Report of the Working Group on International Therapeutic Class Comparison (ITCC) To The Patented Medicine Prices Review Board

April 2008

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1. INTRODUCTION

1.1 This is the report of the Working Group (WG) on International Therapeutic Class Comparison (ITCC) which will be referred to as the WG-ITCC.

1.2. The WG is composed of the following members:

- Sebastien Dao, Chairperson, representative of a brand-name pharmaceutical company, and employee of Bristol-Myers Squibb Canada Inc.
- Olaf Koester, representative of a provincial public drug plan, practicing pharmacist
- Mitch Levine, member of the Human Drug Advisory Panel (HDAP), practicing clinician, and representative of academia
- Lynn Macdonald, representative of the Best Medicines Coalition, a consumer group
- Laurene Redding, representative of BIOTECanada and employee of Novo Nordisk Canada Inc.
- Colette Strnad, representative of international regulatory bodies, Health Canada.
- Rebecca Yu, representative of Canada's Research Based Pharmaceutical Companies (Rx&D), practicing pharmacist and employee of Procter & Gamble Pharmaceuticals Canada, Inc.

1.3 The WG-ITCC held its first meeting on December 14, 2007, to discuss the terms of reference of the WG-ITCC and scope its deliverables. Issues surrounding the conduct of an ITCC were discussed at a second meeting held on January 7, 2008. Further discussions followed via teleconference meetings held on February 12, February 27, March 14, March 25, and April 1, 2008.

2. MANDATE OF THE WORKING GROUP

2.1 The mandate of the WG-ITCC is to recommend, for the Board's consideration, a methodology for appropriately identifying comparable medicines in the comparator countries listed in the *Patented Medicines Regulations, 1994* (Regulations)(see Terms of Reference - Appendix 1).

2.2 The mandate of the WG-ITCC does not include consideration of possible price tests, but rather its focus is to develop a methodology for conducting an ITCC. The PMPRB has stated that a WG to examine price tests will be established upon completion of the reports of the WG-ITCC and the WG on Therapeutic Improvement (TI).

2.3 Although the mandate of the WG-ITCC does not include consideration of price tests, the group recognized that the question of potential price tests is highly relevant in considering a methodology for identifying comparable medicines as provided in the WG-ITCC mandate.

2.4 Participants of the WG-ITCC noted that the work of this group and the other Working Groups (Therapeutic Improvement, Price Tests) are intertwined, and recommendations of one group could have an impact on the recommendations of the other groups. For example, the recommendations of the WG-ITCC might be different if it is known that there will be changes in the Price Tests resulting from the recommendations of the WG on Price Tests. Therefore, the recommendations made by the three working groups cannot be considered in isolation.

3. BACKGROUND

3.1 Pursuant to subsection 85(1) of the *Patent Act*, and for purposes of determining under section 83 whether a medicine is being or has been sold at an excessive price in any market in Canada, the Board shall take into consideration the following factors, to the extent that information on the factors is available to the Board:

a) the price at which the medicine has been sold in the relevant market;

b) the prices at which other medicines in the same therapeutic class have been sold in the relevant market;

c) the prices at which the medicine and other medicines in the same therapeutic class have been sold in countries other than Canada;

d) changes in the Consumer Price Index (CPI); and

e) such other factors as may be specified in any regulations made for the purposes of this subsection.

3.2 Of particular importance to the WG-ITCC is paragraph 85(1)(c): *the prices at which the medicine and other medicines in the same therapeutic class have been sold in countries other than Canada.*

3.3 Currently, there are no guidelines on when an ITCC should be conducted, how comparators should be selected, or how the price tests should be applied. In the past, the ITCC has only been used on an ad hoc basis for the resolution of pricing disputes.

3.4 Recently, in the context of a public hearing, it has been the Board's practice to request that all parties to the hearing submit evidence on each of the factors listed in subsection 85(1). Board Staff is required to conduct an ITCC in the absence of guidelines on how to conduct an ITCC.

