



# Common Drug Review in Canada

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2007-6-8

# Drug Product Life Cycle

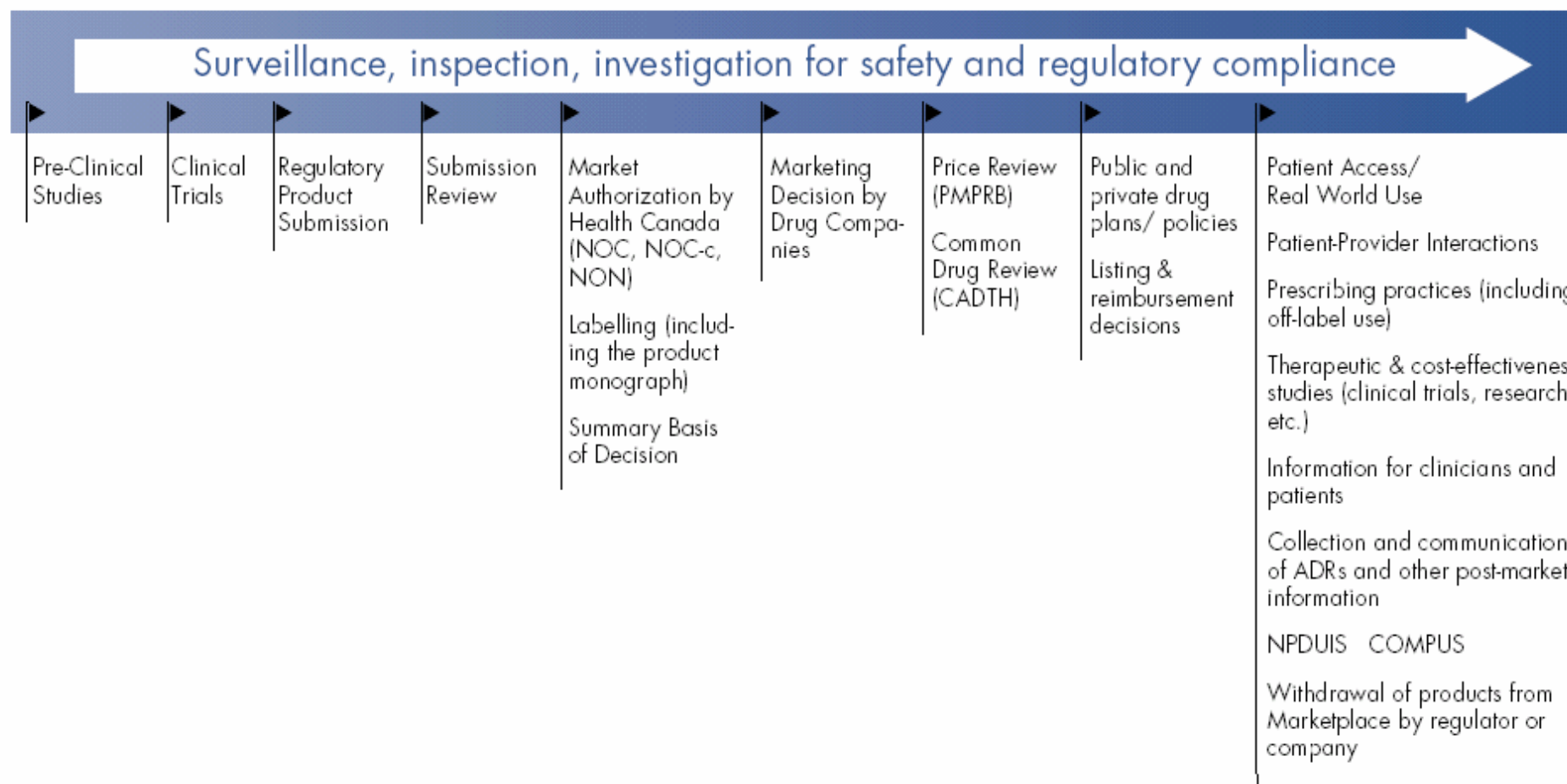
Pre-Market

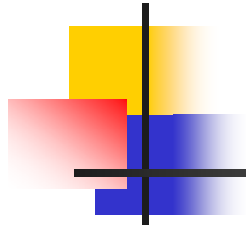
Post-Market

Global Product Development

... safety, quality, efficacy, therapeutic effectiveness, cost-effectiveness ...

