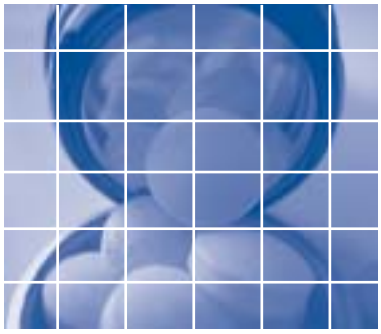
Health Canada Santé Canada

Health Products and Food Branch

Regulatory Review of Pharmaceuticals, Biologics and Medical Devices

2004 Annual Summary of Performance



Canada

Health Products and Food Branch

Regulatory Review of Pharmaceuticals, Biologics and Medical Devices

2004 Annual Summary of Performance

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Executive Summary

Since April 2003, new investments through Health Canada's Therapeutics Access Strategy (TAS) have lead to substantial improvements in the timeliness and efficiency of Canada's review process for therapeutic products.

A number of business improvements have been introduced over the last two years. Project management tools and approaches are being implemented to better coordinate tasks at the various stages of the review process. International harmonization initiatives, such as the adoption by Health Canada of the Common Technical Document standard for the filing of drug submissions, have helped reduce the regulatory burden for manufacturers. Those measures, in addition to investments in internal and external review capacity, are a few examples of new initiatives that have contributed to recent gains in regulatory performance.

The most dramatic improvement in Health Canada's regulatory performance has been the reduction of the review backlog of pharmaceutical submissions by 68% from April 2003 to December 2004 (and by 89% by March 2005). In the biologics area, the backlog was reduced by 23% over the period April 2003 to December 2004 (but this declined to seven percent by March 2005).

Although there is still much progress to be made, more decisions are being made within internationally comparable time targets. For example, the proportion of regulatory decisions made within time targets for new pharmaceutical submissions almost doubled in 2004. Twenty-five percent of regulatory decisions were made within time targets in 2004, up from 13% in 2003. This is particularly significant given that a large proportion of submissions processed in 2004 were in backlog.

Market authorization decision times were reduced for specific submission categories, including decreases in the number of days taken in 2004 to approve brand name priority pharmaceuticals (43% decrease in 2004 in median market authorization time), as well as generic standards (28% decrease in median market authorization time).

Performance improvements are also being made in the medical devices area. Despite a significant increase in the workload of medical device applications (an overall 51% increase in 2004, with the largest growth occurring for Class II devices), 51% of regulatory decisions were made within target and average market authorization times improved for Class III and IV devices, decreasing by 11% and 17%, respectively.

Other business improvement activities are underway. They include: streamlining project management practices; implementing an electronic submission and review system; and developing good guidance and review practices to enhance the quality of submissions and reviews. This will enable Health Canada to increase the proportion of submissions meeting time targets, with the goal of reaching internationally comparable review performance (i.e., 90% of regulatory decisions for new drugs made within time targets) by 2006 for pharmaceuticals and 2007 for biologics.

This report provides an overview of Health Canada's review performance for pharmaceuticals, biologics and medical devices. The report also includes a snapshot of other decision-making processes beyond the regulatory system that ultimately influence access by Canadians to therapeutic products.[1]

[1] For more information on progress, refer to 'Regulation and Beyond: Progress on Health Canada's Therapeutics Access Strategy', available at http://www.hc-sc.gc.ca/hcs-sss/pubs/care-soins/2005-therap-strateg/index_e.html

Introduction

This report provides an overview of Health Canada's pre-market regulatory review performance of new therapeutic products including pharmaceuticals, biologics and medical devices in 2004[2]. This report is not intended to replace the more detailed quarterly and annual Drug Submission Performance Report.[3]

The HPFB strives to maintain a balance between the potential benefits and risks of all health products. Its highest priority in determining the balance is public safety.

The Health Products and Food Branch (HPFB) is a science-based organization within Health Canada that carries out federal responsibilities for the regulation of therapeutic products and food. HPFB evaluates and monitors the safety, efficacy and quality of thousands of human and veterinary drugs, medical devices, natural health products and other therapeutic products available to Canadians.

Before a therapeutic product is authorized for sale in Canada, the manufacturer must file a submission that provides the HPFB with substantial scientific evidence of its safety, efficacy and quality, as required by the *Food and Drugs Act and Regulations*. This evidence is reviewed by skilled scientists to determine whether the potential risks from the product are acceptable when balanced against the positive effects for the product's proposed use. If the product shows satisfactory scientific evidence of safety, efficacy and quality, the product is granted authorization for sale in Canada.[4]

Health Canada's Therapeutics Access Strategy is a comprehensive initiative aimed at helping Canadians maintain and improve their health by ensuring that human drugs and other therapeutic products are safe, of high quality, therapeutically effective, appropriately used and accessible in a timely and cost-effective fashion.

Since 2003, through the Therapeutics Access Strategy, new initiatives have been implemented to modernize Canada's regulatory system by streamlining the review process, encouraging better quality incoming submissions and improving the timeliness, efficiency and transparency of the review process. The Therapeutics Access Strategy is expected to help HPFB reach internationally comparable review performance by 2006 for new pharmaceutical drugs and by 2007 for new biologic drugs.

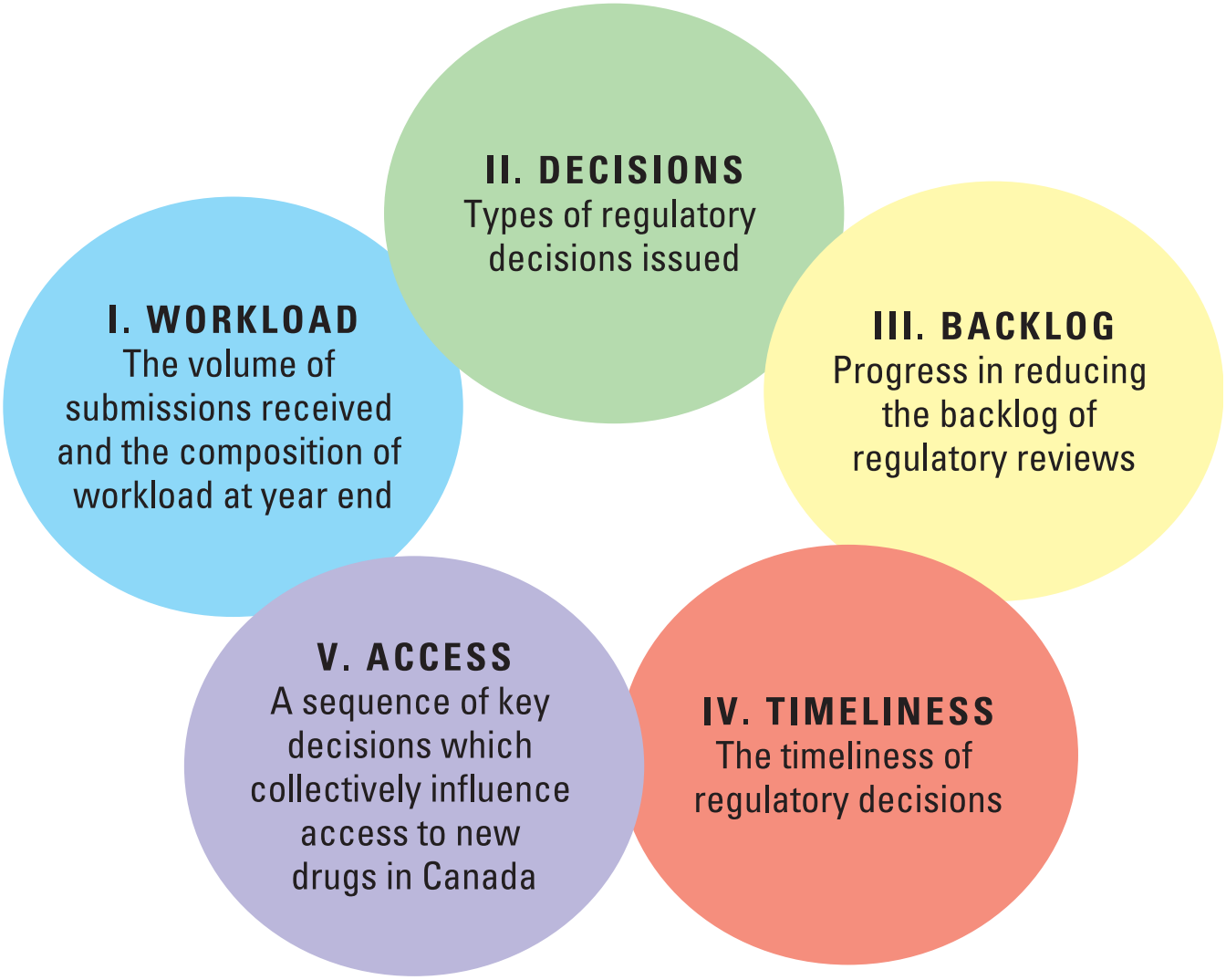
[2] See Annex A page 29 for definitions of pharmaceuticals, biologics and medical devices.

[3] The Drug Submission Performance Report uses different definitions and terminology to outline performance statistics and is therefore not directly comparable. For more information refer to http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/docs/perform-rendement/index_e.html

[4] Cost-effectiveness considerations are examined by organizations outside of HPFB (refer to Section V: Access to New Drugs in Canada).

Review Performance Reporting Framework for Pharmaceuticals, Biologics and Medical Devices

This report is organized into five sections that summarize data on regulatory review performance for new drugs and medical devices[5] including: workload, decisions, backlog, timeliness and access to new drugs in Canada. Definitions of the terms used in the report are provided in Annex A.



[5] For consistency and to simplify terminology, medical device applications are referred to as 'submissions' throughout the report.