3.5 In the past, when Board Staff has considered the ITCC, the selection of comparator drug products has always been based on the domestic TCC, using the same dosage regimens of clinically equivalent medicines sold in Canada. However, Board Staff has derived 2 variations of the application of the price tests for the few drugs that have been the subject of an investigation or hearing.

4. PROPOSED METHODOLOGY FOR ITCC

4.1 Countries Listed in the Regulations

4.1.1 The WG-ITCC did not address whether the basket of countries listed in the Regulations is appropriate as this issue was outside the mandate of the WG-ITCC.

4.2 Selection of Comparators Based on Drug Indication or Therapeutic Use

4.2.1 WG-ITCC members were advised that the PMPRB uses the Human Drug Advisory Panel (HDAP) to determine the basket of clinically equivalent comparator medicines to be used in a domestic Therapeutic Class Comparison. This selection of comparators starts with medicines at the 4th level of the World Health Organization's Anatomical Therapeutic Chemical (ATC) classification system and includes the following additional information:

- Review of clinical trials
- Review of clinical practice guidelines
- Review of clinical literature

4.2.2 For new drugs with multiple indications, the HDAP has to determine the primary indication. For this purpose, primary indication is defined by the approved indication with the greatest therapeutic advantage in relation to alternative therapies for the same indication in a significant patient population. Where there is no apparent single indication for which the new drug offers the greatest therapeutic advantage, the approved indication representing the greatest proportion of sales is the basis for selection of comparators.

4.2.3 As per subsection 9.3 of the Board's current Excessive Price Guidelines (Guidelines), in some instances it may be appropriate to select from the fifth or single chemical substance level. Selection criteria will include the indication or therapeutic use in practice, and could include other factors such as mode of action, spectrum of activity or chemical family.

4.2.4 The WG-ITCC determined that the selection of comparators and dosage regimens should be limited to the comparators and dosage regimens selected for the domestic TCC for the following reasons:

- The international market is too heterogeneous and markets in other countries are not necessarily comparable to the Canadian market;
- Comparator medicines are not necessarily available in all of the comparator countries;
- Differences in availability of product format (e.g., dosage forms and dosage regimens) between countries;
- Differences in indications, prescribing or therapeutic guidelines, and usage between countries;

- The tender process and negotiated access in some markets would influence the prices in the basket of comparator medicines;
- Intensive resources and workload will be required from the Board Staff to conduct an ITCC in a systematic fashion for all products;
- Difficulties in obtaining prices of "old" comparators in international markets;
- Relationships amongst manufacturers are complicated and pricing strategies of companies differ.

4.2.5 The WG-ITCC agrees that if the comparator and its dosage regimen are not sold in Canada, then it should not be included as a comparator for purposes of the ITCC. Since the comparator (in an ITCC) is being identified as a relevant treatment option (for Canadians) that could influence the Canadian price for the product under review, then the comparator be sold in Canada.

4.2.6 The WG-ITCC had discussions with respect to the inclusion of generic drugs in the TCC. It recognizes that generic drugs may be included in the domestic TCC, but notes that this does not ordinarily impact the MNE price, because the price test attached to the domestic TCC is the "top" of the TCC and in most cases the generic drug will not constitute the "top" of the domestic TCC. Similarly, if the price test for the ITCC were the "top" of the ITCC, the inclusion of generics would have little impact. However, the WG-ITCC does not support the inclusion of generic comparators if the price test for the ITCC will be any measure below the "top" of the ITCC. The availability and use of generic drugs varies widely in the comparator countries and there is considerable variation in their prices.

4.3 Derivation of the ITCC Price Test

4.3.1 Two variations that have been developed by Board Staff in the past were discussed by the WG-ITCC:

- The first one deals with the calculation of a ratio of the price of the medicine under review to the price of its respective comparators (identified in the domestic TCC) in the other countries listed in the Regulations;

- The second variation is to use the prices of the comparators (identified in the domestic TCC) in the other countries listed in the Regulations as the basis for calculating a comparable price.

4.3.2 The WG-ITCC also discussed the threshold for pricing purposes when conducting an ITCC test and agrees that several statistical values such as the mean, median and a range (i.e. interval between maximum and minimum) be considered by the Board.