Access by providers and patients and parties through the health care system





- **CADTH**: Canadian Agency for Drugs and Technologies in Health (formerly Canadian Coordinating Office for Health Technology Assessment (**CCOHTA**))
- **CDR**: Common Drug Review
- **PMPRB**: Patented Medicine Prices Review Board
- **COMPUS**: Canadian Optimal Medication Prescribing and Utilization Service
- **NPDUIS**: National Prescription Drug Utilization Information System



# CCOHTA

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- In August of 1990, the Canadian Coordinating Office for Health Technology Assessment (CCOHTA) opened its doors on a three-year trial basis.
- Its mandate was to provide Canadian health care policy managers with evidence-based information on emerging and existing medical devices.
- In **1993**, the Conference of the Deputy Ministers of Health declared CCOHTA a permanent entity.
- Pharmaceutical reviews were added to the organization's mandate



# CETAP

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- In **1997**, CCOHTA introduced its horizon scanning service, the Canadian Emerging Technology Assessment Program (CETAP), and released the first Emerging Technology Bulletin.
- Today called Issues in Emerging Health Technologies, these bulletins provide information about drug and non-drug technologies not yet widely used in Canada.



# CDR

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- In early 2002, the Conference of Deputy Ministers asked CCOHTA to undertake the **Common Drug Review (CDR)**, a single process for reviewing new drugs and providing listing recommendations to participating publicly-funded federal, provincial and territorial drug benefit plans in Canada.
- The review process is intended to provide consistent and rigorous reviews of new prescription drugs so public drug benefit coverage can be directed to the most cost-effective and therapeutically beneficial drugs.
- CDR became a permanent entity at CCOHTA in **2003**

The logo graphic consists of a vertical black line intersected by a horizontal black line. To the left of the vertical line, there are three overlapping squares: a yellow one at the top, a red one in the middle, and a blue one at the bottom. The word "COMPUS" is written in a large, blue, sans-serif font to the right of the vertical line.

# COMPUS

- In **March 2004**, CCOHTA continued to expand with the creation of the Canadian Optimal Medication Prescribing and Utilization Service (COMPUS).
- It identifies and promotes optimal drug prescribing and use among health care providers and consumers.
- CCOHTA received an initial five-year funding agreement from Health Canada to deliver the COMPUS program.



# HTIS

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- In **2005**, CCOHTA's HTA program introduced the Health Technology Inquiry Service (HTIS).
- The service was established to provide Canadian health care decision makers with access to available health technology information in a quick and efficient manner.
- HTIS responds to inquiries about drugs, devices, and procedures.
- Depending on the urgency and/or complexity of the request, information is provided from 24 hours to 30 business days.



# Rebrand of CCOHTA

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- Over the years, CCOHTA has **transformed** from an organization whose mandate related strictly **to** evidence-based information on emerging and existing medical devices. With the addition of CDR and COMPUS and further responsibilities spelled out for the organization in HTS 1.0, it was felt the organization needed to **rebrand** to reflect those changes.

The logo graphic consists of a vertical black line intersected by a horizontal black line. To the left of the intersection, there are three overlapping squares: a yellow one at the top, a red one in the middle, and a blue one at the bottom. The text 'CADTH' is positioned to the right of the vertical line, in a blue, sans-serif font.

# CADTH

- On **April 3, 2006**, the Canadian Coordinating Office for Health Technology Assessment was reborn as the **Canadian Agency for Drugs and Technologies in Health** (CADTH), a name that better reflects the breadth of services the organization now provides to Canadian health care decision makers.

# Patented Medicine Prices Review Board

## Its role and responsibilities

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- The PMPRB was created by Parliament in 1987 under the *Patent Act* as an **independent quasi-judicial tribunal**.
- It has no authority over the prices of non-patented drugs, including generic drugs, and
- does not have jurisdiction over pharmacists' professional fees and any markups that may be applied by wholesalers or retailers.



## PMPRB protects consumer interests and contributes to health care by exercising a two-fold mandate

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- Regulatory mandate
  - to ensure that the **prices charged** by manufacturers, i.e. the ex-factory price, for patented medicines sold in Canada (whether prescribed or not) are **not excessive**; and
- Reporting mandate
  - to inform Canadians about the **price trends** of patented medicines and of all drugs, and the **research & development performance** as reported by patent-holding drug manufacturers.