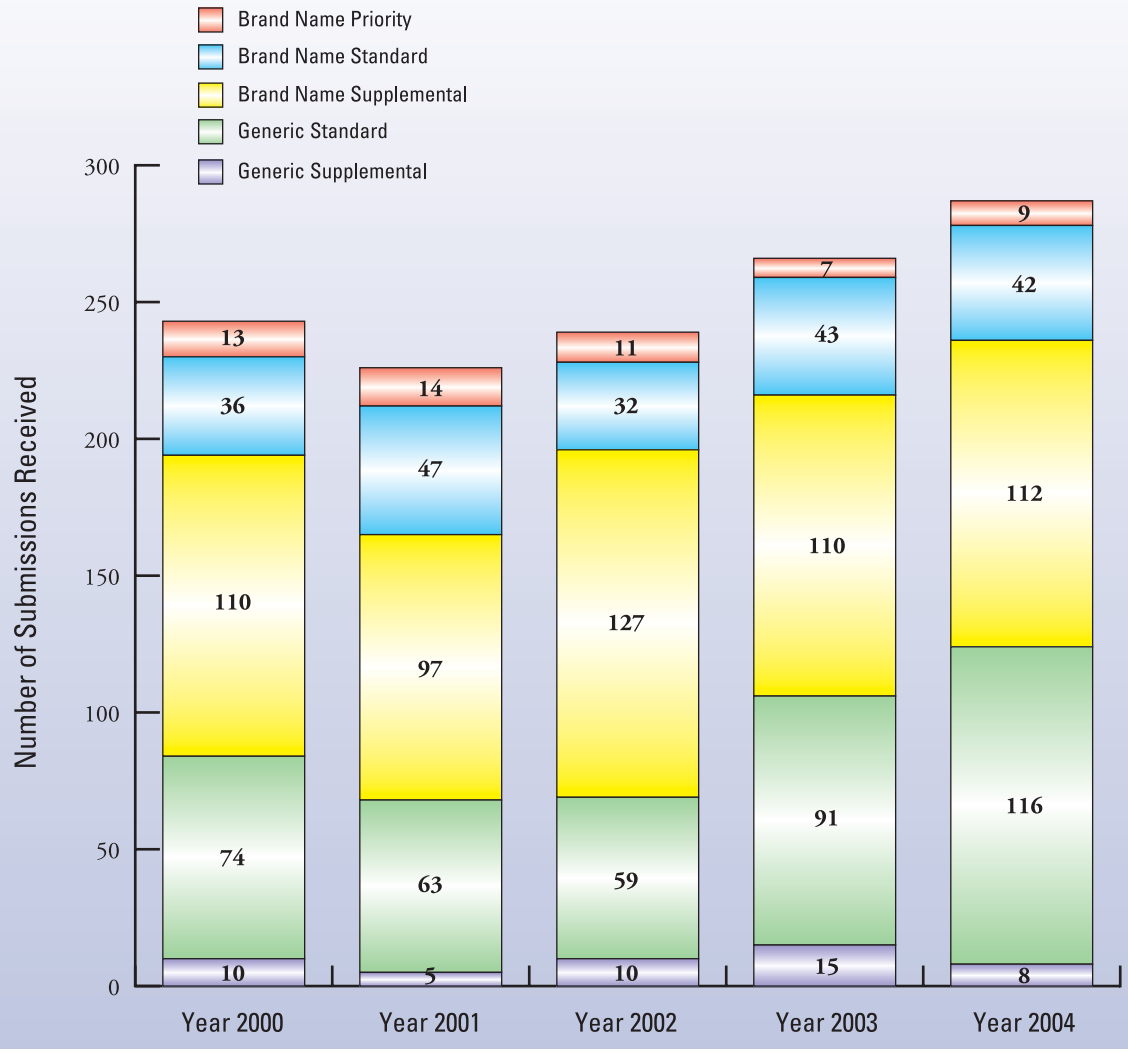
I. Workload

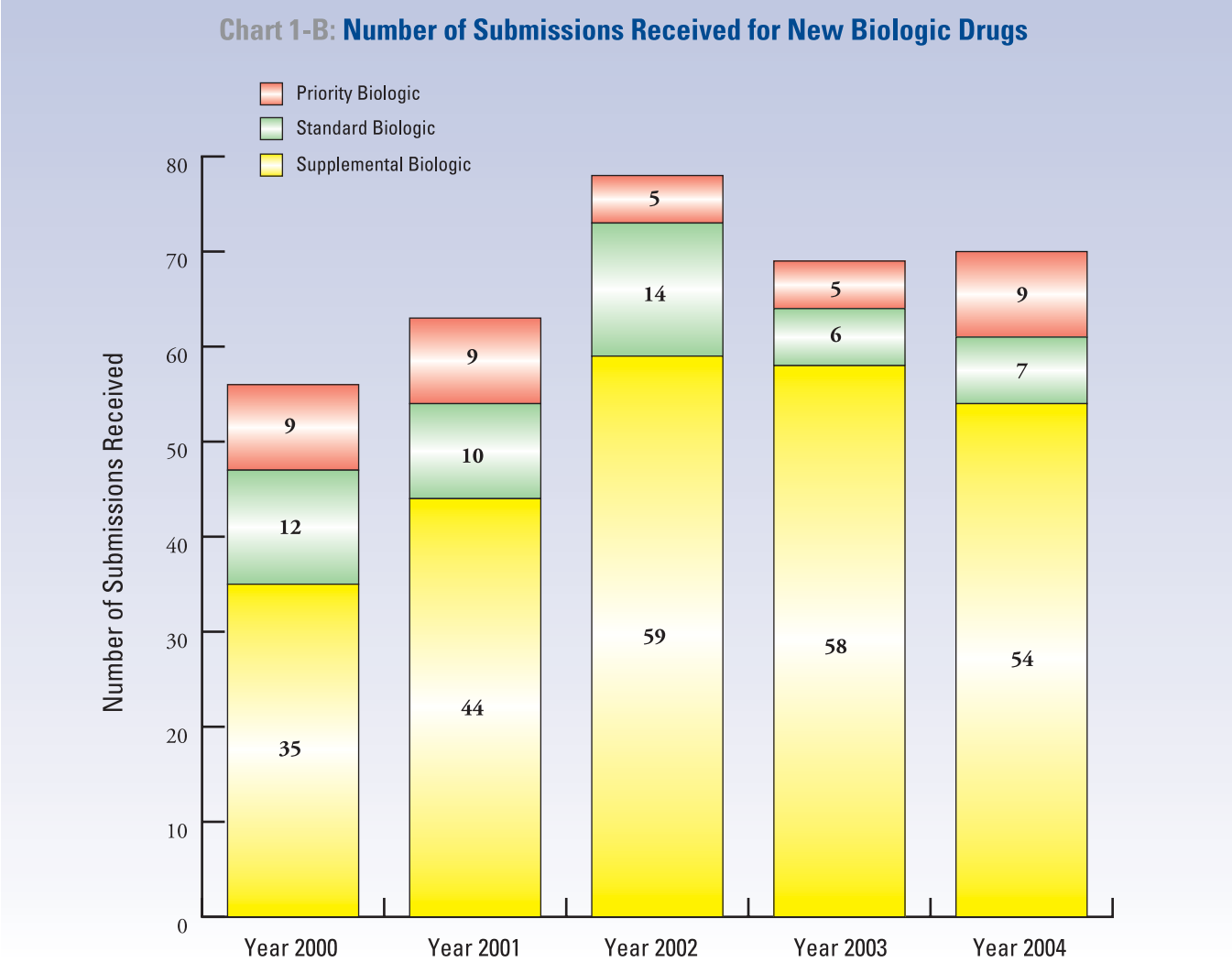
Number of Submissions Received Annually for New Drugs and Medical Devices

In 2004, the number of submissions for new drugs received by HPFB increased by six percent compared with 2003 (*see charts 1-A and B*).

Generic standard submissions account for the highest area of growth for pharmaceuticals, increasing by 27% (from 91 to 116) since 2003. This may be due to an increase in the number of multinational companies seeking to market generic drugs in Canada.

Chart 1-A: Number of Submissions Received for New Pharmaceutical Drugs





Submissions for priority biologics grew by 80% (from five to nine).[6] Breakthrough therapies include those used in combination with other drugs that provide significant improvement in health outcomes; and targeted medicines that are capable of attending to the disease process at multiple sites.

