PATENTED MEDICINE PRICES REVIEW BOARD

IN THE MATTER OF the *Patent Act*, R.S.C. 1985, c. P-4, as amended

AND IN THE MATTER OF Shire BioChem Inc., (the "Respondent") and the medicine "Adderall XR"

STATEMENT OF ALLEGATIONS OF BOARD STAFF

INTRODUCTION

1. This Statement of Allegations results from an investigation by Board Staff into the prices of Adderall XR, a patented medicine sold in Canada by Shire BioChem Inc. ("Shire") in 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, and 30 mg capsules (DINs 02248808, 02248809, 02248810, 02248811, 02248812 and 02248813). According to publicly available information in 2005, Shire sells Adderall XR at a price of $2.7500 per capsule for all six DINs. **(Attachment 1)**

THE MEDICINE

2. Adderall XR is a medicine indicated for the treatment of Attention Deficit Hyperactivity Disorder ("ADHD"). **(Attachment 2)** It is an extended release formulation of mixed salts amphetamine capsules (amphetamine sulfate, amphetamine aspartate, dextroamphetamine sulfate, and dextroamphetamine saccharate), which represents a new active substance. Its 4th level in the Anatomical Therapeutic Chemical ("ATC") Classification System is N06BA known as: Nervous System; Psychoanaleptics; Psychostimulants, Agents used for ADHD and Nootropics; Centrally Acting Sympathomimetics. It is the 4th entry in its 4th level ATC class to be introduced in Canada.

3. Shire began selling Adderall XR (10 mg, 20 mg, and 30 mg) in Canada under the Special Access Program ("SAP") on September 12, 2002.

4. Health Canada issued a Notice of Compliance for Adderall XR (5 mg, 10 mg, 15 mg, 20 mg, 25 mg, and 30 mg) on January 23, 2004. **(Attachment 3)**

5. On April 13, 2004, Shire began selling three additional strengths of Adderall XR (5 mg, 15 mg, and 25 mg).

6. On February 9, 2005, Health Canada suspended the Notice of Compliance for Adderall XR (5 mg, 10 mg, 15 mg, 20 mg, 25 mg, and 30 mg), due to safety concerns, but reinstated the Notice of Compliance on August 26, 2005, following which Shire resumed selling all six DINs of Adderall XR. **(Attachment 4)**

7. Shire issued a revised product monograph for Adderall XR, dated August 26, 2005, which provides additional clarifications to the warning statements for this medicine. **(Attachment 5)**

THE PATENT

8. Canadian Patent No. 2,348,090 ("the '090 patent") pertains to Adderall XR. **(Attachment 6)** This patent was granted to Shire Laboratories Inc., USA, on April 13, 2004 and will expire on October 20, 2019. Shire is the licensee of the '090 patent and is for the purposes of the Patented Medicine Prices Review Board ("PMPRB") considered as the Canadian patentee.

THE REGULATORY FILINGS

9. Following issuance of the '090 patent in April 2004, Shire filed, on June 8, 2004, in accordance with the *Patented Medicines Regulations, 1994* ("Regulations"), its price and sales information for Adderall XR (10 mg, 20 mg, and 30 mg) for the period from September 12, 2002 to May 12, 2004. Shire also filed its price and sales information for the first 30 days of sales of Adderall XR (5 mg, 15 mg, and 25 mg) in Canada, namely the period from April 13, 2004 to May 12, 2004. Shire has since continued to file its price and sales information for all six strengths of Adderall XR as per the Regulations.

APPLICABLE GUIDELINES

10. Following the procedures outlined in the PMPRB's Compendium of Guidelines, Policies and Procedures for new medicines, Board Staff referred the medicine Adderall XR to the Human Drug Advisory Panel ("HDAP") for its review during a meeting held on October 6, 2004. The HDAP was asked for its recommendation as to the categorization and the appropriate comparable medicines and comparable dosage regimens for the comparable medicines.