# Price Guidelines

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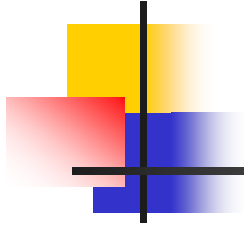
- The prices of other drugs in the same therapeutic class;
- Prices of drugs in other countries; and
- Changes in the Consumer Price Index.



# the Board's Guidelines provide that:

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- the prices of most new patented drugs cannot exceed the price of **the most expensive drug** that treats the same disease;
- the prices of most breakthrough or substantial improvement drugs cannot exceed **the median of the prices** in other industrialized countries which are set out in the *Patented Medicines Regulations* (Regulations), i.e., France, Germany, Italy, Sweden, Switzerland, United Kingdom, United States;



- on a yearly basis, prices cannot increase more than the Consumer Price Index; and
- the price of patented drugs in Canada can **never be the highest** in the world.



# breakthrough or a substantial improvement

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- The PMPRB relies on the advice of the Human Drug Advisory Panel (HDAP), an independent scientific expert group, in reviewing a new drug
  - as a breakthrough or a substantial improvement over what is already on the market.
- The HDAP provides advice on all patented New Active Substances introduced on the market.



## filing price information

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- patentees are required to file price information on each strength of each patented drug on a regular basis with the PMPRB, for **the duration of the patent**.
- The Act authorizes the Board to establish the price guidelines and provides the Board with remedial powers.



# Remedial powers against excessive price

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- If the Board finds that a price is excessive it may **order** the manufacturer to **reduce** the price to a non-excessive level and to **offset** the excess revenues that have been received by way of a payment to the Government.
- In addition, in the event of a policy of excessive pricing, the Board can order the manufacturer offset **double the excess** revenues received.



to improve timely access to  
necessary medications at non-  
excessive prices

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- In order that improvements in therapeutic access not be offset by delays in the review of prices, the PMPRB has embarked on a major initiative to **better align** the timing of its price review process with the Common Drug Review.



CADTH

*Canadian Agency for  
Drugs and Technologies  
in Health*



*Agence canadienne  
des médicaments et des  
technologies de la santé*



# Common Drug Review Submission Guidelines for Manufacturers February 2007

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- The CDR is an initiative undertaken by all Canadian, publicly funded F/P/T Drug Plans, with the exception of Québec
- The goals of the CDR process are to reduce duplication in the performance of reviews, to maximize the use of limited resources and expertise and to provide consistent and rigorous Drug reviews.
- The CDR Drug reviews reflect an evidence-based approach.
- The CDR is managed and overseen by the CDR Directorate of the CADTH in Ottawa.



## CDR reviews consist of

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- an evidence-based review of the available clinical evidence, and
- a critique of Manufacturer-submitted pharmacoeconomic studies and Budget Impact Analyses (BIAs).



# The Canadian Expert Drug Advisory Committee (CEDAC)

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- an appointed, national independent body of physicians, pharmacists and other professionals, uses the CDR reviews to **make common listing recommendations** to participating F/P/T Drug Plans.



# CEDAC Membership

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composed of thirteen (13) Members. Two of them should be **lay persons**. Remaining members must hold qualifications as a physician, a pharmacist, an economist or other professional designation with expertise in one or more areas such as:

- a) general practice
- b) internal medicine
- c) geriatrics
- d) hospital or community pharmacy
- e) clinical pharmacology
- f) pharmacoeconomics
- g) clinical epidemiology
- h) health services research



## listing decisions

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- Each of the participating F/P/T Drug Plans makes its own listing decisions based on CEDAC recommendations plus other factors, including the plan's mandate, priorities and resources.
- Each plan is responsible for **independently advising** the Manufacturer of its listing decision and the coverage status of the Drug.



