Report of the Working Group on Therapeutic Improvement
To
The Patented Medicine Prices Review Board

Working Group on Therapeutic Improvement
April 2008

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1. Mandate

1.1 The mandate of the Working Group (WG) is to develop definitions or parameters relating to "**breakthrough/substantial improvement", "moderate improvement", and "slight or no improvement"** for new drug products, along with supporting evidence requirements and sources. Refer to Appendix 1 for the complete Terms of Reference.

1.2 The Working Group has been asked to provide clear, scientifically/clinically-based definitions (either as a full statement or component parameters) for **"breakthrough/substantial improvement", "moderate improvement", and "slight or no improvement" for newly submitted drug products relative to other clinically equivalent drugs** available in Canada and used to treat the same disease and/or condition. Thresholds of scientific/clinical evidence (with rationale) to evaluate therapeutic improvement (TI) associated with each of the definitions plus other considerations and/or circumstances which may be appropriate to take into account, including the degree of significance or weight each should be accorded, should also be included.

2. Introduction

2.1 Following extensive stakeholder consultations across the country in May 2007 the Patented Medicine Prices Review Board released a preliminary communiqué summarizing the discussions, and indicating that stakeholders had a variety of views on the current TI definitions. The Board believed that some assessment of therapeutic value was needed and work on options for possible revisions to the current definitions was appropriate. Hence, the Board established this Working Group to develop definitions or parameters as outlined in the mandate.

2.2 Please refer to Appendix 2 for the Membership of the Working Group.

3. Issues Discussed

A. Definitions

3.1 The current definitions for drug products were reviewed by the WG members. See Appendix 3 for the current Category 1, 2 and 3 drug product definitions.

3.2 A new series of four definitions for drug products ("**Breakthrough", "Substantial Improvement", "Moderate Improvement" and "Slight or No Improvement"**) was proposed by the WG. Please refer to Appendix 4 for a Table outlining the Proposed Drug Product definitions.

3.3 A **Breakthrough Drug** is now defined as the first one to be sold in Canada that treats effectively a particular illness or addresses effectively a particular indication.

3.4 A drug product offering a **Substantial Improvement** in therapy is now defined as one that, relative to other drug products sold in Canada, provides substantial improvement in therapeutic effects (such as substantially increased efficacy or substantial reductions in the incidence or grade of important adverse reactions) or provides substantial savings to the Canadian healthcare system (private or public payers and employers) and/or to patients and/or caregivers.

3.5 A drug product offering a **Moderate Improvement** in therapy is now defined as one that, relative to other drug products sold in Canada, provides moderate improvement in therapeutic effects (such as moderately increased efficacy or moderate reductions in the incidence or grade of important adverse reactions) or provides moderate savings to the Canadian healthcare system (private or public payers and employers) and/or to patients and/or caregivers.

3.6 A drug product offering **Slight or No Improvement** in therapy is now defined as one that, relative to other drug products sold in Canada, provides slight or no improvement in therapeutic effects (such as slightly or no increased efficacy or slight or no reductions in the incidence or grade of important adverse reactions) or provides slight or no savings to the Canadian healthcare system (private or public payers and employers) and/or to patients and/or caregivers.

3.7 In order to maintain consistency between the four new drug product definitions, the WG proposed that each of the drug product definitions (with the exception of Breakthrough Drug) be essentially the same with the only difference being the degree of therapeutic improvement, for example substantial, moderate, slight or no improvement.

3.8 The WG proposed that the main factor to be used to determine if a drug product will be considered a Substantial Improvement, Moderate Improvement or a Slight or No Improvement is therapeutic effect which includes increased efficacy or reduction of side effects OR economic factors. Economic factors include cost savings to the Canadian healthcare system (private or public payers and employers) and may or may not include costs savings to patients and/or caregivers.

3.9 In their discussions, the WG felt it was not feasible to quantify the relative level of therapeutic improvement consistently within or across therapeutic areas. The WG proposed that the HDAP committee will need to set the standards by their decisions.

B. Level of Evidence

3.10 To determine appropriate evidence on which to base the scientific evaluation of new drug products, the WG proposed the use of Levels of Evidence from a well-recognized and respected source such as the Oxford Centre for Evidence-Based Medicine Levels of Evidence (Appendix 4). The Levels of Evidence should be reviewed and updated as required.

3.11 The WG also proposed that ideally Level 1 evidence (Appendix 4) will be used for the determination of the level of therapeutic improvement and for the identification of comparators. However, the Human Drug Advisory Panel (HDAP) committee may consider other levels of evidence if it is felt these lower levels of evidence provide an adequate demonstration of comparative efficacy or toxicity or economic evaluation.