Category

11. Section 3 of Chapter 3 - Scientific Review Procedures ("Scientific Review Procedures") provides the following guidance with respect to determining categorization for a new drug product:

    3.1 A Category 1 drug product is a new 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.

3.2 A 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.

3.3 A 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.

12. In a report dated October 6, 2004, the HDAP recommended that Adderall XR (10 mg, 20 mg, and 30 mg) be classified as Category 3 drug products as they provide moderate, little or no therapeutic advantage over other available therapies for symptoms associated with ADHD. **(Attachment 7)** As the 5 mg, 15 mg, and 25 mg strengths were introduced on the Canadian market in April 2004 (more than a year and a half after the introduction of the 10 mg, 20 mg, and 30 mg strengths), they were classified as Category 1 drugs products, as they represent new DINs of an existing or comparable dosage form of an existing medicine.

Comparable Medicines and Dosage Regimens

13. With respect to the selection of comparable medicines, Section 9 of the Scientific Review Procedures provides as follows:

9.1 Comparable drug products are selected by identifying both comparable medicines and comparable dosage forms.

9.2 Comparable medicines are clinically equivalent in addressing the approved indication that is anticipated to be the primary use of the new drug product under review. The PMPRB refers to the World Health Organization (WHO) Drug Utilization Research Group's Anatomical Therapeutic Chemical Classification System (ATC) as the starting point for the selection of comparable medicines.

9.3 Comparable medicines will typically be those identified under the ATC classification system at the sub-class level above the single chemical substance. This will normally be the fourth sub-class level. If the appropriate comparable medicines are not identified at this level, then the PMPRB may choose from the next higher sub-class or another sub-class. In some instances, it may be appropriate to select from the fifth or single chemical substance level. Selection criteria will include the indication and therapeutic use, and could include other factors such as mode of action, spectrum of activity or chemical family.

9.4 The PMPRB may omit from the comparison a chemical substance or a drug product of the same ATC therapeutic class as the drug product under review if, in the panel's or Board Staff's opinion, it is not clinically equivalent or is unsuitable for comparison. For example, drug products with primary uses other than to address the indication anticipated to be the primary use of the drug product under review may be omitted from the comparison. Similarly, the PMPRB may choose to add products from other ATC classes if they are clinically equivalent for the appropriate indication to the drug product under review.

14. Based on the scientific information available to the HDAP at the time of its review, the HDAP recommended the following comparable medicines and dosage regimens:

Adderall XR (mixed salts amphetamine) (mg)	Ritalin (methyl-phenidate) (mg)	Ritalin SR (methyl-phenidate) (mg)	Dexedrine (dextro-amphetamine) (mg)	Concerta (methyl-phenidate) (mg)
10	20	20	15	18
20	40	40	30	36
30	60	60	45	54

The Maximum Non-Excessive Prices for Adderall XR (10 mg, 20 mg, and 30 mg)

15. Chapter 1 - Excessive Price Guidelines ("Guidelines") sets out the appropriate price tests for a Category 3 new drug product as follows:

7.1 The price of a new or existing patented drug product will be presumed to be excessive if it exceeds the prices of the same medicine sold in all countries listed in the *Regulations*. These prices will be determined using the International Price Comparison Test described in Schedule 3.

8.5 Category 3 New Drug Product

In addition to the Guideline applicable to all patented drug products detailed in Section 7, the introductory price of a Category 3 new drug product will be presumed to be excessive if it exceeds the prices of all of the comparable drug products based on a Therapeutic Class Comparison Test (Schedule 2).

8.6 When it is inappropriate or impossible to conduct a Therapeutic Class Comparison Test, Board Staff will give primary weight to the median of the international prices identified in an International Price Comparison Test (Schedule 3) to determine if the introductory price of the new DIN is excessive.

8.7 Unless the introductory price of the new DIN is outside the Guidelines, it will establish the benchmark price. If the introductory price exceeds the Guidelines, the maximum non-excessive price will establish the benchmark price. Thereafter, the price will be reviewed using the test applicable to existing DINs.