# CDR Process, Continued

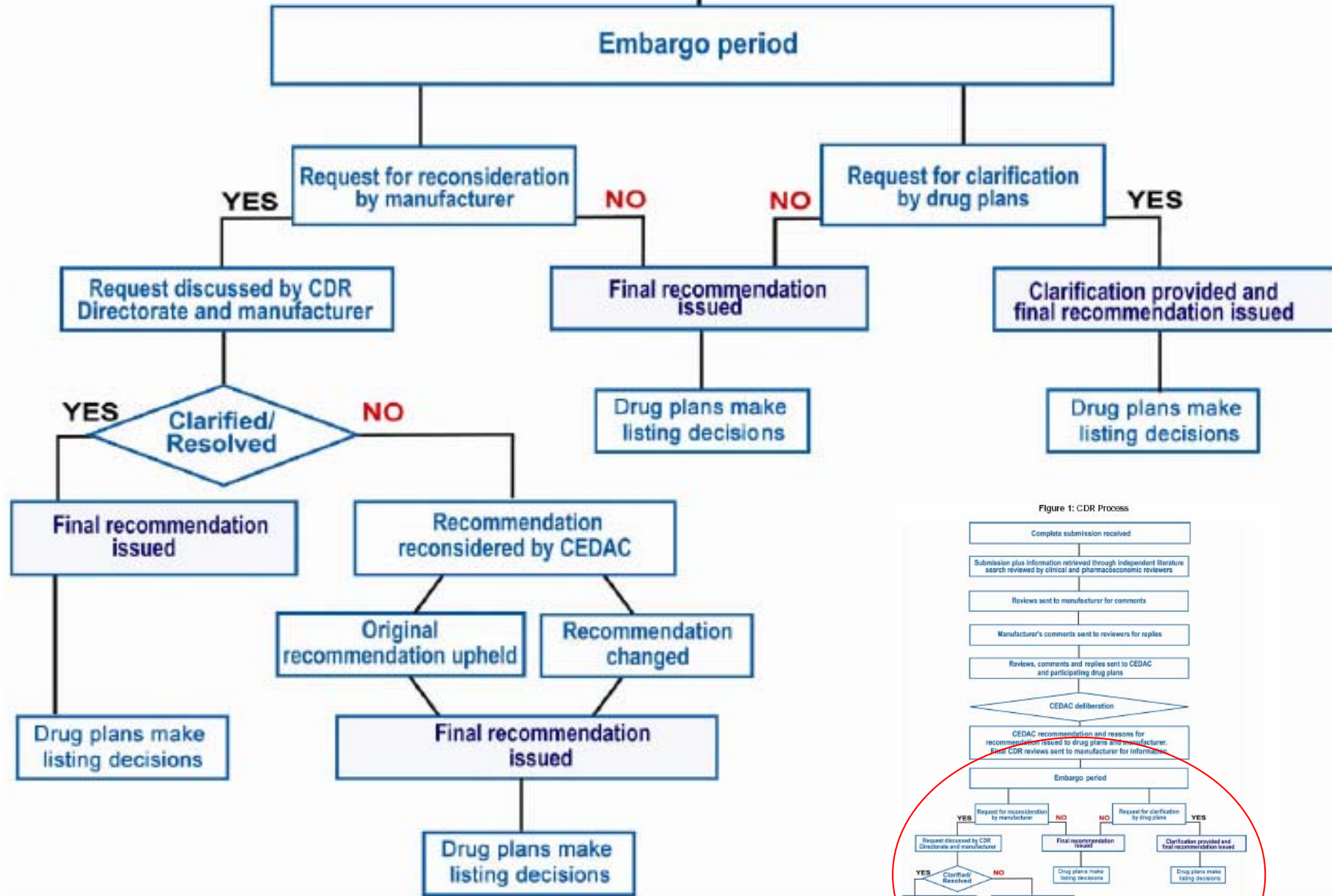
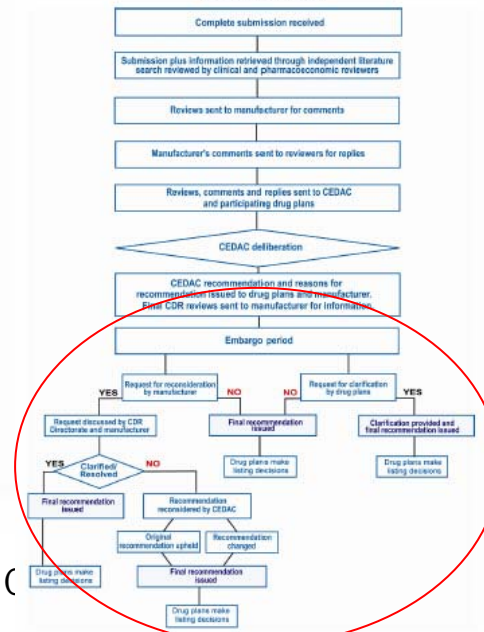


