed that review times at Health Canada were significantly longer compared to Swissmedic, EMEA, and CDER ($P < .01$). Review times at TGA were significantly longer than Swissmedic and EMEA ($P < .05$).

DISCUSSION

The effectiveness and efficiency of the regulatory review process has been the focus of performance studies and improvement initiatives for many regulatory agencies over recent years. There are numerous studies that have looked at overall approval times and made comparisons between different agencies (3–8). This study set out to examine such comparisons in more depth and establish a methodology for benchmarking performance from the date of submission of the dossier to date of legal marketing.

Applications approved within the study's time frame (1997 to 2002) but received by the agencies before January 1, 1997, were not included, which partly explains the surprisingly small number (29) of NASs that obtained approval from all five agencies. Similarly, this number would not include products submitted to the five authorities for which the applications were not all approved before the cutoff date of July 31, 2003.

Some of the results discussed here show a clear picture that confirms observations from other sources. Among these is the decline in submission rates shown in Figure 1, which has led to the widely reported decline in the number of NASs reaching the market in the last few years (14).

Other results need careful interpretation because of the different factors that can influence timelines and review procedures. For example, the comparison of the range of overall approval times for the different agencies, given in Figure 2, showed that TGA and EMEA had fewer outliers, and the difference between the fastest and slowest approval was far less than for the other agencies. This could be interpreted as showing the impact of the rigorously applied time limits for reaching a decision in the TGA and EMEA procedures, and these are no doubt an important factor. The much wider range of approval times seen for Health Canada, Swissmedic, and CDER, however, also reflects the considerable difference in target times for expedited reviews at these agencies compared with a standard review, that is, 180 versus 300 days for Health Canada (15), 120 versus 200 days for Swissmedic, and 6 versus 10 months for CDER (16). In contrast, TGA does not have a formal time frame for priority evaluations (17).

The different types of compound (chemical, biologics, or biotech) included in the data set may also influence the approval time. However, calculation of the median approval times for chemical entities alone showed that this makes little impact on the approval time.

The disparity between the mean approval times for standard versus expedited review might have more impact on the range of approval times than the lack of specified targets and time limits. Nonetheless, it will be interesting to track the future impact of the new Food and Drug Administration *Guidance for Review Staff and Industry, Good Review Management Principles and Practices for PDUFA Products* (18), which will introduce target times for the review and for responses from sponsors.

The need to be aware of the differentials between standard and expedited reviews was also highlighted when studying the apparent impact of presubmission assistance and advice on approval times (Figure 5). Advice was more frequently sought for applications that were destined for expedited review, and there are therefore dangers, without taking other factors into account, in making simple comparison of approval times for applications that were and were not subject to presubmission advice.

EMEA assessed the impact of scientific advice on the outcome of the review (19). Their experience since 1998 has been that, although scientific advice is not a guarantee of a positive outcome, it appears to have a favorable influence. It would be of interest to investigate the other agencies in this study to see whether applications that have had presubmission advice are more likely to have been approved than those that did not have advice.

The number of review cycles in relation to the overall approval time has also been investigated in this study (data not shown). This revealed that, within an agency, the approval times were longer when an application required a higher number of cycles; however, this was not the case when making a comparison across agencies, that is, the approval time did not correlate with the number of review cycles. For example, applications to CDER were more likely to go through multiple review cycles in comparison to TGA or Health Canada, although CDER had the shortest median approval time for each of the years except in 1998.

THE IMPACT OF REGULATORY CHANGE

One of the objectives of the study was to provide benchmarking data that can be used to define performance targets and focus on ongoing performance improvement initiatives. Because the study spanned some 6 years, many major and minor regulatory changes took place that have had an impact on the data or that may be expected to show up in continued studies. Examples include

- *TGA:* The introduction of time limits for sponsor response in 1997 and the introduction of 100% funding by user fees in 1998 with financial penalties for the agency if target times for review were not met resulted in the significant decline in overall approval time. The sponsor time was relatively constant until 1999, when a significant reduction could be seen (Figure 3). This may reflect an initiative to work with sponsors to reduce clock stop time in the process (20).
- *Health Canada:* In March 2003, the assignment of

special resources and improvement of processes to decrease the backlog of applications and the queuing time before the scientific assessment began. In the 2 years from April 2003 to March 2005, an 89% reduction in review backlog had been achieved for pharmaceutical submissions, and 99% of the backlog had been eliminated as of September 1, 2005 (13).

- *Swissmedic:* A major revision of the legislation and the merger of the Intercantonal Office for the Control of Medicines and the Therapeutics Products Section of the Swiss Federal Office of Public Health in 2002. The impact of this could be seen in the review time for compounds submitted in 2000 as the transfer of the old legislation to the new started in 2001, which would have affected the review of compounds submitted in 2000.
- *CDER:* PDUFA authorized revenues from user fees to be used to expedite reviews and to recruit additional staff (21). Approval times declined by more than 50% since PDUFA took effect (22).