16. As per the above Guidelines, Board Staff conducted International Price Comparison ("IPC") Tests on the 10 mg, 20 mg, and 30 mg capsules of Adderall XR and the results, based on Shire's regulatory filings, indicated that during the introductory period, the 10 mg, 20 mg, and 30 mg capsules were sold in 1 country (USA) listed in the Regulations, and Canada had the lowest publicly available ex-factory price. **(Attachment 8)**

17. As per the above Guidelines, Board Staff also conducted Therapeutic Class Comparison ("TCC") Tests comparing each of the three strengths of Adderall XR (10 mg, 20 mg, and 30 mg) to Dexedrine, Ritalin, and Ritalin SR. Concerta (methylphenidate), one of the comparable medicines recommended by HDAP, was excluded from the TCC Tests since it was not available in Canada at the time of introduction of Adderall XR (10 mg, 20 mg, and 30 mg) in 2002. The results of the TCC Tests **(Attachment 9)** were as follows:

a) For the 10 mg strength of Adderall XR, the results of the TCC Test indicated that the introductory price per capsule exceeded the maximum non-excessive price ("MNE") of $0.5048 per capsule by more than 445% in 2002.

b) For the 20 mg strength of Adderall XR, the results of the TCC Test indicated that the introductory price per capsule exceeded the MNE price of $0.9672 per capsule by more than 180% in 2002.

c) For the 30 mg strength of Adderall XR, the results of the TCC Test indicated that the introductory price per capsule exceeded the MNE price of $1.4508 per capsule by more than 85% in 2002.

The Maximum Non-Excessive Prices for Adderall XR (5 mg, 15 mg, and 25 mg)

18. The appropriate price tests for a Category 1 new drug product are set out in subsection 7.1 of the Guidelines, referred to above, and section 8.3 of the Guidelines which provides as follows:

8.3 In addition to the Guideline applicable to all patented drug products detailed in Section 7, the introductory price of a Category 1 new drug product will be presumed to be excessive if it does not bear a reasonable relationship to the average price of other DINs of the same medicine in the same or comparable dosage forms (Schedule 1).

When the above methodology is not considered adequate or appropriate, Board Staff may conduct a Therapeutic Class Comparison Test (Schedule 2) to determine if the introductory price of the new DIN is excessive. This could be relevant if, for example, the new DIN has a therapeutic use or dosage regimen that differs materially from the other DINs of the same or comparable dosage forms of the medicine.

While the introductory price of a Category 1 DIN will normally be compared against DINs of the same patentee, Board Staff may consider it appropriate in some instances to include DINs of other patentees. (For example, another voluntary licensee of the same patent as that pertaining to the new drug product, or a patentee marketing a drug product containing the same active ingredient as the new drug product but for which a different patent pertains.)

19. As per the above Guidelines, Board Staff conducted IPC Tests on the 5 mg, 15 mg, and 25 mg capsules of Adderall XR, and the results, based on Shire's regulatory filings, indicated that the 5 mg, 15 mg, and 25 mg capsules were sold in 1 country (USA) listed in the Regulations, and Canada had the lowest publicly available ex-factory price. **(Attachment 8)**

20. As per the above Guidelines, Board Staff also conducted Reasonable Relationship ("RR") Tests comparing Adderall XR (5 mg, 15 mg, and 25 mg) to Adderall XR (10 mg, 20 mg and 30 mg). The results of the RR Tests **(Attachment 10)** were as follows:

    i) For the 5 mg strength of Adderall XR, the results of the RR Test indicated that the introductory price per capsule exceeded the MNE price of $0.2901 per capsule by more than 845% for the period April 2004 to June 2004.

    ii) For the 15 mg strength of Adderall XR, the results of the RR Test indicated that the introductory price per capsule exceeded the MNE price of $0.7816 per capsule by more than 250% for the period April 2004 to June 2004.

    iii) For the 25 mg strength of Adderall XR, the results of the RR Test indicated that the introductory price per capsule exceeded the MNE price of $1.2732 per capsule by more than 115% for the period April 2004 to June 2004.