Figure 1: CDR Process





# The CDR process is initiated

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- either:
  - By the Manufacturer, the Advisory Committee for Pharmaceuticals (ACP), or one or more Drug Plans filing a **Submission** with the CDR Directorate; or
  - by the ACP, or one or more Drug Plans, filing a **Request for Advice** with the CDR Directorate; or
  - by the Manufacturer, the ACP, or one or more Drug Plans filing a **Resubmission** with the CDR Directorate



# Eligible Submissions from Manufacturers

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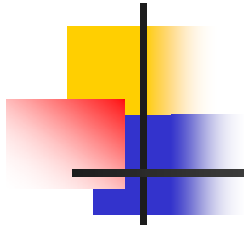
- Submissions from Manufacturers are limited to New Drugs and New Combinations that have received, from Health Canada,
  - a Notice of Compliance (NOC) or
  - a Notice of Compliance with Conditions (NOC/c)



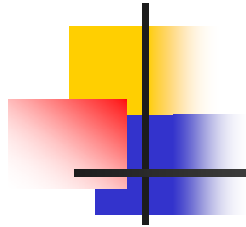
# New Drugs and New Combinations

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- New Drugs
  - are New Active Substances that have not been marketed in Canada, regardless of when the NOC or NOC/c was issued. New Active Substances include new salts of marketed products, but do not include new dosage forms or line extensions.
- New Combinations
  - consist of two or more Drugs that have not been marketed in Canada in that combination. They may consist of either two or more New Drugs or two or more marketed Drugs or a combination of New Drug(s) and marketed Drug(s).



- All New Drugs or New Combinations, including new HIV/AIDS agents and “hospital” Drugs that may be potentially funded by one or more of the participating Drug Plans **should be** submitted by Manufacturers to the CDR for review to be **eligible for consideration for coverage** by participating Drug Plans



- The ACP may request that the CDR Directorate undertake the review of Submissions, including Drugs that are **not** New Drugs or New Combinations.
- In these cases, the CDR Directorate will contact the Manufacturers for clinical and pharmacoeconomic data.



## review queue is as follows

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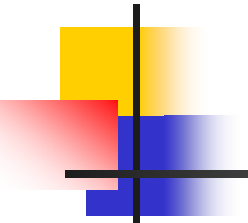
- Submissions or Resubmissions assigned a Priority Review status
  - Reconsiderations
  - Regular Submissions
  - ACP or Drug Plan initiated reviews
  - Requests for Advice
  - Resubmissions



# Submissions may be considered for Priority Review if the Drug is

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- A New Drug that is effective for the treatment of an immediately life-threatening disease or other serious disease for which no comparable drug is marketed in Canada; or
- A New Drug that will have a significant impact in reducing the drug expenditures of the Drug Plans. The total combined annual savings to the CDR Drug Plans must be projected to be at least \$2.5 million dollars.



## The Submission Requirements are subdivided into Category 1, Category 2, and Additional Information.

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- Category 1 information must all be included when the Submission is filed in order for the review to proceed.
- Category 2 information must be provided as a single package within 20 Business Days of filing the initial Submission.
- Category 2 requirements must be satisfied before the Drug review is placed on the CEDAC agenda.
- The Category 2 requirements may be submitted concurrently with Category 1 requirements.



# Category 1 Requirements

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1. Cover Letter
2. Executive Summary
3. Health Canada NOC or NOC/c.
4. Product Monograph
5. Efficacy, Effectiveness and Safety Evidence
6. Economic and Epidemiologic Information
7. Pricing and Availability Information
8. Letter Confirming Ability to Supply
9. Letter Authorizing Unrestricted Sharing of Information
10. Bibliography of Included References Supporting Validity of Outcome Measures



# Category 2 Requirements

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1. Drug Notification Form
2. Economic and Epidemiologic Information
3. Compendium of Pharmaceuticals and Specialties (CPS) listing
4. Pharmaceutical Advertising Advisory Board (PAAB)-approved promotional
5. materials – or a draft copy of material submitted to PAAB
6. Certified Product Information Document (CPID)
7. Product Patent Expiration Date



# Additional information may be requested by the CDR Directorate

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1. Harm and Safety Information
2. Health Canada Reviewer's Report
3. Periodic Safety Update Reports (PSURs)
4. Economic Model and Supporting Documentation



# Resubmissions

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- Manufacturers may file Resubmissions when they have New Information.
- New Information is new clinical information or new cost information that significantly impacts the cost-effectiveness of the Drug.
- If the New Information is in support of improved efficacy, it must be from a randomized controlled trial.
- If the New Information is in support of improved safety, case-control or cohort studies will be accepted if randomized controlled trials are not available.