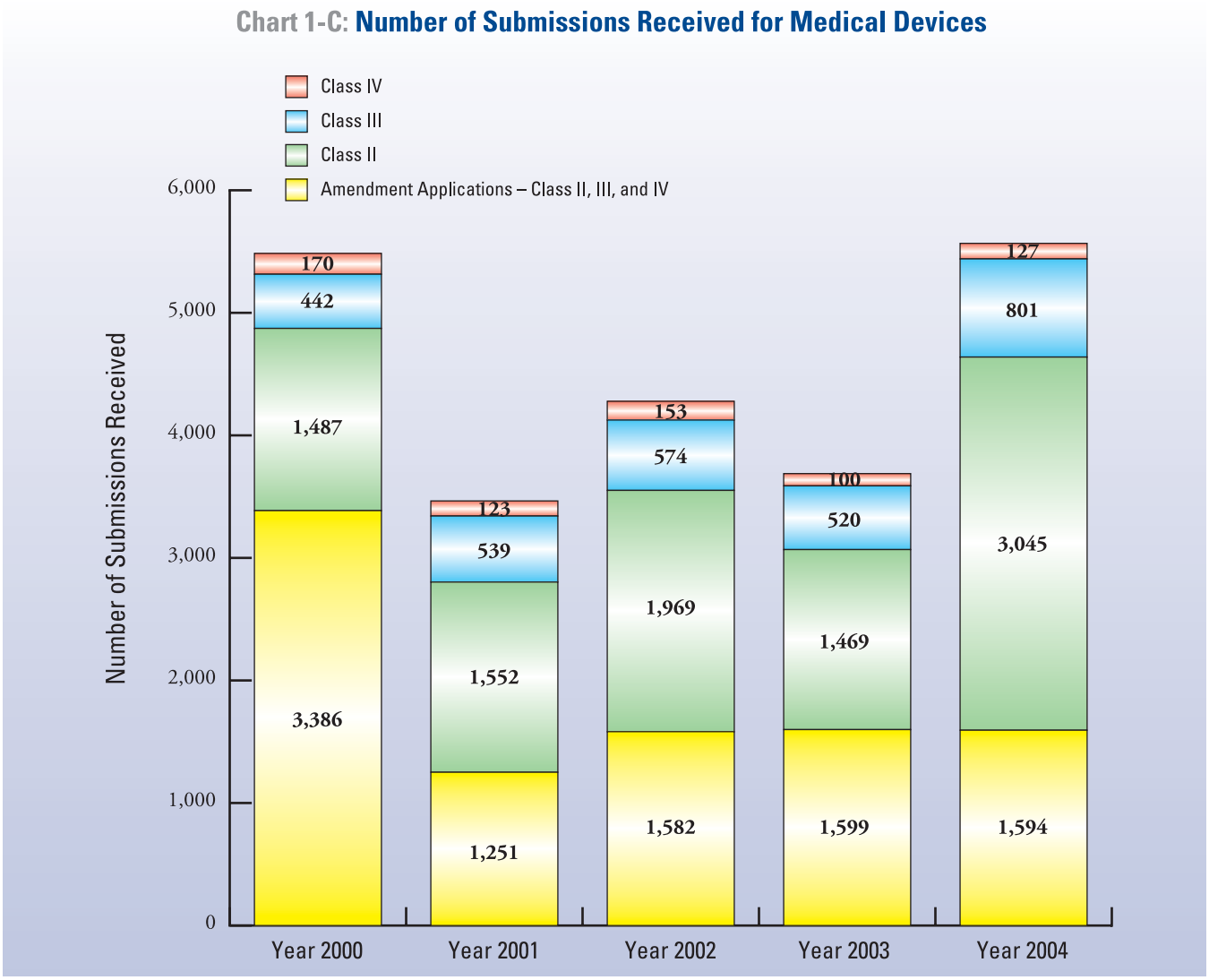
[6] Compared to other therapeutic products, a high proportion of biologics are designated as priority submissions.

Over 5500 medical device submissions were received in 2004, up by 51% from the previous year (*see chart 1-C*). Class II and III medical device submissions increased significantly in 2004, with Class II medical device submissions more than doubling, growing by 107%; and Class III medical device submissions increasing by 54%.

The recent increase of medical device submissions is indicative of the degree of technological innovation within the medical devices industry.

In addition to review of submissions for new drugs and medical devices, the HPFB review workload includes various other types of submissions that are not covered in this report.[7]

Chart 1-C: Number of Submissions Received for Medical Devices



[7] Other submission types not included in this report are Clinical Trial Applications, Investigational Testing Applications (for medical devices), Notifiable Changes, Drug Identification Number Applications and Faxback Amendment Applications (for medical devices).

End-of-Year Workload Status of Submissions for New Drugs and Medical Devices

This section provides data on the number and composition of new drug and medical device submissions on hand at the end of the calendar year 2004. Backlog refers to submissions for new drugs or medical devices which have exceeded their review time performance target without the issuance of a regulatory decision.

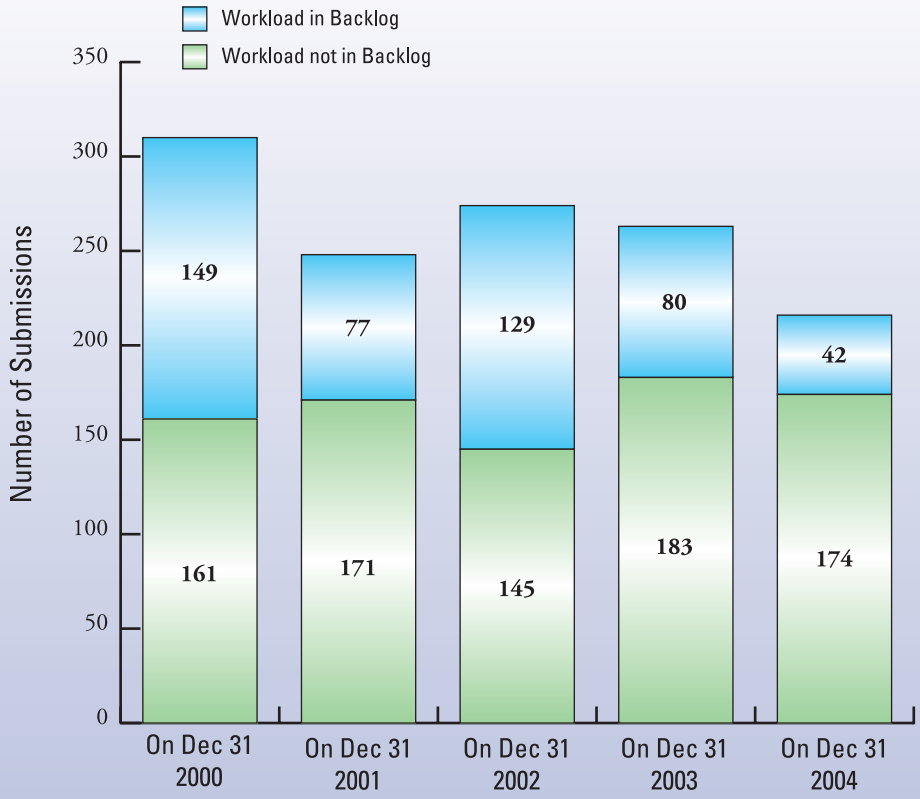
Through the Therapeutics Access Strategy, many improvements have been made to more efficiently manage the workload of submissions for new drugs. Submissions are now managed as 'projects' that are planned and coordinated to meet performance targets.

By December 31, 2004, the end-of-year workload of submissions for new pharmaceutical drugs included fewer backlogged submissions compared to previous years (*see chart 2-A*).

Pharmaceuticals backlog accounted for 19% of the total end-of-year workload in 2004, the smallest such percentage for the past five years.

Since 2004, HPFB has been receiving submissions for new drugs in the Common Technical Document (CTD) format. The CTD is a common international format that may be used by manufacturers to submit submissions for new drugs to regulatory authorities. The CTD format will make it easier for submissions to be filed in Canada and in other countries at the same time.

Chart 2-A: End-of-Year Workload Status of Submissions for New Pharmaceutical Drugs



The percentage of the end-of-year workload of submissions for new biologic drugs in backlog was 51% in 2004, down from 68% in 2003 and the lowest it has been since 2000, when the backlog was 47% of the end-of-year workload (*see chart 2-B*).

At the end of 2004, 18% of the medical device submissions workload was in backlog (*see chart 2-C*).[8]

Biologics are made from living organisms. Their processes carry risks related to bacterial or viral contamination. Due to their complexity, biologics require extensive controls to assure their safety, purity, efficacy and consistency in production.

In addition to the paper based scientific review, the HPFB conducts a laboratory evaluation of both the product and the key test methods used to control it; and an on-site-evaluation (inspection of the facilities) and personnel involved in production.

Chart 2-B: End-of-Year Workload Status of Submissions for New Biologic Drugs

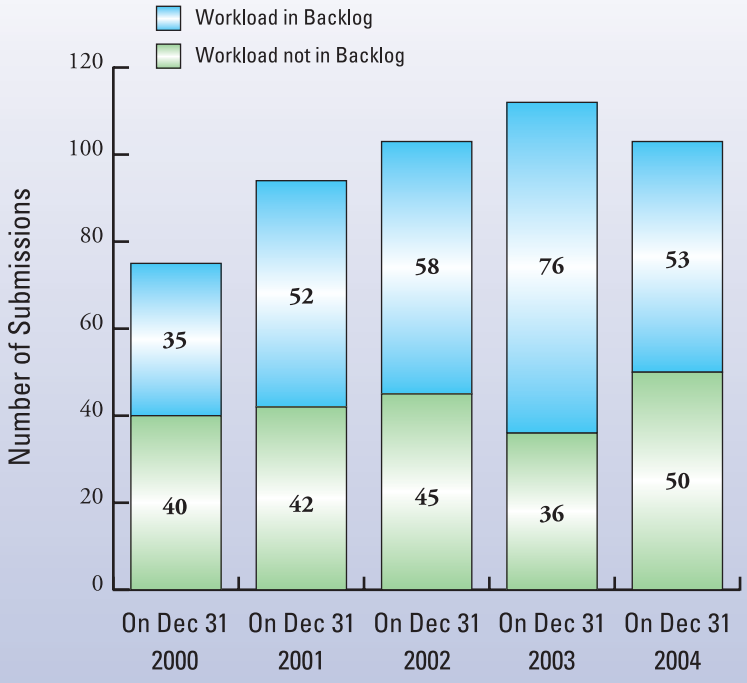
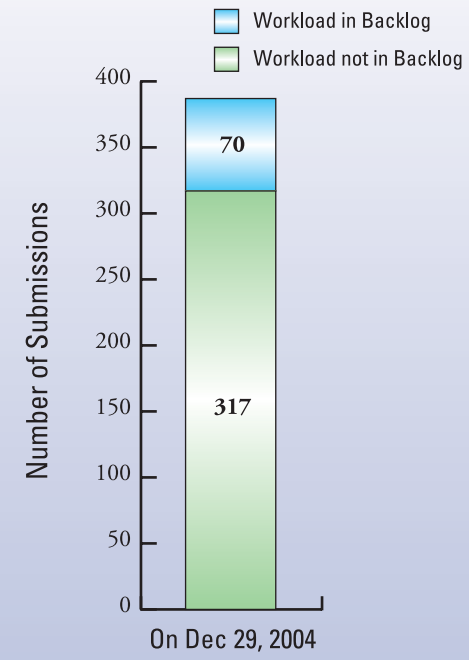


Chart 2-C: End-of-Year Workload Status of Medical Device Submissions



[8] Data on medical devices workload prior to 2004 is not available.