21. By letter dated November 29, 2004, Board Staff advised Shire of the results of the price review of Adderall XR (5 mg, 10 mg, 15 mg, 20 mg, 25 mg, and 30 mg) and that an investigation was commenced into the introductory price of Adderall XR. **(Attachment 11)**

22. In response, Shire filed additional material on January 28, 2005 with Board Staff requesting the expansion of the therapeutic class. **(Attachment 12)**

23. In light of the additional material filed by Shire, Board Staff referred the medicine, Adderall XR (5 mg, 10 mg, 15 mg, 20 mg, 25 mg, and 30 mg) to the HDAP for a further review and recommendations.

24. In a report dated September 6, 2005, the HDAP maintained its previous recommendations found in its initial report of October 6, 2004. **(Attachment 13)**

25. By letter dated November 15, 2005, Board Staff advised Shire that it had completed its investigation of Adderall XR (5 mg, 10 mg, 15 mg, 20 mg, 25 mg, and 30 mg) and that the prices of each of these strengths continued to be excessive under the Guidelines. **(Attachment 14)**

OTHER

26. Board Staff reserves the right to make such other allegations and submissions and introduce other additional documents as Board Staff may advise and the Board may permit.

27. Pursuant to section 86 of the *Patent Act*, a hearing shall be held in public unless the Board orders otherwise. Board Staff submits that any hearing conducted by the Board into the price of Adderall XR should be held in public and, subject to orders of the Board, all information and documents filed should form part of the public record.

ORDER REQUESTED

28. It is respectfully submitted that there are grounds for the Board to conclude pursuant to section 83 of the *Patent Act* that Shire is selling or has sold the medicine known as Adderall XR in any market in Canada at prices which are or were excessive.

29. Board Staff seeks the issuance of an Order as against Shire, the terms of which would be as follows:

a) The maximum non-excessive prices of Adderall XR (10 mg, 20 mg, and 30 mg) in Canada for the period September 12, 2002 to December 31, 2005 inclusive shall be as follows:

Adderall XR 10 mg	Price/Unit	Adderall XR 20 mg	Price/Unit	Adderall XR 30 mg	Price/Unit
Reporting Period	MNE	Reporting Period	MNE	Reporting Period	MNE
Sep02-Dec02	$0.5048	Sep02-Dec02	$0.9672	Sep02-Dec02	$1.4508
Jan03-Dec03	$0.5189	Jan03-Dec03	$0.9943	Jan03-Dec03	$1.4914
Jan04-Dec04	$0.5280	Jan04-Dec04	$1.0117	Jan04-Dec04	$1.5175
Jan05-Dec05	$0.5356	Jan05-Dec05	$1.0262	Jan05-Dec05	$1.5393

b) The maximum non-excessive prices of Adderall XR (5 mg, 15 mg, and 25 mg) in Canada for the period April 13, 2004 to December 31, 2005 inclusive shall be as follows:

Adderall XR 05 mg	Price/Unit	Adderall XR 15 mg	Price/Unit	Adderall XR 25 mg	Price/Unit
Reporting Period	MNE	Reporting Period	MNE	Reporting Period	MNE
Apr04-Dec04	$0.2898	Apr04-Dec04	$0.7809	Apr04-Dec04	$1.2720
Jan05-Dec05	$0.2950	Jan05-Dec05	$0.7950	Jan05-Dec05	$1.2949

c) The maximum non-excessive prices of Adderall XR (5 mg, 10 mg, 15 mg, 20 mg, 25 mg, and 30 mg) in Canada in future years shall be calculated in accordance with the Guidelines.

d) In accordance with subsection 83(1) of the *Patent Act*, Shire shall cause the maximum prices at which it sells Adderall XR in Canada to be reduced to the maximum non-excessive prices effective on or before 30 days from the date of the Board's Order.

