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August 17, 2006

Sylvie Dupont
Secretary of the Board
Patented Medicine Prices Review Board
Box L40, Standard Life Centre
333 Laurier Avenue West, Suite 1400
Ottawa, Ontario
K1P 1C1

RE: ***Discussion Guide for the Consultations on the Board's Excessive Price Guidelines*** **– Lilly Canada Comments**

Dear Ms. Dupont,

I am writing to provide comments on behalf of Eli Lilly Canada Inc. (Lilly) with respect to the issues raised in the *Discussion Guide for the Consultations on the Board's Excessive Price Guidelines*, released by the PMPRB in May 2006.

As noted in the attached submission, there is no evidence to suggest that patented drugs are priced excessively. In fact, the prices of patented medicines have not kept pace with inflation. Therefore, changes to the Guidelines that would act to lower prices further are inappropriate. Instead, Canada's pricing regime should be altered to better recognize the value of pharmaceutical innovation to the health care system and the economy. A medicine should only be considered to be priced excessively if it exceeds the prices in designated comparator countries and the CPI-adjusted prices of all other drugs in the therapeutic class. This would be more in keeping with Parliament's original intent when the *Patent Act* was amended and the PMPRB was created.

Lilly trusts that the PMPRB will take our input into consideration as it moves forward with this Guideline consultation process. If you have questions, or require further information, please contact Lauren Fischer at T.: 416-699-7446 or E-mail: fischer_lauren@lilly.com.

Sincerely,

Terry McCool
Vice President, Corporate Affairs

CC David Ricks, President & General Manager, Eli Lilly Canada Inc.
Lauren Fischer, Manager, Government & Economic Affairs, Eli Lilly Canada Inc.

Attachment

***Discussion Guide for the Consultations on the Board's Excessive Price Guidelines* (released May 2006)**
Lilly Canada Comments

BACKGROUND

When Canada's Parliament created the Patented Medicine Prices Review Board (PMPRB), its intention was to ensure that there was not excessive pricing of patented medicines as a result of *Patent Act* amendments that restricted the issuance compulsory licenses. The PMPRB Guidelines and their application deviate significantly from Parliament's original intent; the PMPRB has become, in effect, a price control board. The Guidelines would better reflect Parliament's original intent if "excessive pricing" was defined as a price that exceeds the prices in all relevant markets.

The PMPRB's statutory mandate has been expanding since its inception. For example, the PMRPB has claimed jurisdiction over the prices of patented medicines in the patent pending period. In addition, the PMPRB's definition of "patented medicine" is more expansive than that applied by the Health Canada Patent Register. A drug may be subject to PMPRB price review, yet enjoy none of the intellectual property protection afforded by the Patent Register. The PMPRB has also proposed amendments to the regulations (*Canada Gazette*, December 31, 2005) that would require patentees to file information on introductory prices and price changes in advance. The *Patent Act* limits price reviews to prices at which a medicine "is or has been sold".

The PMPRB stated in 1993 that its objective was that prices, on average, should be at the international median. Since then, the PMPRB has imposed greater regulation on patentees by periodically changing its definition of excessive pricing. For example, in 1994, the PMPRB limited permissible increases to three year changes in the CPI. In 2000, the PMPRB changed the calculation of the US price by averaging in the discounted price to the US Department of Veteran Affairs - a customer that represents only 1.5% of US sales[1]. In 2005, the PMPRB stated that, when the forecast CPI is lower than the actual CPI, patentees would be held to the forecast CPI in the calculation of future MNE prices.

The Guidelines do not have the force of law or regulations. In practice, however, prices are considered to be "excessive" if they exceed the allowable price under the Guidelines. This, in turn, can result in a hearing before a Board panel. Recently, the PMPRB's mechanistic application of the Guidelines has resulted in an unprecedented number of expensive, time-consuming Board panel hearings. This creates delays in the price review process, as the PMPRB is unable to review prices for new drugs when relevant reference drugs are still under review.