II. Decisions

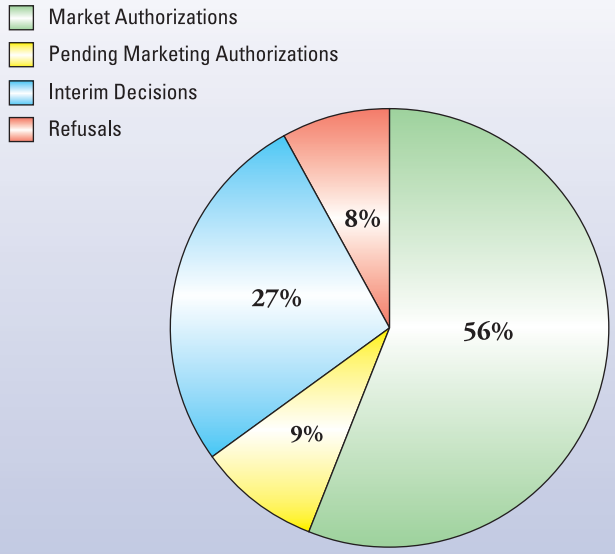
Regulatory Decisions Issued for Submissions for New Drugs and Medical Devices[9]

Once a submission for a new drug or medical device is accepted for scientific review, it can be subject to a number of possible decisions. For example, if additional information is required from the manufacturer to support proper review of the submission, an interim decision may be issued that gives the manufacturer a specified period of time to provide the necessary information.

In 2004, the majority of regulatory decisions that were issued for submissions for new pharmaceutical and biologic drugs as well as medical devices were market authorizations (*see charts 3-A, B and C*).

In 2004, nine percent of pharmaceutical regulatory decisions were pending marketing authorizations. Many of these submissions from earlier years have since been authorized for sale.[10]

Chart 3-A: Types of Decisions Issued for Pharmaceuticals in 2004



[9] See Annex A, page 29 for definitions of regulatory decisions for submissions for new drugs and medical devices.

[10] Note: Pending Market Authorizations are counted once; those that have subsequently been approved for sale are not counted again as Market Authorizations.

Chart 3-B: Types of Decisions Issued for Biologics in 2004

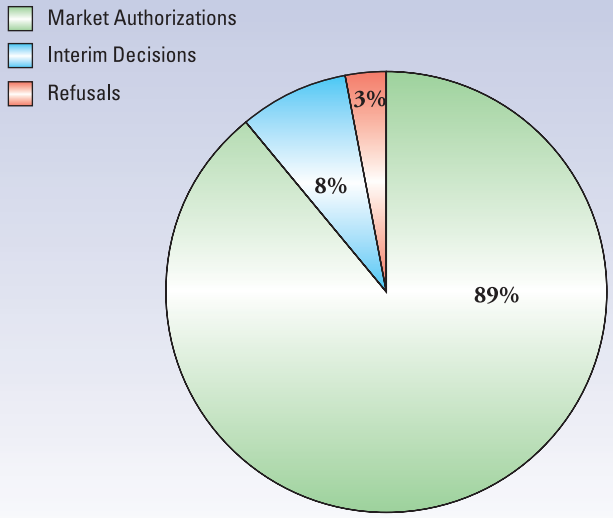
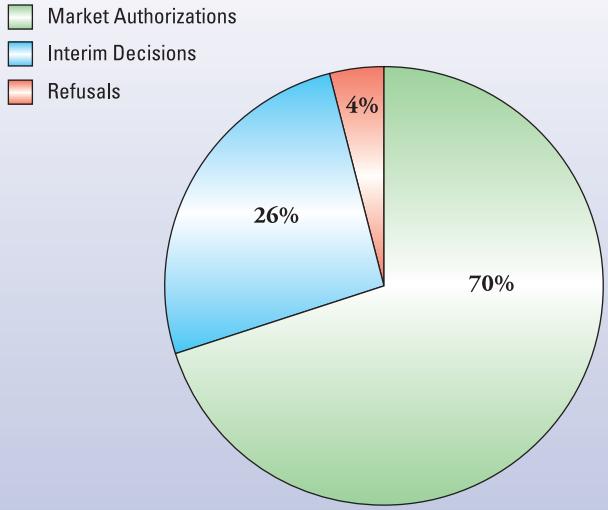


Chart 3-C: Types of Decisions Issued for Medical Devices in 2004



III. Backlog

Progress in Backlog Reduction of Submissions for New Drugs[11]

Backlog refers to submissions for new drugs or medical devices which have exceeded their review time performance target without the issuance of a regulatory decision. The number of submissions in backlog as well as the "age" of the backlog (i.e. the number of days over target) are important and can be an indicator of underlying issues such as submission complexity, gaps in internal expertise or available resources, process inefficiencies, or workload increase.

Backlog is a part of the overall review workload and is constantly changing in composition as submissions fall into backlog and previous backlog is eliminated. Addressing the causes of backlog and ensuring that it remains at low levels will allow for an increasing number of submissions to be reviewed within internationally comparable targets.

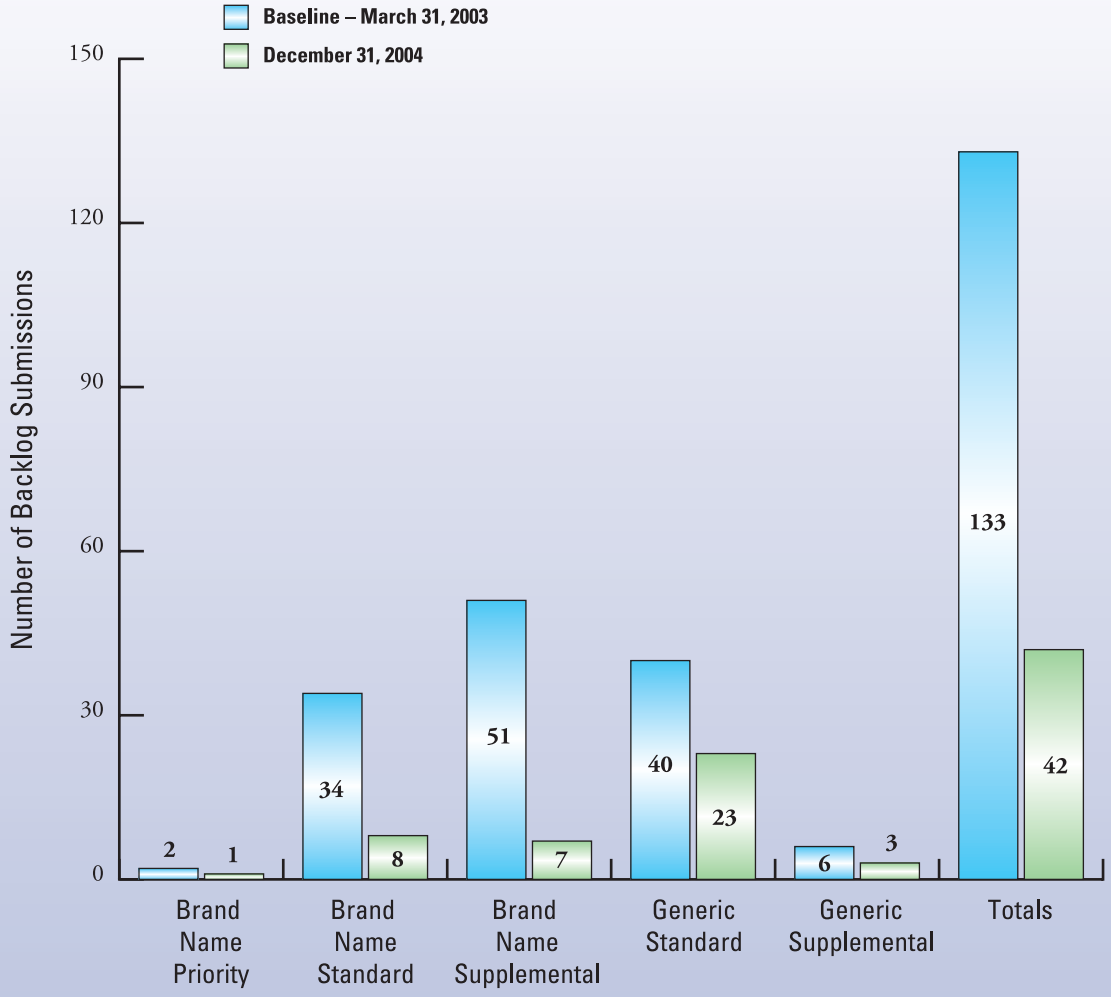
Business improvements introduced through the Therapeutics Access Strategy have contributed to better workload management and reduction of backlog. This includes new project management tools and approaches that improve coordination of tasks at various stages of the review process. In addition, internal and external regulatory review capacity has been enhanced by hiring additional review staff and introducing improvements to the contracting procedure to enable acquisition of the right external scientific expertise at the right time.

[11] Backlog information for medical devices is not included since baseline data is not available. Backlog data for medical devices will be provided in future editions of this report.

Progress has been made in reducing the number of submissions in backlog. As of December 31, 2004, the accumulated backlog had been reduced by 68% for pharmaceuticals compared to the baseline date of March 31, 2003 (*see chart 4-A*).[12]

Notably, the backlog of brand name standard and supplemental submissions had been significantly reduced (by 76% and 86%, respectively). Backlog of generic standards remained relatively high.