# CDR Directorate may accept Resubmissions when:

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- New Information becomes available during the review process before the Notice of Final Recommendation has been issued; or
- New Information becomes available after Notice of Final CEDAC Recommendation has been issued; or
- New Information becomes available that affects coverage criteria recommended by CEDAC and accepted by the Drug Plans in their decisions to list a drug in their formularies; or
- A Drug that has been considered by CEDAC receives a new NOC or NOC/c for a new indication



# Review of a Manufacturer's Submission 1

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- a) The Review Team develops a protocol for the review of the Submission with input from participating Drug Plans, CEDAC members and other experts as required.
- b) The Review Team designs and conducts an independent systematic literature search to address the protocol and to supplement the data provided by the Manufacturer.
- c) Regular and frequent interactions occur amongst the members of the Review Team regarding the review of the Submission.



# Review of a Manufacturer's Submission 2

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- d) A list of studies included in the Systematic Review portion of the Clinical Review Report is sent to the Manufacturer for information.



# Review of a Manufacturer's Submission 3

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- e) The Review Team undertakes a review of the relevant information provided by the Manufacturer and identified through the independent literature search and prepares a Clinical Review Report.



# Review of a Manufacturer's Submission 4

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- f) The Review Team reviews and critiques the PE information submitted by the Manufacturer. The results and conclusions reported in the Clinical Review Report are used in the assessment of the PE information submitted by the Manufacturer.



# Review of a Manufacturer's Submission 5

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- g) The Review Team may request an extension of deadlines from the CDR Directorate. The Manufacturer will be notified of any extensions and reasons for the extensions, granted by the CDR Directorate.



# Review of a Manufacturer's Submission 6

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- h) Once the Review Team has completed the Reports, they are forwarded to the Manager of Drug Reviews who has five Business Days to check that the Reports are complete and to finalize the documents for inclusion in the CEDAC Brief.



# CIRCULATION OF INFORMATION

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- Distribution of Reviewers' Reports for Manufacturer's Comments
- Manufacturer's Comments
- Reviewers' Replies to Manufacturer's Comments
- Final Versions of CDR Reports
- Compilation of CEDAC Brief

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# CEDAC

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- Scheduling Review of CEDAC Brief
- CEDAC Meeting
- CEDAC Recommendation
- Reasons for Recommendation
- Releasing Recommendation and Reasons for Recommendation
- Releasing Record of Advice

## Drug Name

**Brand name** XXXXX  
**Manufacturer** XXXXX Inc.

**Indication** Hepatitis B

**Submission type** Initial

**Date submission received** 2006-04-24

**Status** Completed

**Date recommendation issued** 2006-11-29

**Recommendation** Do not list

[Submission status report](#)

[Detailed recommendation](#)

## Drug Name

**Brand name** XXXXXXX

**Manufacturer** XXXXXXX

**Indication** HIV infection

**Submission type** Initial

**Date submission received** 2003-12-16

**Status** Completed

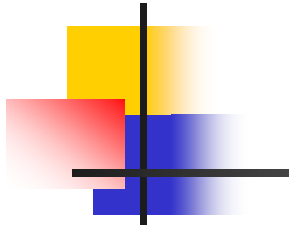
[Submission status report](#)

**Date recommendation issued** 2004-05-27

**Recommendation** List in a similar manner to other drugs in class

[Detailed recommendation](#)