When the *Patent Act* was amended, the concern was that patentees would rapidly increase prices. PMPRB data show that this has not occurred - even by the PMPRB's own rigid definition of excessive pricing. By this definition, one would expect some prices would be above, and some below, the international median price. Since 1993, Canadian drug prices have, on average, remained below the international median. In 2005, they were 8% below the international median, on average[2]. In fact,

[1] Danzon P, *Price Comparisons for Pharmaceuticals*, April 1999.
[2] PMPRB Annual Report, 2005

pharmaceutical expenditure in Canada as a share of national income in 2004, as measured by Gross Domestic Product (GDP) is 1.8%, well within the range of values reported for other countries; 2.0% and 1.9% in France and the U.S. and 1.1% in Sweden (OECD Annual Update, 2006), which provides further evidence that Canadians do not spend excessively on pharmaceuticals relative to other major economies.

Moreover, the prices of patented medicines have not kept pace with inflation, despite the rising cost of doing business. The cost of developing new medicines and bringing them to the market has increased. This includes the cost of fulfilling the increasing data requirements from Health Canada, the Canadian Agency for Drugs and Technologies in Health (CADTH) and the PMPRB. At the same time, regulatory hurdles have risen; given the long approval times in Canada, companies have, on average, only eight to ten years to benefit from patent exclusivity[3].

It is also widely acknowledged that Canada's pricing regime represents a classic example of the unintended consequences of regulation. Price review policies that link the prices of new products to those of older products deter manufacturers from lowering the prices of older products. Inflexible application of the regulations with respect to reporting requirements in introductory and subsequent periods may potentially provide incentive for manufacturers to delay product launches or discourage the introduction of programs (free goods, customer care) to benefit patients in cases where there is a risk of artificially lowering average transaction prices which are used to benchmark future price increases.

In general, PMPRB regulations and practices are creating unnecessary complexity and bureaucracy within the process with no incremental benefit to the Canadian public. As a result, compliance is becoming increasingly difficult. Negotiations with the PMPRB are becoming more cumbersome. This is demonstrated by the increasing involvement of legal counsel in the resolution of cases, the increasing number of cases that are being decided at expensive hearings as well as the fact that an entire consulting industry exists around this process. This was not the original intent when the regulations were published.

At the same time, requirements such as bi-annual price reporting for products late in their life-cycle may have been appropriate prior to 1993 when intellectual property protection was less stable and the opportunity to maximize returns was less certain. During this time, manufacturers had greater incentive to adopt excessive pricing practices. These requirements are somewhat onerous in an environment where manufacturers now have certainty with respect to patent protection. They are particularly redundant given market factors such as provincial price controls and reimbursement restrictions which effectively act to prevent excessive pricing anyway.

With new drugs entering various classes, market competition acts to restrain prices. In addition, government interventions already exist to control drug costs/prices at every level, from CADTH at the federal level which includes the Common Drug Review (CDR) process for recommendations with respect to reimbursement of pharmaceuticals, to the provincial drug plans that ultimately make the reimbursement decisions. Given that the mandate of the scientific committees- experts in the fields of therapeutics and health economics- within these decision making bodies is to recommend

[3] Rx&D website, www.canadapharma.org

reimbursement of drugs that provide sufficient clinical and economic value, clearly these are the agencies that are in the best position to make the necessary tradeoffs which ultimately act to prevent manufacturers from pricing excessively if they want to continue to be successful in the public market. The provincial and private drug plans also institute broader reimbursement policies such as mandatory substitution, lowest cost alternative, reference pricing and restrictive access measures which effectively work to control prices. The resulting shift of costs to patients creates an additional level at which market forces act to prevent prices from becoming excessive. And, as noted above, there is no evidence to suggest that the prices of patented drugs are priced excessively. Therefore, changes to the Guidelines that would act to lower prices further are inappropriate.

The process could be greatly simplified if the PMPRB limited its scope to monitoring price increases and accepting the prices of new chemical entities if they do not exceed the prices in the relevant comparator countries.

The existing price regime is contrary to the interests of patentees, taxpayers and patients. New medicines may be introduced later in Canada, or not at all. This is potentially detrimental to patient care and to the health care system, since pharmaceuticals are often substituted for more costly hospital and physician care. In addition, existing regulation has a chilling effect on investment. Pharmaceutical innovation makes a significant contribution to the Canadian economy, resulting in highly-skilled job creation, increased scientific knowledge, economic growth, and the elevation of our international ranking on innovation. However, any investment decision must contemplate the attractiveness of the market where the investment will reside. The pricing regime is an important element in the comparative evaluation of competing investment locations. Restrictions and lack of certainty with respect to pricing work to discourage commercial investment in Canada, due to their significant impact on returns to the innovator, which support ongoing operations and innovation.