C. Other Factors to be considered

3.12 The WG proposed other factors which will be considered in the evaluation of therapeutic improvement including clinical factors and economic/pharmacoeconomic factors (refer to Appendix 4 for the complete list of factors).

D. Factors that were excluded:

3.13 The WG proposed factors (mechanism of action, a new chemical entity and a different pharmacokinetic profile) which will not be considered in the evaluation of the level of therapeutic improvement of a new drug product. These factors are considered irrelevant variables in determining therapeutic improvement.

4. Areas where the WG reached agreement

4.1 The WG agreed that the numbering of definitions may not need to be done at all. The WG agreed that the way drugs are currently numbered is confusing; for example, a breakthrough drug is categorized as “2” rather than “1”.

4.2 The WG agreed that a table format with the four definitions of level of therapeutic improvement (“breakthrough”, “substantial improvement”, “moderate improvement” and “slight or no improvement”), the Levels of Evidence for consideration by HDAP (based on the Oxford Levels of Evidence), factors that will be weighted and considered and factors that will not generally be taken into consideration would improve the clarity and ease of use as outlined in Appendix 4.

4.3 The WG agreed that the patient's perspective needed to be included when considering a drug's level of therapeutic improvement. These include patient convenience/preference, caregiver's convenience/preference and disability cost avoidance/savings. The WG felt that these criteria were appropriately captured under the description of patient savings in the definition and furthermore in the factors outlined in Appendix 4.

4.4 The WG agreed that the inclusion of data to demonstrate improved patient compliance was of value when considering a drug's level of therapeutic improvement. Proof of improved patient compliance may change a drug's level of therapeutic improvement.

4.5 The WG agreed that the inclusion of pharmacoeconomic evidence would be beneficial when considering a drug's level of therapeutic improvement. A demonstrated economic benefit may change a drug's level of therapeutic improvement.

4.6 The WG agreed that transparency and clarity were extremely important in determining a drug's level of therapeutic improvement. Wherever possible, the process used to determine the definition of a drug's level of therapeutic improvement should be publicly available (see paragraph 3.9)

4.7 The WG recommended that on those occasions where the HDAP committee did not have the expertise to review a submission or were unable to determine the magnitude of therapeutic improvement, they could seek guidance from external clinical experts.

4.8 The WG agreed that it is difficult to quantify substantial improvement versus moderate improvement, versus slight or no improvement. This decision should be left to the HDAP committee to determine. Furthermore, the HDAP committee will need to set the standard by their decisions.

5. Rx&D Comments

5.1 The Pharmaceutical Industry felt their position on the mandate and implications of this committee needed to be more clearly presented (please refer to Appendix 5 for further information).

5.2 This represents the position adopted by Rx&D and its membership. It is supported by members of Rx&D but is not endorsed or reviewed by the other members of this WG. This position in no way binds, constrains or limits the positions of individuals Rx&D members in the context of product specific matters.

6. Recommendations

6.1 The WG-TI recommends that each of the three Working Groups (International Therapeutic Class Comparison, Therapeutic Improvement and Price Test) must not be considered in isolation from each other. Furthermore, the information gained from each WG must be shared among the three WGs.

6.2 The WG recommends a review of the levels of therapeutic improvement from time to time. The frequency of the review is at the discretion of the Board.

Appendix 1: Terms of Reference

Mandate

The mandate of the Working Group (WG) is to develop definitions or parameters relating to “breakthrough/substantial improvement”, “moderate improvement”, and “little or no improvement” for new drug products along with supporting evidence requirements and sources.

Deliverables

1. Clear, scientifically/clinically-based definitions (either as a full statement or component parameters) for “breakthrough/substantial improvement”, “moderate improvement”, and “little or no improvement” of new drug products relative to other clinically equivalent drug products available in Canada and used to treat the same disease and/or condition.

2. Thresholds of scientific/clinical evidence, with rationale, to evaluate therapeutic improvement associated with each of the definitions above.

3. Other considerations and/or circumstances which may be appropriate to take into account, including the degree of significance or weight each should be accorded.

Reports & Timeframe

- Status/progress report in November 2007
- Final report to the Board by the end of January 2008

Membership

The 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)
- Representative(s) of the pharmaceutical industry
- Representative(s) of a public drug plan
- Consumers

A key consideration will be expertise relative to the domestic and international drug markets, pharmaceutical drug pipeline, and the review of scientific and clinical evidence.