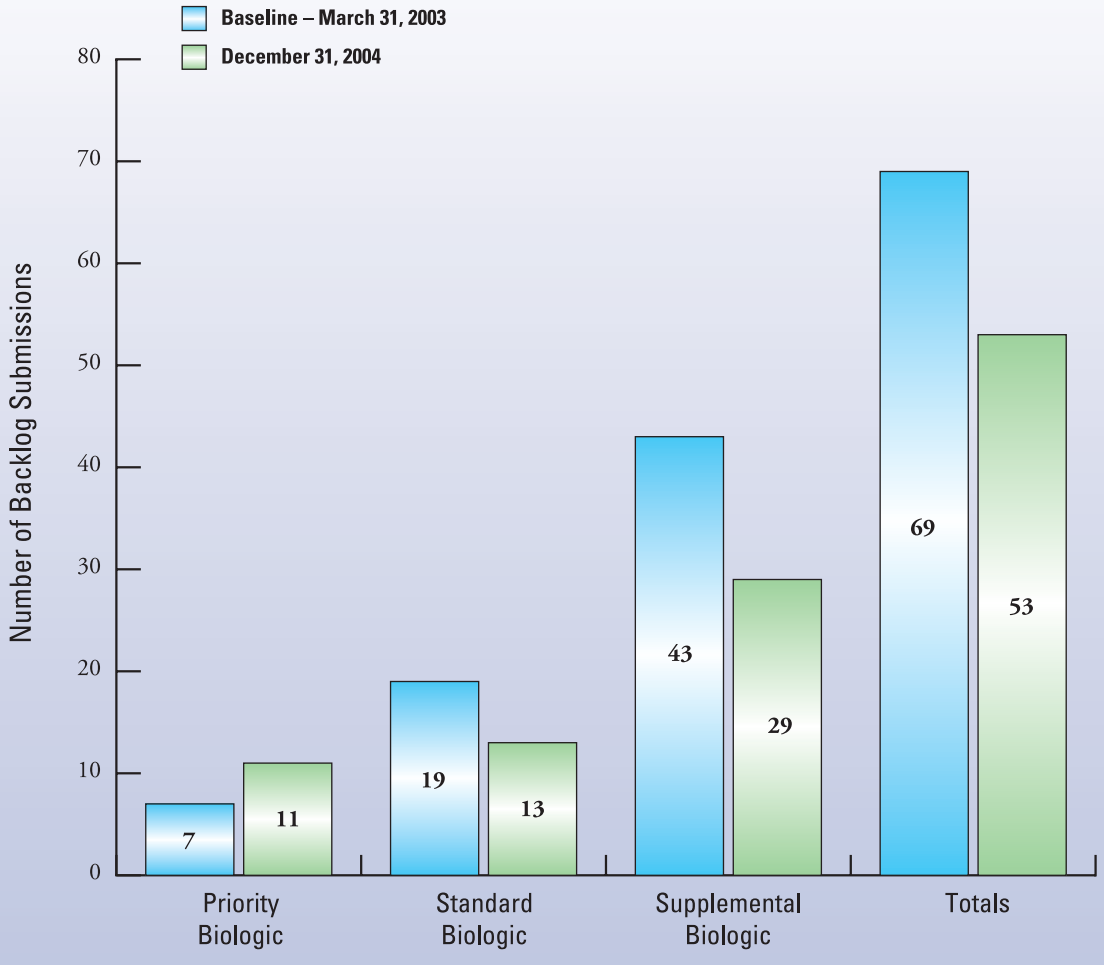
Chart 4-A: Progress in Backlog Reduction of Submissions for New Pharmaceutical Drugs



[12] As of March 31, 2005, 89% of the pharmaceuticals backlog and seven percent of the biologics backlog had been eliminated.

The total backlog of submissions for new biologic drugs was reduced by 23% as of December 31, 2004 compared to the baseline date of March 31, 2003 (*see chart 4-B*). Supplemental biologics accounted for the greatest reduction in backlog, with 33% of the backlog eliminated. However, the number of priority biologics in backlog increased from seven to 11 submissions, (or 57%).

Chart 4-B: Progress in Backlog Reduction of Submissions for New Biologic Drugs



IV. Timeliness

Performance for Review of Submissions for New Drugs and Medical Devices

Performance targets differ by the type of submission. Different classes of therapeutic products have different target times for completion of reviews. For example, target review times are significantly shorter for all classes of medical devices than for other therapeutic products. HPFB's goal is to meet 90% of review performance targets for new drugs by 2006 for pharmaceuticals and 2007 for biologics.

Review Performance Targets for First Decision Concerning Market Authorization[13]

Submission for New Drug (Pharmaceutical and Biologic)	**Target Times (Calendar days)***
Brand Name Priority/Priority Biologic	180 or 120 or 200**
Brand Name Standard/Standard Biologic	180 or 300
Brand Name Supplemental/Supplemental Biologic	180 or 300
Generic Standard	180
Generic Supplemental	180 or 300

Medical Device Application	**Target Times (Calendar days)**
Class II	15
Class III	75
Class IV	90
Class II, III and IV Amendment Applications are the same as above	

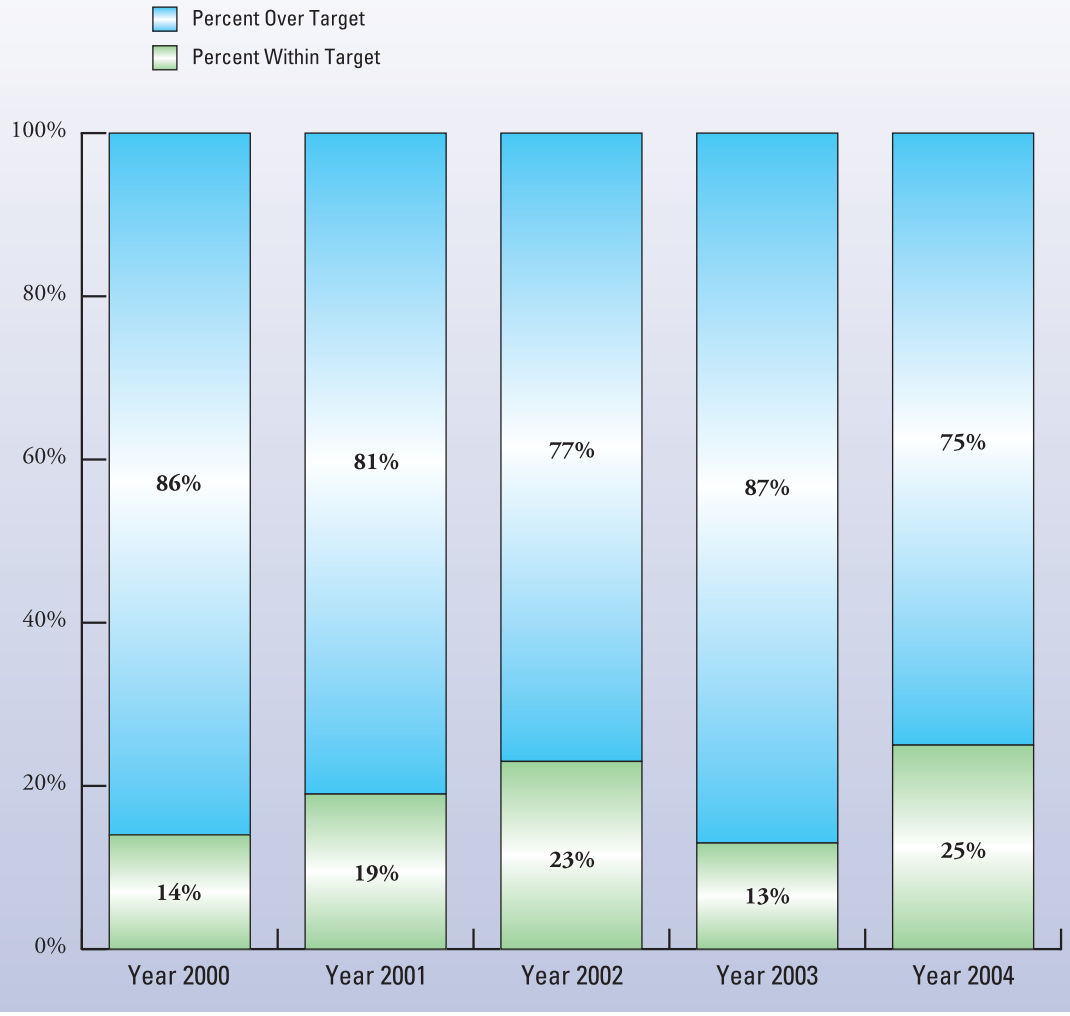
*Performance targets do not include processing or screening of submissions for new drugs.
**Target times vary depending on the submission class.

[13] For further information on performance targets, refer to *The Guidance for Industry on the Management of Drug Submissions* and *The Management of Applications for Medical Device Licenses and Investigational Testing Authorizations* available at http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/mgmt-gest/index_e.html and http://www.hc-sc.gc.ca/dhp-mps/md-im/applic-demande/pol/mdlapp_demhim_pol_e.html respectively.

Charts 5-A, B and C provide performance information on all review decisions for submissions for new drugs and medical devices, including authorizations, pending authorizations, refusals and interim decisions.

In 2004, the proportion of regulatory decisions made within time targets for new pharmaceutical drugs almost doubled to 25% compared with 13% in 2003 (*see chart 5-A*).[14] Of the 359 decisions issued, 90 were within target in 2004 compared with 39 within target for the 304 decisions issued in 2003. This is a significant achievement given that a large proportion of submissions processed in 2004 were in backlog.