4.4 When to Use the ITCC Test

4.4.1 The WG-ITCC discussed when it would be appropriate to use the ITCC test and agrees that its use should be limited to dispute resolutions; it should not be used as a primary test.

4.4.2 The 3-year/ 5 countries rule for international price comparisons could require unreasonably frequent ITCC (pending status for a 3-year period) if it were used as a primary test.

4.5 Minimum Number of Countries or Comparators

4.5.1 The WG-ITCC did not consider if there may be a need to establish a minimum number of countries and/or comparators below which an ITCC may not be appropriate; the WG-ITCC expects that this question will be addressed by the WG on Price Tests.

4.5.2 There is possible lack of relevance of an ITCC if only one other country has launched the product.

5. RECOMMENDATIONS

The WG-ITCC recommends the following:

5.1 The WG-ITCC recommends that an ITCC only be conducted when Board Staff finds that the price of a new medicine appears to exceed the Guidelines and, the circumstances are within the established criteria for commencing an investigation. The ITCC should not be considered a primary price test. The ITCC should not be applied routinely to new drugs unless the Board Staff finds that the price exceeds the Guidelines and it should not be applied retroactively to existing drugs whose prices are within the Guidelines.

5.2 Further, WG-ITCC recommends that the test only be used in cases of dispute resolutions.

5.3 In the context of dispute resolutions, the WG-ITCC recommends that the ITCC test be one of many considerations to be taken into account by the Board.

5.4 The WG-ITCC recommends, for the purposes of the ITCC, that the selection of comparators and dosage regimens in each country listed in the Regulations will be the same as the ones derived from the domestic TCC, that is, the comparators will be sold in Canada, will have the same Canadian indication or be used for the same Canadian indication as the drug under review and the dosage regimens will also be the ones derived from the domestic TCC.

5.5 The WG-ITCC further recommends that generic drugs should not be included in the ITCC if the Board decides that the determination of the maximum non-excessive (MNE) price will be established by using any measure below the "top" of the ITCC.

5.6 The WG-ITCC recommends that when selecting a comparator sold in Canada, the Canadian indication/use will be used in the conduct of the ITCC (even if in other countries that same drug has a different indication/use). Similarly, if a comparator identified in another country is sold in Canada but has a different indication/use, it will not be selected as a comparator for the conduct of the ITCC.

5.7 The WG-ITCC recommends that if there are no comparators available in Canada, the ITCC should not be changed to allow the inclusion of drugs that are not available in Canada

5.8 The WG-ITCC recommends, for purposes of the ITCC, that the Board consider all of the following statistical values: mean, median and a range (i.e., interval between maximum and minimum) along with the other factors described in subsection 85(1) of the *Patent Act* in determining the MNE price of the medicine. However, the WG-ITCC recommended that any specific issues regarding the guidance as to which value should be

used is beyond the mandate of the WG-ITCC and this issue should be deferred to the WG on Price Tests.

5.9 The WG-ITCC recommends for purposes of the ITCC that the PMPRB use the publicly available list prices and provide the sources for these prices.

5.10 The WG-ITCC recommends that there should be ongoing dialogue and the sharing of information, including any written information (i.e. draft and final reports, notes, etc…) between the WGs (TI, ITCC and Price Tests), to ensure a cohesive approach between the three WGs.

5.11 The WG-ITCC recommends that membership of the WG for the Price Tests include interested members from both the WG-ITCC and WG on Therapeutic Improvement.

5.12 The WG-ITCC recommends that the reports of the three Working Groups (International Therapeutic Class Comparison, Therapeutic Improvement and Price Test) must not be considered in isolation from each other.

6. ASSUMPTIONS

6.1 It is assumed that if the ITCC and guidelines for its application come into effect, it will not be applied retroactively to drugs that are priced within the Guidelines. It is further assumed that the Board's Guidelines will be developed in an open manner with opportunity for full consultation with interested parties.