Canada's pricing regime should be altered to better recognize the value of pharmaceutical innovation to the health care system and the economy. A medicine should only be considered to be priced excessively if it exceeds the prices in designated comparator countries and the CPI-adjusted prices of all other drugs in the therapeutic class.

ISSUES FOR DISCUSSION

ISSUE 1: Is the current approach to the categorization of new patented medicines appropriate?

Question 1: Are the new patented drug categories and their definitions appropriate?

The current categories and their definitions do not allow returns to pharmaceutical innovation that are commensurate with its value to society. As noted above, pharmaceuticals are, in many instances, a cost-effective alternative to hospital or physician care. In addition, pharmaceutical innovation makes a significant contribution to the Canadian economy. And though the cost of developing and bringing new drugs to market has been rising over time, the prices of patented drugs in Canada have not kept up with inflation.

The Health Canada priority review mechanism is relevant in this context. Health Canada has defined specific criteria which must be met in order to be granted "Priority Review Status"[4].

Health Canada has extensive experience in risk-benefit assessments on product safety and efficacy. Moreover, it has the historical perspective of having reviewed other compounds within the same therapeutic class, and has access to non-published comparator trials. Yet, a significantly larger number of medicines have met Health Canada's standard for priority review than have been accorded Category 2 ("breakthrough/substantial improvement") status by the PMPRB[5]. The PMPRB's approach could be better informed with reference to other accepted standards of innovation.

Question 2: Is it important to distinguish a medicine that offers "moderate therapeutic improvement" from a medicine that provides "little or no therapeutic improvement"? If yes, why is it important? If not, why not?

Distinguishing a medicine that offers "moderate improvement" from a medicine that provides "little or no therapeutic improvement" would represent an improvement over the current categorization system. Contrary to the Board's conclusions during prior consultations on this matter, it is possible to implement a system that makes this kind of distinction.

In fact, a system that recognizes varying levels of therapeutic value is currently in place in France. Once a product is approved for sale in France, the French Transparency Committee determines the added medical value of the product, taking into account available comparators, indication and forecasted population. This Committee issues two ratings for each new drug:

1. SMR (*service medical rendu*), which is used for determining the level of reimbursement, rates the "importance" of the disease or condition and the drug in treating that disease or condition. The SMR includes up to six levels of "importance".

2. ASMR (*amelioration de services medical rendu*), which is used for price negotiations, considers the improvement offered by the new drug:
    - ASMR I - Major medical advance
    - ASMR II - Important improvement in terms of efficacy/ safety
    - ASMR III - Modest progress
    - ASMR IV - Minor progress
    - ASMR V- No therapeutic progress, but may be reimbursed
    - ASMR VI - No therapeutic progress, but not reimbursed

Question 3: If the answer to question 2 above is yes, on what basis would a new medicine that offers "moderate therapeutic improvement" be distinguished from a new medicine that provides "little or no therapeutic improvement"?

As noted above, Health Canada has a well-established priority review policy. Specifically, the policy applies to a drug submission for a serious, life-threatening or severely debilitating illness or condition for which there is substantial evidence of clinical effectiveness that the drug provides:

[4] Health Canada website, "Priority Review of Drug Submissions", www.hc-sc.gc.ca
[5] Bain and Company, *The Impact on Canada of Pharmaceutical Regulations and Pricing Policies*, 2004.

- Effective treatment, prevention or diagnosis of a disease or condition for which no drug is presently marketed in Canada; or

- A significant increase in efficacy and/or significant decrease in risk such that the overall benefit/risk profile is improved over existing therapies, preventatives or diagnostic agents for a disease or condition that is not adequately managed by a drug marketed in Canada.

In defining whether a condition is "serious", Health Canada considers several factors, such as survival, day-to-day functioning or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one.