The names of the WG 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 WG in September 2007 to confirm the terms of reference and work plans
- Monthly teleconference/videoconference meetings (meeting 1-2 hours with clear agenda) as needed
- A face-to-face meeting in January 2008 to finalize the report
- If requested, a presentation of the final report to the Board in February 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: Membership of the Working Group

Member	Title
Gagnon, Nicolas	Government and Stakeholder Relations, Pfizer Canada Inc.
Gray, Jean	Professor Emeritus, Medical Education, Medicine & Pharmacology, Dalhousie University (HDAP member)
Gudaitis, Edward	General Manager, Gilead Sciences Canada
Harczy, Martha	Manager, Division of Oncology (OD), Bureau of Metabolism, Oncology & Reproductive Sciences Therapeutic Products Directorate
Hollis, Aidan	Associate Professor, Department of Economics, University of Calgary, and Fellow, Institute for Advanced Policy Research
Holloway, Don	Vice-President of the National Pensioners & Senior Citizens Federation of Canada
Koester, Olaf	Director Drug Management Policy Unit, Manitoba Health
Lun, Eric	Executive Director, Drug Intelligence, Pharmaceutical Services Division, BC Ministry of Health
McCormack, James	Pharmacist, Professor & Acting Co-Chair, Clinical Pharmacy, University of British Columbia (HDAP member)
Neuber, Claudia	Senior Manager, Senior Manager Pricing, AstraZeneca Canada Inc.
Pagotto, Sandy	Director of CDR
Paterson, Michael	Scientist, Institute for Clinical Evaluative Sciences
Wang, Jian	Chief, Premarket Clinical Review Division
Wilhelm, Linda	Canadian Arthritis Patient Alliance Chair of Access to Medications Committee

Appendix 3: Current Definitions for Category 1 (Line Extension), Category 2 (Breakthrough, Substantial Improvement) and Category 3 (Moderate, Little or No Improvement) as per the Compendium of Guidelines, Policies and Procedures

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.

Appendix 4: Proposed Drug Product Definitions

Evaluation Component	Breakthrough	Substantial Improvement	Moderate Improvement	Slight or No Improvement
Definition and Primary Factors of Consideration When a drug product offers different levels of improvement (for example substantially increased efficacy and slight or no savings to the healthcare system) it should generally be classified in the higher category**.**	A **breakthrough drug** product is the first one to be sold in Canada that treats effectively a particular illness or addresses effectively a particular indication.	A drug product offering **substantial improvement** is one that, relative to other drug products sold in Canada, provides **substantial** improvement in therapeutic effects (such as **substantially** increased efficacy or **substantial** reductions in the incidence or grade of important adverse reactions) or provides **substantial** savings to the Canadian healthcare system (private or public payers and employers) and/or to patients and/or caregivers.	A drug product offering **moderate improvement** is one that, relative to other drug products sold in Canada, provides **moderate** improvement in therapeutic effects (such as **moderately** increased efficacy or **moderate** reductions in the incidence or grade of important adverse reactions) or provides **moderate** savings to the Canadian healthcare system (private or public payers and employers) and/or to patients and/or caregivers.	A drug product offering **slight or no improvement** is one that, relative to other drug products sold in Canada, provides **slight or no** improvement in therapeutic effects (such as **slightly or no** increased efficacy or **slight or no** reductions in the incidence or grade of important adverse reactions) or provides **slight or no** savings to the Canadian healthcare system (private or public payers and employers) and/or to patients and/or caregivers.

Levels of Evidence for Consideration by HDAP

Typically, Level 1 evidence will be used for determination of categorization and for the identification of comparators, however, HDAP may consider other levels of evidence if it is felt these lower levels of evidence provide an adequate demonstration of comparative efficacy or toxicity or economic evaluation.

Level	Therapy/Prevention	Economic and decision analyses
1a	SR (with homogeneity*) of RCTs	SR (with homogeneity*) of Level 1 economic studies
1b	Individual RCT (with narrow Confidence Interval)	Analysis based on clinically sensible costs or alternatives; systematic review(s) of the evidence; and including multi-way sensitivity analyses
1c	All or none§	Absolute better-value or worse-value analyses †
2a	SR (with homogeneity*) of cohort studies	SR (with homogeneity*) of Level >2 economic studies
2b	Individual cohort study (including low quality RCT; e.g., <80% follow-up)	Analysis based on clinically sensible costs or alternatives; limited review(s) of the evidence, or single studies; and including multi-way sensitivity analyses
2c	"Outcomes" Research; Ecological studies	Audit or outcomes research
3a	SR (with homogeneity*) of case-control studies	SR (with homogeneity*) of 3b and better studies
3b	Individual Case-Control Study	Analysis based on limited alternatives or costs, poor quality estimates of data, but including sensitivity analyses incorporating clinically sensible variations.
4	Case-series (and poor quality cohort and case-control studies§§)	Analysis with no sensitivity analysis
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on economic theory or "first principles"