Chart 5-A: Performance for Submissions for New Pharmaceutical Drugs

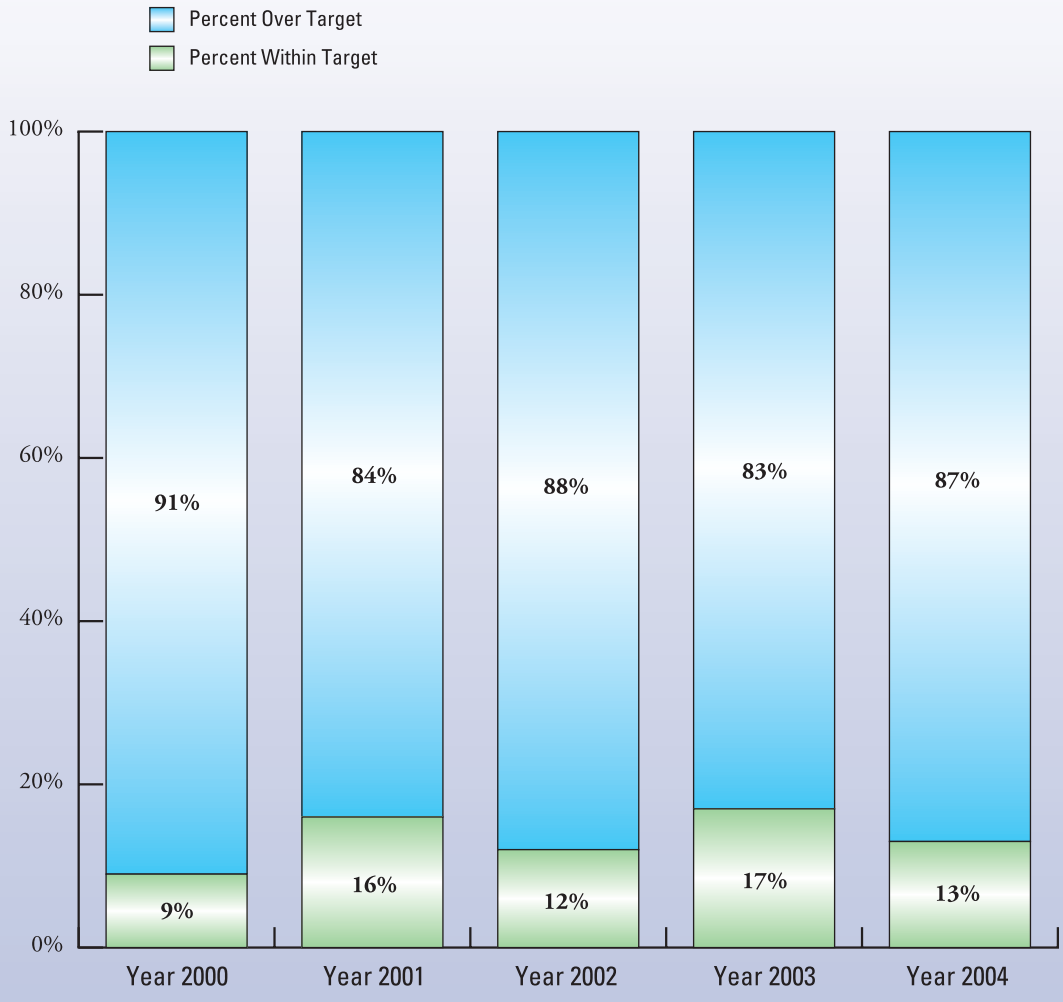


[14] Cancellations are excluded from charts 5-A, B and C.

Compared with all five years, 2004 had the highest number of review decisions issued for biologics (totalling 78); 32% more compared with the second highest number (59 decisions issued in 2002 and 2003).

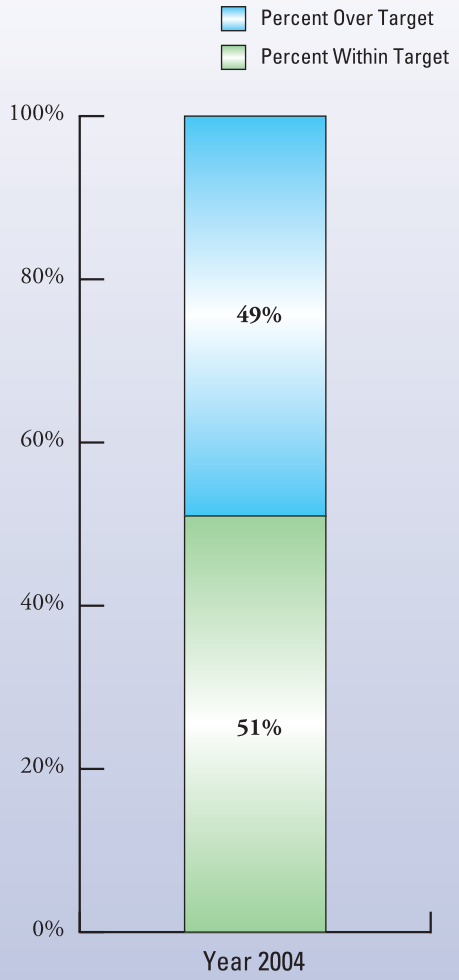
In 2004, 13% of biologic review decisions were made within performance targets compared with 17% in 2003 (see chart 5-B). The drop in performance may have been influenced by the progress made in reducing backlog submissions, resulting in fewer decisions made on time, but more decisions made overall.

Chart 5-B: Performance for Submissions for New Biologic Drugs



In 2004, 51% of review decisions for medical device submissions were made within target (*see chart 5-C*).[15] Work on new initiatives is continuing to help better manage the workload so that an increasing number of decisions will be made within performance targets.

Chart 5-C: Performance for Submissions for Medical Devices



[15] Data for medical devices covers the third and fourth quarter (last six months) and not the full year of 2004. Validated data on medical devices review performance prior to 2004 is not available.

Market Authorization Times

This section provides data about all new drug products and medical devices authorized for sale in Canada. In measuring Canada's time to market authorization, HPFB includes the time from receipt of a submission to authorization, including the company time required to respond to any questions or requests for additional information, as well as the time taken to improve deficient submissions. In many cases, more than one review cycle is required before a new therapeutic product is authorized for market access.[16] Market authorization times are different from review performance target times since the time taken for scientific review is one component of the overall process that is considered in determining time to authorization.

With fewer submissions in backlog and a greater number of submissions meeting performance targets, average and median authorization times can be expected to decrease in the year to come.

Table 1-A: Market Authorization Times for Pharmaceuticals from 2002–2004

	Brand Name Priority			Brand Name Standard			Brand Name Supplemental		
Year	Number Approved	Average Days	Median Days	Number Approved	Average Days	Median Days	Number Approved	Average Days	Median Days
2002	9	322	286	24	741	671	68	429	402
2003	6	366	382	29	707	688	110	496	433
2004	5	217	217	36	876	736	101	404	374

	Generic Standard			Generic Supplemental		
Year	Number Approved	Average Days	Median Days	Number Approved	Average Days	Median Days
2002	57	517	489	4	490	379
2003	57	551	512	10	569	410
2004	83	436	369	10	379	328

[16] Market authorization times are not directly comparable between countries since they reflect different processes and procedures and each country varies in its approach. These differences include legislation, operational procedures, performance targets and approaches that are used to track, count and report on performance.

In 2004, Brand Name Standard submissions had a 24% increase in average market authorization times since 2003. This may be a result of the clearance of many backlogged submissions in 2003 and 2004. Since 2002, all other average market authorization times for pharmaceutical new drug submissions improved, with the greatest decline observed for Brand Name Priority drugs, decreasing by 41% since 2003.

Table 1-B: Market Authorization Times for Biologics from 2002–2004

	Priority Biologic			Standard Biologic			Supplemental Biologic		
Year	Number Approved	Average Days	Median Days	Number Approved	Average Days	Median Days	Number Approved	Average Days	Median Days
2002	5	751	688	7	951	957	39	405	399
2003	5	894	958	7	928	876	33	527	404
2004	6	874	915	8	1,033	1,019	54	478	493

Average market authorization times for Standard Biologics increased by 11% in 2004. Although the authorization time in 2004 was higher than that of 2002, the area of greatest improvement was Supplemental Biologics, with a reduction in average days to authorization by nine percent compared to 2003. Priority Biologics had a 16% increase in average authorization times in 2004 compared to 2002 with a slight improvement between 2003 and 2004 by two percent.

Table 1-C: Market Authorization Times for Medical Devices from 2002–2004

Year	Class II			Class III			Class IV		
	Number Approved	Average Days	Median Days	Number Approved	Average Days	Median Days	Number Approved	Average Days	Median Days
2002	1,725	12	8	455	101	75	106	161	136
2003	1,478	21	13	554	104	91	111	178	132
2004	2,745	29	25	613	93	84	106	148	136

Year	Amendment Applications (Class II, III and IV)		
	Number Approved	Average Days	Median Days
2002	1,082	8 (Class II) 60 (Class III) 115 (Class IV)	4 (Class II) 33 (Class III) 45 (Class IV)
2003	1,099	7 (Class II) 79 (Class III) 110 (Class IV)	4 (Class II) 56 (Class III) 103 (Class IV)
2004	1,044	18 (Class II) 67 (Class III) 69 (Class IV)	19 (Class II) 68 (Class III) 85 (Class IV)

Class II authorization times increased by 38% in 2004 compared with 2003. This may be due to the increase in workload of this class of devices by 107% (almost 1600 more submissions compared to 2003).

Market authorization times for medical devices improved in 2004 for Class III and IV devices when compared with 2002 and 2003. Since 2003, time to authorization decreased, on average, by 11% for Class III and 17% for Class IV.

V. Access to New Drugs

The time it takes for the public to have access to new therapeutic products in Canada is determined by many factors, including:

(1) Global marketing strategies of individual manufacturers, which influence where and when they file their regulatory submissions; and whether and when they will market launch their product in Canada following a market authorization decision.

(2) The length of time HPFB takes to review a submission and authorize sale of the product.[17]

(3) Decisions taken by other bodies including pricing decisions by the Patented Medicine Prices Review Board (PMPRB).[18]

(4) Formulary listing recommendations by the Common Drug Review (CDR).

(5) Formulary listing decisions taken by federal, provincial and territorial drug plans and privately financed drug plans.[19]

Table 2 displays key decisions that influence access to new drugs in Canada. The drugs listed in table 2 are those which have been subject to a formulary listing recommendation by the CDR between January 2004 and April 2005. The CDR does not review generic or over-the-counter drug products, medicines for use in hospitals, blood products, or vaccines. Hence, this table does not include every drug which received a market authorization since the fall of 2003.[20]

[17] Note that HPFB has mechanisms in place such as the Special Access Program, that enable interim access to new drugs or medical devices. For more information, refer to: http://www.hc-sc.gc.ca/dhp-mps/acces/index_e.html.

[18] More details on the role of the PMPRB and CDR are provided in Annex B.