In this article, it has only been possible to review a small section of the analyses and comparisons that the data have made possible. Examples of other aspects of the data that have been examined include the following:

- A comparison of the number of applications, by agency and year of submission, that reach each of the four outcomes: refuse to file, approved, rejected, withdrawn and ongoing
- An inter- and intra-agency breakdown of the number of review cycles that applications go through before approval analyzed according to year of submission and therapeutic category
- The impact of the number of cycles on review times and on the ratio of sponsor time to authority time
- The impact of the therapeutic category on the median review times, tracked by year of submission and regulatory agency

APPLICATIONS APPROVED BY ALL AGENCIES

The applications that were submitted to and approved by all five agencies within the time frame of the study (Table 6) provides a unique set of data on the way the same applications were handled in the different regions. This allows hypotheses to be tested for specific compounds. For example, it might be assumed that it would be quicker and easier to review a product that had previously been approved by other authorities and was already on the market, but in several cases the data did not confirm this. It could therefore be argued that the assessment may be prolonged because of the need to consider additional data gathered in the postmarketing stage.

Again, the difference in the way in which the applications were processed—whether as standard or expedited reviews—needs to be taken into account. As noted, there were disparities in the way applications were handled, which raises the question of why the same application was treated as priority by some agencies but not by others. This could reflect different rules between the agencies or could mean that the company had not applied for an expedited review in some regions.

CONCLUSIONS

The study, using a methodology based on common, agreed milestones, has provided a basis for a detailed analysis of the timelines for review and approval of submissions made to five authorities between 1997 and 2002. The unique methodology has enabled comparisons to be made both within agencies and between different authorities and has identified differences in the length of time that applications spend in different stages of the review as well as highlighting differences in activities and the order in which they occur.

The study, however, has only evaluated time and does not include any information related to the quality of the review (23). The study also did not cover resources or the variation in the content of applications sent to different authorities within the same time frame. All of these would help to place the results in full context and assist agencies to improve their procedures in the future.

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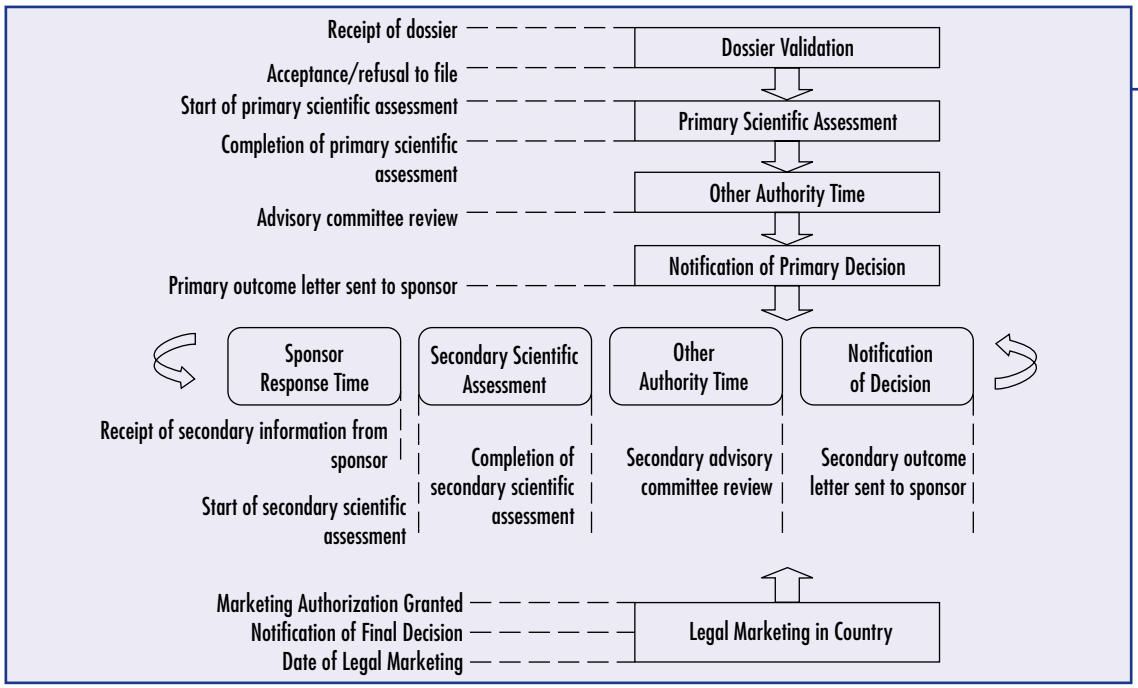
APPENDIX



Schematic representation of key milestones in the regulatory review process.

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