e) In accordance with subsection 83(2) of the *Patent Act*, Shire shall offset the amount of excess revenues estimated to have been derived by Shire from the sale of Adderall XR (10 mg, 20 mg, and 30 mg) at excessive prices from September 12, 2002 until the date on which the price reductions referred to in paragraph d) above come into effect:

i) With respect to the period from September 12, 2002 to June 30, 2005, Shire shall pay to Her Majesty in right of Canada,

within 30 days of the date of the Board's Order, an amount equal to the amount set out in **Attachment 15**; and

ii) With respect to the period from July 1, 2005 to the date on which the price reductions referred to in paragraph d) come into effect, Shire shall pay to Her Majesty in right of Canada, a further amount equal to the amount of the excess revenues estimated by the Board to have been derived by Shire from the sales of Adderall XR (10 mg, 20 mg, and 30 mg) at excessive prices and make the payment within 30 days of receipt of a notification from the Board of its estimate of excess revenues based on the information filed in response to paragraph g) below.

f) In accordance with subsection 83(2) of the *Patent Act*, Shire shall offset the amount of excess revenues estimated to have been derived by Shire from the sale of Adderall XR (5 mg, 15 mg, and 25 mg) at excessive prices from April 13, 2004 until the date on which the price reductions referred to in paragraph d) above come into effect:

i) With respect to the period from April 13, 2004 to June 30, 2005, Shire shall pay to Her Majesty in right of Canada, within 30 days of the date of the Board's Order, an amount equal to the amount set out in **Attachment 15**; and

ii) With respect to the period from July 1, 2005 to the date on which the price reductions referred to in paragraph d) come into effect, Shire shall pay to Her Majesty in right of Canada, a further amount equal to the amount of the excess revenues estimated by the Board to have been derived by Shire from the sale of Adderall XR (5 mg, 15 mg, and 25 mg) at excessive prices and make the payment within 30 days of receipt of a notification from the Board of its estimate of excess revenues based on the information filed in response to paragraph g) below.

g) Shire shall, within 30 days of the date of the Board's Order:

i) Notify federal/provincial/territorial ministers of health or their representatives and all customers of the price decreases as required by the Board's Order (a copy of which shall be included in such notifications) and the effective date of such price decreases;

ii) Submit copies of the above-noted notifications and any other notice to the Board; and

iii) Provide to the Board information concerning the quantity of Adderall XR (5 mg, 10 mg, 15 mg, 20 mg, 25 mg, and 30 mg) sold and either the average price per package or the net revenue from sales of all six strengths of Adderall XR in Canada, in the same form as required by subsection 4(1) of the Regulations for the period July 1, 2005 to the date on which the price reductions referred to in paragraph d) come into effect.

Dated at Ottawa this 11th day of January 2006.

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LIST OF ATTACHMENTS

Attachment 1	Pharmaceutical Product Reference Price Listing (2005) for Adderall XR
Attachment 2	Product monograph for Adderall XR dated March 22, 2004
Attachment 3	Notice of Compliance - Prescription Products for Human Use, Jan 1 - Dec 31, 2004
Attachment 4	Suspension of Notice of Compliance on February 9, 2005 and reinstatement on August 26, 2005
Attachment 5	Product monograph for Adderall XR dated August 26, 2005
Attachment 6	Canadian Patent No. 2,348,090 granted April 13, 2004
Attachment 7	HDAP New Medicine Review dated October 6, 2004
Attachment 8	Adderall XR - International Prices
Attachment 9	Adderall XR - Therapeutic Class Comparison Test
Attachment 10	Adderall XR - Reasonable Relationship Test
Attachment 11	Letter dated November 29, 2004 from Board Staff to Shire Biochem Inc.
Attachment 12	Letter and supplementary information dated January 28, 2005 from Shire Biochem Inc. to Board Staff
Attachment 13	HDAP New Medicine Review dated September 6, 2005
Attachment 14	Letter dated November 15, 2005 from Board Staff to Shire Biochem Inc.
Attachment 15	Adderall XR - Calculation of Excess Revenues