*	Homogeneity means a systematic review that is free of worrisome variations (heterogeneity) in the directions and degrees of results between individual studies. Not all systematic reviews with statistically significant heterogeneity need be worrisome, and not all worrisome heterogeneity need be statistically significant. As noted above, studies displaying worrisome heterogeneity should be tagged with a "-" at the end of their designated level.
§	Met when all patients died before the Rx became available, but some now survive on it; or when some patients died before the Rx became available, but none now die on it.
§§	Poor quality cohort study is defined as a study that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both exposed and non-exposed individuals and/or failed to identify or appropriately control known confounders and/or failed to carry out a sufficiently long and complete follow-up of patients. A poor quality case-control study is defined as a study that failed to clearly define comparison groups and/or failed to

<table>
<tr><th>Evaluation Component</th><th>Breakthrough</th><th>Substantial Improvement</th><th>Moderate Improvement</th><th>Slight or No Improvement</th></tr>
<tr><td></td><td colspan="4">
<table>
<tr><td></td><td>measure exposures and outcomes in the same (preferably blinded), objective way in both cases and controls and/or failed to identify or appropriately control known confounders.</td></tr>
<tr><td>†</td><td>Better-value treatments are clearly as good but cheaper, or better at the same or reduced cost. Worse-value treatments are as good and more expensive, or worse and the equally or more expensive.</td></tr>
</table>
The above is based on the Oxford Centre for Evidence-based Medicine Levels of Evidence (May 2001) - produced by Bob Phillips, Chris Ball, Dave Sackett, Doug Badenoch, Sharon Straus, Brian Haynes, Martin Dawes since November 1998.
</td></tr>
<tr><td>Other factors that will be weighted and considered</td><td colspan="4">Other factors that can be considered include some or all of the following:

<u>Clinical factors:</u>

• Duration of usual treatment course
• Success rate
• Geographic site of administration (e.g. institution (acute vs outpatient) vs home)
• Percentage of affected population treated effectively
• Time required to achieve the optimal therapeutic effect
• Route of administration (for example, oral vs injectable, etc.)

<u>Economic/Pharmacoeconomic factors:</u>

• Patient convenience/preference
• Caregivers convenience/preference
• Disability cost avoidance/savings
• Compliance improvements
• Reduction in acute care or institutional healthcare costs</td></tr>
<tr><td>Factors that will <u>not</u> generally be taken into consideration</td><td colspan="4">• The mechanism of action
• A new chemical entity
• A different pharmacokinetic profile</td></tr>
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Appendix 5: Position of Canada's Research-Based Pharmaceutical Companies (Rx&D)
Therapeutic Improvement (TI)

The industry has previously expressed concerns about the mandate of the Therapeutic Improvement Working Group given the Patented Medicine Prices Review Board (PMPRB) has not made its intentions clear with respect to whether or not it proposes to introduce new Guidelines pertaining to Therapeutic Improvement. In addition the PMPRB has not demonstrated the need for such a Working Group, nor did patentees request one.

However, given the PMPRB decided to proceed with this Working Group as part of its Guidelines Consultation Process, Rx&D did agree to participate and with that spirit; recognizes its role in contributing to the information presented in the "tables" of the report.

Participation though was difficult given it has remained unclear as to how definitions or parameters relating to therapeutic improvement along with supporting evidence requirements and sources will be applied and used relative to existing or emerging new price tests within the PMPRB Guidelines.

Furthermore, Rx&D has clearly expressed in previous consultations and discussions with the PMPRB its position on the use of categories by the Board. The industry is of the opinion that the PMPRB would be able to fulfill its mandate of assessing and setting a non-excessive price without the use of categories. The current system of categories employed by the PMPRB for new patented medicines has proven to be unworkable and unnecessary.

Revisions to the definitions and criteria for the existing categories or an expansion of the existing categories to four (4) or more will not address the concerns and issues raised by stakeholders during the current consultation process. The expansion of categories will likely not decrease but rather increase the level of confusion, debate and issues in the assessment of new patented medicines.

Attempting to define innovation or incremental innovation within the confines of product categorization cannot reflect the current medical environment or various stakeholders perspectives. Innovation cannot be defined in broad general reference terms, it varies greatly within therapeutic areas and its margins and reference points are constantly moving as science continues to evolve.

Rx&D recommends the PMPRB refocuses its efforts on developing a system which considers a true definition of excessive in the context of abuse of patent rights as originally intended by Parliament.