# APPENDIX 7: Submission and Resubmission Checklists (for CDR Directorate Use)



## Submission Checklist

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Drug Name: \_\_\_\_\_

Manufacturer: \_\_\_\_\_

### Category and Designation

- New Drug
- New Combination
- ACP Request

### Submission Type

- First review  File number: \_\_\_\_\_
- Resubmission  File number: \_\_\_\_\_

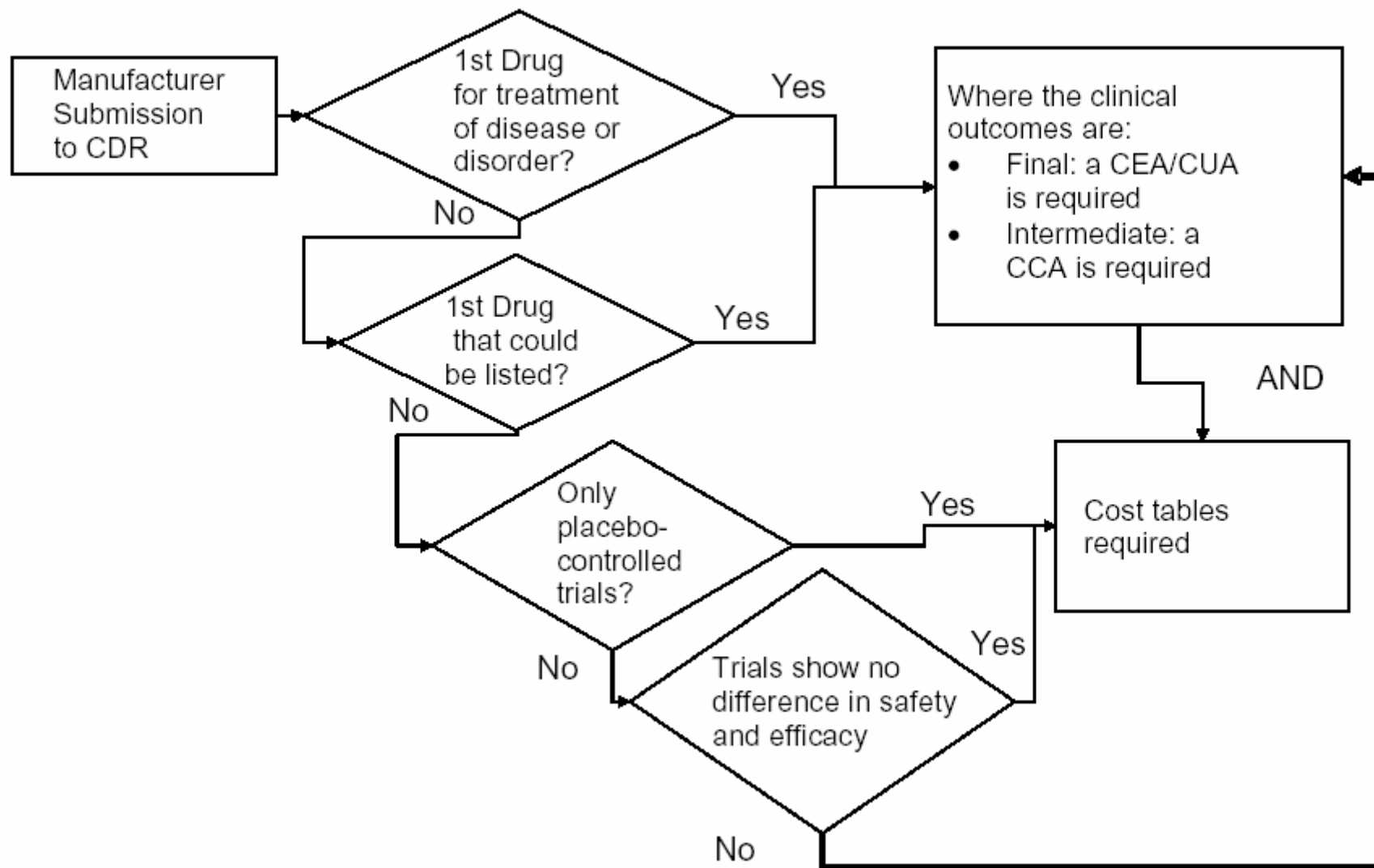
### Priority Review Submission

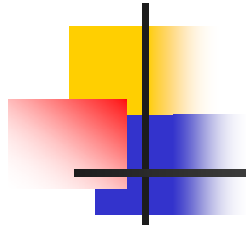
- Request for Priority Review
- Justification provided

### Administrative Issues

- Complete set of Category 1 Submission Requirements provided \_\_\_\_\_  
*(See list of Submission Requirements)*
- Number of binders that make up Submission set \_\_\_\_\_

**Figure 1:** Summary of the Guidelines for Type of Economic Analysis to Submit





- CEA=cost-effectiveness analysis;
- CCA=cost-consequence analysis;
- CUA=cost-utility analysis;
- Final Clinical Outcome= an event that is relevant and noticeable to patients;
- Intermediate Clinical Outcome=includes subjective clinical measures where extrapolation of health benefits to lifeyears or quality-adjusted life-years (QALYs) is more difficult, non-clinical endpoints or surrogate endpoints.