In the conduct of Health Canada's benefit/risk evaluation, a significant clinical improvement may consist of:

- Improvement in one or more of the serious outcomes of the condition on which the effect is claimed;
- A favourable effect on a serious symptom or manifestation of the condition for which there is no existing therapy;
- A clinical benefit in individuals unable to tolerate, or unresponsive to, existing therapies;
- Demonstration of effectiveness in combination with other critical agents, where no information is available or where combined use with existing therapy(ies) is not feasible due to safety or efficacy considerations;
- Demonstration that the new agent is able to provide clinical benefits that are similar to existing therapies while a) avoiding serious toxicity present in existing therapies and/or b) avoiding less serious toxicity, common to the therapy, which results in the discontinuation of treatment of a serious disease; and,
- The ability to provide similar clinical benefit to existing therapies while demonstrating improvement in a factor that has been shown to be significant during the conduct of the pivotal trial.

These considerations better reflect the true value of the innovation from the individual clinical perspective. According to Sackett et al (1996)[6], this perspective is just as important as external clinical evidence which, "can inform, but can never replace, individual clinical expertise, and it is this expertise that decides whether the external evidence applies to the individual patient at all, and if so, how it should be integrated into a clinical decision."

Of particular note is the fact that Health Canada's priority review process - unlike the PMPRB's system of categorization - accords significance to a medicine's mechanism of action. In any disease state, segments of the affected population will not respond to a particular class of medications, or will have intolerance or contraindications. Medications with a novel mechanism of action add value by offering the potential to remit symptoms in these populations.

[6] Sackett DL. Rosenberg WMC. Gray JAM. Haynes RB. Richardson WS. Evidence based medicine: What it is and what it isn't. It's about integrating individual clinical expertise and the best external evidence. [Journal: Editorial] British Medical Journal. Vol. 312(7023)(pp 71-72), 1996.

ISSUE 2: Is the current approach used to review the introductory prices of new patented medicines appropriate?

Question 1: Are the price tests currently used to review the prices of new medicines in the various categories appropriate for that category? Why? Why not? If not, how could these tests be amended to improve their appropriateness?

For almost all new patented drugs, the introductory price cannot exceed the range of prices in the therapeutic class – prices that have not kept pace with inflation. As a result, new products are entering the market at lower prices in nominal and real terms. This is confirmed by PMPRB data for category 3 drugs, which indicate that, in most years, the majority of category 3 drugs have been priced more than 10% below the maximum allowable price permitted by the Guidelines. As demonstrated by the PMPRB's own figures in its 2005 annual report, the market itself is an appropriate restraint on pharmaceutical prices[7]. The evidence suggests that the Guidelines should allow for higher prices, which would better reflect the value of pharmaceutical innovation. This, in turn, would be more in keeping with Parliament's original intent when the *Patent Act* was amended.

The therapeutic class comparison (TCC) test could be improved via revisions to address situations where:

- the comparator products represent either an older class of medicines or a substantially different method of treating a condition that does not appropriately compare to the action of the new drug; or
- the comparator product prices have not been CPI-adjusted such that the prices do not adequately reflect increases over time in the cost of operations and R&D.

In each of these cases, appropriate modifications to the TCC test should be made, which may include removing these products from the list of comparators, or applying appropriate CPI adjustments to the current prices of the comparator products. As per the current Guidelines, if it is determined that there are no appropriate comparators, the International Price Comparison (IPC) test should apply.

The Alertec precedent is a case in point where the PMPRB determined that the TCC test was inappropriate because the comparators were "older drugs and, although used in the treatment of narcolepsy, are not primarily used for this indication." The flexibility and discretion reflected in this decision represent a more appropriate approach to the application of the Guidelines than that which has been in evidence more recently.

Question 2: If you think that medicines that offer "moderate therapeutic improvement" should be distinguished from medicines that provide "little or no therapeutic improvement" what would the appropriate new price test be?

Such medicines should be entitled to the international median price; in other words, the appropriate price test is the IPC test. This is a simple and practical approach, which is used currently in situations where there are no appropriate comparators for a category 3 product.