6.2 Recommendations provided in this report are based on the assumptions that the current categories (as described in Appendix 3) and their related price tests have not changed.

7. DISSENTING OPINION

7.1 With reference to paragraph 5.8, the representatives of pharmaceutical patentees wish to note that the range of "statistical values: mean, median, and a range (i.e. interval between maximum and minimum)" represents statistical approaches, but is much broader than is appropriate for the Board's mandate, which is to determine if a price is "excessive." Rx&D has recommended that a price should only be considered excessive if it exceeds the price in all other countries and the CPI-adjusted prices of all other drugs in the therapeutic class.

7.2 The representatives of pharmaceutical patentees on the Working Group wish to note that their participation in the WG-ITCC and this report are subject to the qualifications set out in the letter of December 18, 2007 from the President of Rx&D to the Chair of the PMPRB. (Appendix 2)

7.3 They wish to note that nothing in their participation in the WG-ITCC nor in this report should be taken as detracting from or limiting the ability of a patentee to make submissions and present evidence on relevant questions to the Board Staff in a price review and to the Board itself in any proceedings under the Act.

Appendix 1: Terms of Reference

MANDATE

The mandate of the Working Group (WG) is to develop a methodology for appropriately identifying comparable medicines in comparator countries listed in the *Patented Medicine Regulations, 1994* (Regulations).

DELIVERABLES

1. Parameters to guide the selection of comparable medicines

2. A methodology and rationale for identifying drugs that meet the parameters, including sources of data to be used

3. Considerations/rationales as to when comparators may appropriately be added/deleted from the initial list.

REPORTS &TIMEFRAME

- Status/progress report in February 2008
- Final report to the Board by the end of April 2008

MEMBERSHIP

The Working Group (WG) shall be composed of 8 to 10 members including:

- At a minimum, one member of the PMPRB's Human Drug Advisory Panel (HDAP)
- Clinical pharmacologist(s) or pharmacist(s)
- Practicing clinician(s)
- International pharmaceutical expert(s)
- Representative(s) of international regulatory bodies/International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)[1]
- Representative(s) of the pharmaceutical industry
- Representative(s) of a public drug plan
- Consumers

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[1] The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is a unique project that brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of product registration.

The purpose is to make recommendations on ways to achieve greater harmonization in the interpretation and application of technical guidelines and requirements for product registration in order to reduce or obviate the need to duplicate the testing carried out during the research and development of new medicines.

A key consideration will be expertise relative to the domestic and international drug markets, drug regulation, and international drug formularies.

The names of the Working Group members will be publicly available on PMPRB's Web site.

ORGANIZATION AND STRUCTURE

Each member of the WG will have equal status. A Chairperson will be nominated during the first meeting of the WG...The Chairperson's responsibilities include keeping the team focused on the exercise; maintaining open and effective communication; and ensuring issues and thoughts are raised and recorded. The PMPRB Staff will provide Secretariat services.

CONFIDENTIALITY OF WORKING GROUP DELIBERATIONS

The deliberations of the WG are confidential and members are expected to respect the confidentiality of any materials provided by the PMPRB Staff and/or collected by the WG as during the course of its work.

MEETINGS

- An initial face-to-face meeting of the Working Group in November 2007 to confirm the terms of reference and work plans
- Monthly teleconference/videoconference meetings (meetings 1-2 hours with clear agenda), as needed
- A face-to-face meeting in February 2008 to finalize the report
- If requested, a presentation of the final report to the Board in May 2008

LOCATION OF MEETINGS

WG meetings will take place on PMPRB premises in Ottawa, unless availability of space or other rationale necessitates off-site meetings.