# Drug Plan Decision

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- Upon receipt of the Notice of Final Recommendation, each of the Drug Plans may proceed to take steps to make a listing decision in respect of the applicable Drug.



# Withdrawal or suspension


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- Withdrawal Process
  - Withdrawal of Market Authorization by Health Canada
  - Voluntary Withdrawal of a Submission or Resubmission
- Temporary Suspension of Review

## CDR Timeframe

	<b>Task within Review Process</b>	<b>Timeframe (in Business Days)</b>	<b>Weeks</b>
<b>Administrative Tasks*</b>			
<b>1</b>	Submission deemed complete	5	1
	Resubmission deemed complete	10	2
<b>2</b>	Manufacturer's binders received by CDR	5	1
<b>3</b>	Manufacturer's binders received by CDR Reviewers	3	0.6
<b>Review Process</b>			
<b>4</b>	CDR Reviewers' Reports completed <ul style="list-style-type: none"> <li>• Reviewers selected and contracted</li> <li>• Literature search and selection completed</li> <li>• Systematic review of clinical data completed</li> <li>• Critical appraisal of pharmacoeconomic (PE) data completed</li> <li>• Clinical and PE reports written</li> <li>• Reports edited and finalized</li> <li>• Reviewers' reports sent to manufacturer</li> </ul>	45	9
<b>5</b>	Comments from Manufacturer on Reviewers' Reports received by CDR	7	1.5
<b>6</b>	Reviewers' Reply to Manufacturer's comments completed	7	1.5
<b>7</b>	CEDAC Brief completed and sent to CEDAC Members and Participating Drug Plans	5	1


		Business Days	Weeks
8	CEDAC meeting (placement on CEDAC agenda)	10 to 40	2 to 8
9	CEDAC Recommendation and Reasons for Recommendation sent to Drug Plans, ACP and Manufacturer; Final CDR Reviews sent to Manufacturer for information	5	1
10	Embargo Period† Manufacturers may make Request for Reconsideration, and Drug Plans may make Request for Clarification of Recommendation and Reasons for Recommendation	10	2
11 (a)	Final Recommendation sent to Drug Plans, ACP, and Manufacturer (no Requests for Clarification AND no Request for Reconsideration; or Request for Reconsideration resolved)	5	1
<b>OR</b>			
11 (b)	Clarification and Final Recommendation sent to Drug Plans, ACP, and Manufacturer (Clarification requested, no Request for Reconsideration)	5	1
	<b>Total Review Time for Submissions*</b>	94 to 124 days	19 to 25 weeks
	<b>Total Review Time for Resubmissions*</b>	94 to 124 days	19 to 25 weeks
<b>OR</b>			
11 (c)	Placed on CEDAC agenda for Reconsideration (at Manufacturer's request)	25 Depends on Meeting Dates	5
12	Final Recommendation sent to Drug Plans, ACP, and Manufacturer	5	1



# most common challenges faced by the CDR (cited from a paper)

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- determining the effectiveness of a drug (particularly interpreting the importance of surrogate markers and changes in QOL measures);
- the massive rise in the cost of new drugs, which does not seem to be accompanied by a massive increase in effectiveness;
- interpreting complex pharmacoeconomic evaluations which often do not provide straightforward answers about the cost effectiveness of a drug;



# most common challenges faced by the CDR (cited from a paper)

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- prescription creep. The tendency for drugs in the real world to be used in patients who were not studied in clinical trials, thus raising concerns about a drug's real-world cost effectiveness;
- ethical and societal issues, particularly the reimbursement of expensive drugs for rare diseases.

Andreas Laupacis: Economic Evaluations in the Canadian Common Drug Review.  
*Pharmacoeconomics* 2006; 24 (11): 1157-1162 CONFERENCE PAPER



# 研究團隊

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李喜鳳

賴冠郎

黃維瑄

謝謝蒐集與整理資料

Thank you  
for your attention

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