[7] PMPRB Annual Report, 2005

Question 3: For price review purposes, "comparable medicines" are medicines that are clinically equivalent. Do you have any suggestions as to principles or criteria that should be used in determining how to identify "comparable medicines" for the purpose of inclusion in the above price tests?

For price review purposes, comparable medicines should include medicines with an approved indication that is the same as the primary indication of the new medicine and/or evidence that the medicine is used in clinical practice to treat that indication. Comparable medicines should be seen as appropriate alternatives to the new medicine that reflect the current standard of care in the treatment of that primary indication.

The ATC code should not be used as a criterion for selection of comparators. The ATC system was originally developed with the objective to become the international standard for drug utilization studies. The system was never intended for use in the establishment of comparators by pricing and reimbursement authorities. Its use for this purpose poses important problems. First, the system lacks transparency. The members of the ATC advisory board are not publicly known and ATC decision letters lack a detailed rationale. The minutes of advisory board meetings are not made available to manufacturers. Written appeals are possible, but very rarely successful. Secondly, the system lacks flexibility. Due to advances in clinical knowledge and the introduction of new medicines, classes originally set out in the ATC system can become outdated. As a result, the determination of comparable medicines should be based solely on indication and clinical use, with appropriate adjustments made based on the clinical relevance of the comparator and inflation, as discussed above.

Question 4: Under the current Guidelines, Board Staff compares the Canadian average transaction price of the new medicine to the prices of the same medicine sold in the seven countries listed in the Regulations. However, Section 85(1) of the *Patent Act* states that the Board should take into consideration "the prices of other comparable medicines in other countries". Should the Guidelines address this factor? If so, how could this factor be incorporated into the price test for new medicines?

Where the initial test determines that the price of a drug exceeds the range of prices in the therapeutic class and the international median, the prices of comparable medicines in other countries should be considered. Indeed, the PMPRB has used this approach in the price reviews of Humalog and Viread.

* * *

With reference to the discussion under Issue 2 in the *Discussion Guide* (p. 11), the following statement is of note:

... in 65% of the cases in 2004, a category 3 DIN could have achieved a "price premium" above what would have been allowed for a category 2 (breakthrough or substantial improvement) drug and it still would have been determined to have been priced within the Board's current Guidelines.

This statement is false and misleading. Category 2 new medicines are allowed the higher of the median international price and the highest price in the therapeutic class. It may be true that in some

cases a category 3 new medicine can achieve the same price as if it had been declared category 2. By definition, however, a category 3 new medicine can never achieve a price premium over a category 2 new medicine. The inclusion of the above statement in a public document is misleading and potentially prejudicial. The statement should, therefore, be publicly retracted.

ISSUE 3: Should the Board's Guidelines address the direction in the *Patent Act* to consider "any market"?

Question 1: Given the price variations be provinces/territories and classes of customer illustrated in the previous figures, is it appropriate for the Board to only consider an ATP calculated based on the total revenues from the sales for all provinces/territories and all classes of customer? Why? Why not?

Question 2: If the current ATP calculation is not appropriate, should the Board review the prices to the different classes of customers and/or the different provinces and territories for all DINs? Or should this level of review be done on a case-by-case basis, where there is a significant variation in the prices charged?

It is most efficient for the Board to review prices at the Canadian aggregate level. As illustrated by the data presented under Issue 3 of the *Discussion Guide*, the current system of review is already adequate. As outlined in Figures 9 and 10, the vast majority of drug prices run up to 5% below the established MNE price, whether reviewed by province or customer class.

The current Guidelines provide sufficient clarity on what variables should be included in determining average selling price. When one considers the volume of data that is currently provided in terms of net sales, quantity, international data, first 30 days sales and a variety of forms, the PMPRB has ample data available to determine if prices comply with regulations. Any additional reporting volume would not change the determination of the average selling price, but would generate a significant amount of additional non-value added work for both the manufacturer and the PMPRB reviewers. If the PMPRB requires further clarity in how the average selling price was determined, it can currently seek this information from the manufacturer on an as-needed basis.

Finally, it should be note that the current Guidelines allow for hospitals to benefit from preferred pricing arrangements, based on a long-standing tender system. This system has provided substantial savings to the benefit of Canadian patients. This system should be maintained so that hospitals can continue to achieve these cost savings.