[19] Federal, provincial and territorial governments manage drug formularies and assess the drugs for which reimbursement from government plans is available. In some cases, drugs have a restricted status limiting coverage to particular types of patients or situations.

[20] CDR commenced during the fall of 2003.

Table 2: Access to New Drugs in Canada

Submissions for New Drugs	Health Canada a. Filing Date b. Approval Date	Market Notification Date	PMPRB Price Decision a. Date of first sale b. Under PMPRB jurisdiction c. Status	Common Drug Review a. Filing b. Recommendation and Decision Date	United States Food and Drug Administration (FDA) a. Filing Date b. Approval Date
1. Adderall XR – for treatment of Attention Deficit Hyperactivity Disorder (ADHD).	a. Dec 29 2000 b. Jan 23 2004	Jan 30 2004	a. Jul 2002 b. Apr 13 2004 c. Under review	a. Apr 13 2004 b. *Not to be listed* on Nov 24 2004[21]	a. Oct 3 2000 b. Oct 11 2001
2. Avodart – for treatment of symptomatic Benign Prostatic Hyperplasia (BPH) in men with enlarged prostates.	a. Dec 3 2001 b. Jul 22 2003	Nov 14 2003	a. Jan 7 2004 b. Jan 7 2004 c. Within Guidelines, Nov 2004	a. Aug 24 2004 b. For listing on Jan 20 2005	a. Dec 21 2000 b. Nov 20 2001
3. AXERT – for the acute treatment of migraine headache in adults.	a. Sep 17 2001 b. Sep 29 2003	Dec 8 2003	a. Jan 9 2004 b. Jan 9 2004 c. Within Guidelines, Sep 2004	a. Dec 24 2003 b. For listing on May 27 2004	a. Dec 17 1999 b. May 7 2001
4. Ciprodex – for treatment of ear infections: acute otitis media with otorrhea through tympanostomy tubes in pediatric patients aged six months and older and for acute otitis externa in pediatric and adult patients aged one year and older.	a. Nov 22 2002 b. May 10 2004	May 13 2004	Not under PMPRB jurisdiction	a. Jun 11 2004 b. *Not to be listed* on Jan 26 2005	a. Sep 23 2002 b. Jul 18 2003
5. Combigan Ophthalmic Solution – for treatment of glaucoma/ocular hypertension.	a. Jul 18 2002 b. Dec 9 2003	Dec 11 2003	a. Dec 9 2003 b. Dec 9 2003 c. Within Guidelines, Sep 2004	a. Dec 15 2003 b. For listing on May 27 2004	*Information not available on FDA website*
6. Evra – to prevent pregnancy.	a. Apr 2 2001 b. Aug 20 2002	Oct 24 2002	a. Oct 2002 b. Oct 2002 c. Voluntary Compliance Undertaking, Feb 2005	a. Dec 19 2003 b. *Not to be listed* on Jun 23 2004	a. Dec 21 2000 b. Nov 20 2001

[21] Adderall XR was resubmitted to CDR for review and subsequently withdrawn as it was suspended from the Canadian market on Feb 9, 2005. Adderall XR returned to the Canadian market in August 2005 following recommendations made by an independent New Drug Committee appointed by Health Canada. For more information, refer to http://www.hc-sc.gc.ca/ahc-asc/media/nr-cp/2005/2005_92_e.html

Table 2: **Access to New Drugs in Canada** *(cont'd)*

Submissions for New Drugs	Health Canada a. Filing Date b. Approval Date	Market Notification Date	PMPRB Price Decision a. Date of first sale b. Under PMPRB jurisdiction c. Status	Common Drug Review a. Filing b. Recommendation and Decision Date	United States Food and Drug Administration (FDA) a. Filing Date b. Approval Date
7. Fabrazyme – for use as a long-term enzyme replacement therapy in patients with Fabry disease.	a. Aug 7 2000 b. Jan 23 2004	Apr 8 2004 – for DIN 02248966 Sep 17 2004 – for DIN 02248965	Not under PMPRB jurisdiction	a. Feb 24 2004 b. *Not to be listed* on Nov 24 2004[22]	a. Jun 2000 b. Apr 24 2003
8. Forteo – for treatment of osteoporosis.	a. Nov 16 2001 b. Jun 3 2004	Jul 15 2004	a. Jul 15 2004 b. Aug 17 2004 c. Under review	a. Jun 28 2004 b. *Not to be listed* on Dec 22 2004	a. Nov 29 2000 b. Nov 26 2002
9. Gynazole.1 – for local treatment of vulvovaginal infections caused by *Candida albicans.*	a. Jul 30 2001 b. Dec 23 2003	Apr 20 2004	a. Apr 27 2004 b. Apr 27 2004 c. Within Guidelines, Nov 2004	a. Jun 30 2004 b. *Not to be listed* on Jan 26 2005	a. *Information not available on FDA website* b. Feb 7 1997
10. Humira – for adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs.	a. May 15 2002 b. Sep 24 2004	Sep 24 2004	a. Sep 29 2004 b. Sep 29 2004 c. Within Guidelines, Mar 2005	a. Sep 24 2004 b. For listing on Feb 11 2005	a. *Information not available on FDA website* b. Dec 31 2002
11. Iressa – for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of prior platinum-based and docetaxel chemotherapy.	a. Nov 25 2002 b. Dec 17 2003	Dec 17 2003	a. Dec 17 2003 b. Dec 17 2003 c. Within Guidelines, Oct 2004	a. Dec 22 2003 b. *Not to be listed* on Jun 23 2004	a. Aug 2 2002 b. May 5 2003

[22] Fabrazyme was resubmitted to CDR for review and recommended not to be listed on May 18 2005.

Table 2: **Access to New Drugs in Canada** *(cont'd)*

Submissions for New Drugs	Health Canada a. Filing Date b. Approval Date	Market Notification Date	PMPRB Price Decision a. Date of first sale b. Under PMPRB jurisdiction c. Status	Common Drug Review a. Filing b. Recommendation and Decision Date	United States Food and Drug Administration (FDA) a. Filing Date b. Approval Date
12. Neulasta – reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes).	a. Jun 28 2001 b. Mar 12 2004	Mar 12 2004	a. Apr 12 2004 b. Apr 12 2004 c. Under review	a. Mar 29 2004 b. To be listed on Oct 27 2004	a. *Information not available on FDA website* b. Jan 31 2002
13. Pegasys RBV – for treatment of adults with chronic hepatitis C who have compensated liver disease and who have not been previously treated with interferon alfa 2.	a. Aug 20 2002 b. May 10 2004	May 26 2004	a. May 26 2004 b. May 26 2004 c. Under review	a. May 14 2004 b. To be listed on Oct 14 2004	a. Jun 3 2002 b. Dec 3 2002
14. Relpax – for the acute treatment of migraine with or without aura in adults.	a. Mar 21 2003 b. Aug 5 2004	Oct 13 2004	a. Nov 1 2004 b. Nov 1 2004 c. Within Guidelines, Mar 2005	a. Sep 21 2004 b. *Not to be listed* on Mar 23 2005	a. Oct 27 1998 b. Dec 26 2002
15. Remodulin – for the treatment of pulmonary arterial hypertension (PAH).	a. Dec 17 2001 b. Oct 4 2002	Apr 30 2004	a. Oct 7 2004 b. Oct 7 2004 c. Within Guidelines, Mar 2005	a. Jul 14 2004 b. *Not to be listed* on Nov 17 2004	a. Oct 16 2000 *withdrawn Jul 5 2001* Re-filed: Aug 9 2001 b. May 21 2002
16. Replagal – for long-term enzyme replacement therapy in patients with Fabry Disease.	a. Sep 10 2000 b. Feb 6 2004	Mar 18 2004	Not under PMPRB jurisdiction	a. Feb 19 2004 b. *Not to be listed* on Nov 24 2004	a. Jun 16 2000 b. *Information not available on FDA website*
17. Reyataz – for the treatment of HIV-1 infection in combination with other anti-retroviral agents.	a. Mar 21 2003 b. Dec 5 2003	Jan 9 2004	a. Jan 2004 b. Nov 2 2004 c. Under review	a. Dec 16 2003 b. To be listed on May 27 2004	a. Dec 20 2002 b. Jun 20 2003

Table 2: **Access to New Drugs in Canada** *(cont'd)*

Submissions for New Drugs	Health Canada a. Filing Date b. Approval Date	Market Notification Date	PMPRB Price Decision a. Date of first sale b. Under PMPRB jurisdiction c. Status	Common Drug Review a. Filing b. Recommendation and Decision Date	United States Food and Drug Administration (FDA) a. Filing Date b. Approval Date
18. Sensipar – for the treatment of secondary hyperparathyroidism in patients with Chronic Kidney Disease.	a. Nov 14 2003 b. Aug 9 2004	Sep 16 2004	Not under PMPRB jurisdiction	a. Aug 20 2004 b. *Not to be listed* on Mar 23 2005	a. Sep 5 2003 b. Mar 8 2004
19. Teveten Plus – for treatment of mild to moderate essential hypertension in patients for whom combination therapy is appropriate.	a. Feb 22 2001 b. Jun 8 2004	Jul 6 2004	a. Jul 6 2004 b. Jul 6 2004 c. Within Guidelines, Mar 2005	a. Jul 8 2004 b. To be listed on Dec 15 2004	a. Aug 30 2000 b. Nov 1 2001
20. Viread – for treatment of HIV-1 infection in combination with other anti-retroviral agents in adults who have experienced virologic failure on other regimens.	a. Dec 28 2001 b. Mar 18 2003	Mar 15 2004	a. Mar 15 2004 b. Mar 15 2004 c. Advance Ruling Certificate, Jun 3 2004	a. Feb 23 2004 b. *Not to be listed* on Aug 25 2004	a. Apr 30 2001 b. Oct 26 2001
21. VFEND – for treatment of invasive aspergillosis.	a. Sep 3 2003 b. Aug 20 2004	Nov 12 2004	a. Nov 15 2004 b. Nov 15 2004 c. Within Guidelines, Mar 2005	a. Oct 25 2004 b. To be listed on Apr 14 2005	a. Nov 17 2000 b. May 24 2002
22. Zavesca – for treatment of adults with mild to moderate Type 1 Gaucher disease for whom enzyme replacement therapy is not a therapeutic option.	a. Aug 27 2003 b. Mar 31 2004	May 26 2004	a. May 26 2004 b. May 26 2004 c. Within Guidelines, Nov 2004	a. May 13 2004 b. *Not to be listed* on Nov 24 2004	a. Apr 20 2001 b. Jul 31 2003

Annex A: Definitions

These plain language definitions are intended for general understanding and are not necessarily the formal definitions used by Health Canada or those that appear in the legislation or regulations.