Appendix 2 Letter from Rx&D to the PMPRB

Canada's Research-Based Pharmaceutical Companies R&D Les compagnies de recherche pharmaceutique du Canada

President's Office / Bureau du Président

December 18th, 2007

Dr. Brien Benoit, BA, MD, MSc, FRCSC, FACS
Chairperson
Patented Medicine Prices Review Board
Box L40
Standard Life Center
333 Laurier Avenue West, Suite 1400
Ottawa, ON
K1P 1C1

Re: Working Group on International Therapeutic Class Comparison and PMPRB Consultation Plan

Dear Dr. Benoit:

On behalf of *Canada's Research-Based Pharmaceutical Companies* (Rx&D), I am writing to you regarding the Working Group on the International Therapeutic Class Comparison (ITCC). The ITCC Working Group was initiated by the Patented Medicine Prices Review Board (PMPRB) as part of its ongoing review of the Excessive Price Guidelines (Guidelines).

The Working Group's first meeting took place by teleconference on December 14, 2007. At the meeting, it is my understanding that several Working Group members had questions about the underlying rationale and motivation for convening a group to discuss ITCC issues. Given some other aspects of the Guidelines may be in flux, it was also noted by several Working Group members that it will be challenging for them to provide meaningful conclusions or advice to the PMPRB Board on ITCC.

Rx&D previously expressed concern about the mandate of the ITCC Working Group. It is difficult to provide an opinion on comparisons when it is unclear how such a price test might apply, or whether there will be changes in categorization. Rx&D notes that a separate Working Group has been tasked with reviewing and making recommendations with respect to categorization.

Rx&D has never requested, nor encouraged the creation of, an ITCC Working Group. As noted in our recent submission on the Guidelines, while we are cognizant of the factor set out in Section 85(1)(c) of the *Patent Act*, we also believe that the rationale for this Working Group has never been clearly established. However, given that the PMPRB decided to proceed with this Working Group as part of the Guidelines consultation process, Rx&D agreed to participate.

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Rx&D believes that the present issues with the ITCC Working Group are symptomatic of a larger issue. Several of the PMPRB's present or anticipated consultation processes pertain to overlapping and related issues. Therefore it is in the interest of the PMPRB, patentees and other stakeholders that these processes should be approached in a cohesive, coordinated and transparent fashion. Accordingly, Rx&D would like to request again that all stakeholders be provided with the PMPRB's overall plan for the entire Guidelines consultation process, including how this process corresponds to the consultations initiated on the proposed changes articulated in the April 2007 NEWSletter, and with the Canada Gazette process underway pertaining to proposed amendments to the *Patented Medicines Regulations, 1994* (*Regulations*).

In conclusion, Rx&D strongly encourages PMPRB to revisit the mandate and timing of the ITCC Working Group. More broadly, we would encourage the PMPRB to share publicly its overall consultation plan related to the Guidelines.

I wish you and your family a happy holiday season, and please accept my best wishes for the New Year.

Sincerely,

Russell Williams
President

RW/dh

cc: Mary Catherine Lindberg, BSP, Vice Chairperson
Tim Armstrong, Q.C., O. Ont.
Anthony Boardman, BA, PhD
Anne Warner La Forest, LLB, LLM
Barbara Ouellet, Executive Director, PMPRB
Sylvie Dupont, Secretary to the Board, PMPRB
Rx&D PMPRB Sub-Committee

Appendix 3: Drug Product Categories

The current categories are as follows:

3.1A **Category 1 drug product** is a new Drug Identification Number (DIN) of an existing dosage form of an existing medicine, or a new DIN of another dosage form of the medicine that is comparable to the existing dosage form as per Schedule 7.

3.2A **Category 2 drug product** is one that provides a breakthrough or substantial improvement. It is a new DIN of a non-comparable dosage form of an existing medicine or the first DIN of a new chemical entity.

5.1A breakthrough drug product is the first one to be sold in Canada that treats effectively a particular illness or addresses effectively a particular indication.

5.2A drug product constituting a substantial improvement is one that, relative to other drug products sold in Canada, provides substantial improvement in therapeutic effects (such as increased efficacy or major reductions in dangerous adverse reactions) or provides significant savings to the Canadian health care system.

3.3A **Category 3 drug product** is a new DIN of a non-comparable dosage form of an existing medicine or the first DIN of a new chemical entity. These DINs provide moderate, little or no therapeutic advantage over comparable medicines. This group includes those new drug products that are not included in Category 2 above.