1. Therapeutic Product Types

The following therapeutic product types are described in this report.

(a) Pharmaceuticals: drugs that are mostly synthetic products that are made from chemicals. Pharmaceuticals include prescription and non-prescription drugs such as antibiotics, disinfectants, as well as low risk products such as sunscreens, antiperspirants and toothpaste.

(b) Biologics: drugs that are made from biological starting material, including those produced using recombinant DNA procedures. They include vaccines, blood and blood products and many hormonal products such as insulin. Radiopharmaceuticals (drugs that contain radioactive components) are included as part of this product group in this report as they are regulated by the same program within the HPFB.

(c) Medical Devices: any article or instrument used in the diagnosis, treatment, mitigation, or prevention of a disease, disorder, or abnormal physical state and in restoring, correcting, or modifying organic functions in humans or animals. Devices range from band-aids to pacemakers and also include those used in the prevention, diagnosis and care of pregnancy.

2. Submissions for New Drugs and Medical Devices

The focus of this report is on submissions for new drugs and medical devices. Definitions are provided below.

I. Submission for New Drugs: *include the following submission types for pharmaceuticals and biologics, where 'brand name' and 'generic' refers to pharmaceuticals.*

(a) Priority (Brand Name or Biologic): submissions for products intended for the treatment, prevention, or diagnosis of serious, life-threatening, or severely debilitating illnesses or conditions where: no product is presently marketed in Canada or; the new product represents a significant increase in efficacy and/or significant decrease in risk such that the overall benefit/risk profile is improved over existing therapies. Submissions granted priority review status are subject to the same quality, safety and efficacy requirements as non-priority submissions – with shorter performance target times. In this report, priority includes the Notice of Compliance with Conditions submission type (refer to Regulatory Decision Types below for more information).

(b) Standard (Brand Name or Biologic): a submission that contains scientific information about the product's safety, efficacy and quality and is typically 100 to 800 binders of data. It includes: the results of both the pre-clinical and clinical studies; details regarding the production of the drug; its packaging and labelling; information regarding therapeutic claims; conditions for use; and side effects.

(c) Supplemental (Brand Name, Generic, or Biologic): submissions to support proposed changes to already authorized products. Such changes might include: changes to the dosage form or strength of the drug product; labelling; recommended route of administration; and expanded indications (claims or conditions of use) for the drug product.

(d) Generic Standard: submissions that demonstrate that the proposed generic product is as safe and efficacious and manufactured to the same quality standards as the brand name product. Typically between 10 and 20 binders of data, the submission includes scientific information that shows how the generic product performs compared with the brand name product, as well as details regarding production, packaging and labelling.

II. Medical Device Submissions: *includes the application types listed below.*

(a) Medical Device Applications: medical devices are categorized into four classes based on the classification rules of the Medical Devices Regulations. Class I devices present the lowest potential risk (e.g. thermometers) and do not require a medical device licence for their sale in Canada. Class II, III and IV devices range from low, moderate, to high risk, respectively and manufacturers must obtain a medical device licence before their products can be legally sold in Canada. As the class of the device increases, more data is required from the manufacturer in support of safety and effectiveness of the device.

(b) Medical Device Amendment Applications: changes to a licensed medical device (Class II, III, or IV) – such as a change in design, indications, or additions/deletions of identifiers.

3. Regulatory Decision Types

For this report, four decision types are provided, including: market authorizations; pending market authorizations; interim decisions; and refusals. Further detail on each decision type is outlined below.

I. Market Authorizations: *apply to submissions for new drugs and medical devices that have been authorized for sale in Canada.*

(a) Notice of Compliance: if, at the completion of a review of a submission for a new drug, HPFB concludes that the benefits outweigh the risks and that the risks can be mitigated and/or managed, the product is issued a Notice of Compliance (NOC). This allows the manufacturer to sell the product in Canada.

(b) Notice of Compliance with Conditions (NOC/c): may be granted to provide earlier market access to potentially life-saving drugs. Eligibility is restricted to drugs intended for the treatment, prevention, or diagnosis of serious, life-threatening, or severely debilitating illnesses or conditions where promising clinical evidence indicates that the product provides an effective treatment where: no alternative therapy is available on the Canadian market; or the new product represents a significant improvement in the benefit/risk profile over existing products. An NOC/c provides the manufacturer authorization to market a drug with the condition that it undertakes additional studies to confirm the clinical benefit. Conditions associated with approval allow HPFB to monitor the safety and effectiveness of the drug through enhanced post-market surveillance.

(c) Medical Device Licence: upon completion of a medical device application review, HPFB concludes that the evidence exists to support the safety and effectiveness of the device as required by the regulations, a Medical Device Licence is issued, allowing the manufacturer to sell the device in Canada.

(d) Medical Device Licence with Conditions: HPFB may issue a Medical Device Licence with Conditions when there is reasonable assurance that the device is safe and effective, but where supplemental information would further support this conclusion. Such information must be submitted within a prescribed timeframe.

II. Pending Market Authorizations: *apply to those submissions for new drugs that have been provided with an 'issuable' NOC but are not yet authorized for sale due to outstanding regulatory issues that require resolution. Examples of situations where a "pending market authorization" would be issued include submissions where an NOC cannot be issued due to the Patented Medicine (Notice of Compliance) Regulations or submissions where changes are required to existing Food and Drug Regulations to change the drug status from prescription to non-prescription.*

(a) Issuable NOC (Patent): HPFB may issue an NOC that is on hold due to Patent Regulations.

(b) Issuable NOC (Rx to OTC): HPFB may issue an NOC that is on hold due to a change in status of the drug from prescription to over-the-counter.

III. Interim Decisions: *apply to submissions for new drugs and medical devices that contain deficiencies and are deficient vis a vis the regulatory requirements for market authorization. These regulatory decisions (described below) have provided the manufacturer with a notice of the information required and a time period in which to respond with the missing documentation.*

(a) Notice of Deficiency: If a major deficiency is detected that prevents completion of the scientific review of a submission for a new drug, HPFB can issue a Notice of Deficiency (NOD). The manufacturer is provided with a specified period in which to respond with the required information.

(b) Notice of Non-Compliance: If, upon completion of the new drug review, the submission is found to be deficient vis a vis the requirements of the *Food and Drugs Act and Regulations*, a Notice of Non-Compliance (NON) may be issued. This notice outlines all the outstanding issues and requests for information that HPFB has about the submission. The manufacturer has a specified period in which to respond with the required information.

(c) Additional Information Letter: If, during the course of the scientific review of a medical device application, there remains insufficient information to determine whether the device meets the safety and effectiveness requirements, an Additional Information Letter may be issued, providing the manufacturer with a specified period in which to respond with the required information.

IV. Refusals: *are final decisions where the manufacturer has been provided with the opportunity to improve the submission or application but has been unable to satisfy the requirements of the Food and Drugs Act and Regulations. In the case of a refusal, a manufacturer may re-file a new application at a future time, without prejudice. Refusal decision types are outlined below.*

(a) Notice of Deficiency Withdrawal Letter: May be issued if the manufacturer fails to submit the requested information in response to a NOD within the required time period, or the response contains unsolicited information, is incomplete or deficient.

(b) Notice of Non-Compliance Withdrawal Letter: May be issued if the manufacturer fails to submit the requested information in response to a NON within the required time period, or the response contains unsolicited information, is incomplete or deficient.

(c) Refusal Letter: May be issued if the manufacturer fails to submit the requested information in response to an Additional Information Letter within the required time period, or the response contains unsolicited information, is incomplete or deficient.

Annex B: The Role of the Patented Medicine Prices Review Board and the Common Drug Review

Price Review – The Patented Medicine Prices Review Board

The Patented Medicine Prices Review Board (PMPRB) is an independent quasi-judicial administrative agency, responsible for regulating the prices that patentees charge, the "factory-gate" price for prescription and non-prescription patented drugs sold in Canada to wholesalers, hospitals, or pharmacies for human and veterinary use, to ensure that they are not excessive. The PMPRB regulates the price of each patented drug product, including each strength of each dosage form of each patented medicine sold in Canada.

Under the *Patented Medicines Regulations*, patentees are required to file price and sales information twice a year for each strength of each dosage form of each patented medicine sold in Canada for price regulation purposes. Patentees are also required to file research and development expenditures once a year for reporting purposes. Manufacturers must inform the PMPRB of their intention to sell a new patented medicine but are not required to obtain approval of the price before they do so.

Common Drug Review – The Canadian Coordinating Office for Health Technology Assessment

The Canadian Coordinating Office for Health Technology Assessment (CCOHTA) is Canada's health technology agency whose goal it is to increase access to and use of evidence as a basis for informed decisions about technology use in Canada's publically funded health care system.

Since September 2002, CCOHTA's mandate was expanded to include the Common Drug Review (CDR), a single process to assess new drugs for potential coverage by participating federal, provincial and territorial drug benefit plans. CCOHTA develops evidence-based clinical and pharmacoeconomic reviews which are used by the Canadian Expert Drug Advisory Committee, an independent advisory body of professionals in drug therapy and evaluation, as the basis for its formulary listing recommendations to the participating drug plans. Federal, provincial and territorial governments continue to make final formulary listing decisions, taking into account recommendations provided by CDR.