SEVERED

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 Amgen Canada Inc., (the "Respondent") and the medicine "Neulasta"

STATEMENT OF ALLEGATIONS OF BOARD STAFF

INTRODUCTION

1. This Statement of Allegations results from an investigation by Board Staff into the price of Neulasta (DIN 02249790), a patented medicine currently sold in Canada by Amgen Canada Inc. ("Amgen"). Neulasta is sold in Canada in a 0.6 mL single-use syringe of 10 mg/mL solution. According to publicly available information in 2008, Amgen sells Neulasta in Canada at a price of $2,380.00 per syringe (Liste des médicaments de l'Association québécoise des pharmaciens propriétaires, February 2008, **Attachment 1**).

THE MEDICINE

2. Neulasta is a new active substance (pegfilgrastim) indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with cancer receiving myelosuppressive chemotherapy (Neulasta Product Monograph, **Attachment 2**). Neulasta is a long-acting form of an existing medicine, Neupogen (filgrastim), and is administered as a single injection per course of chemotherapy.

3. Health Canada issued a Notice of Compliance for Neulasta (a copy of which is included as **Attachment 3**) to Amgen Canada Inc. ("Amgen") on March 12, 2004. Amgen began selling Neulasta in Canada on April 12, 2004.

THE PATENTS

4. Canadian Patents Nos. 2,178,752; 1,297,004; 1,339,071; 1,312,569; 1,297,005; and 1,341,537 pertain to Neulasta. Copies of the cover page and abstract of each of these patents are included as **Attachment 4**. The most recently issued of these patents is Patent No. 1,341,537 (the '537 patent) which was granted to Kirin-Amgen Inc. U.S. on July 31, 2007 and will expire on July 31, 2024.

5. Amgen is, for the purposes of the Patented Medicine Prices Review Board (the "PMPRB"), considered the Canadian patentee.

6. In accordance with the *Patented Medicines Regulations* (the "Regulations"), Amgen began reporting price and sales information for Neulasta on May 28, 2004 and has continued to report its price and sales information in accordance with the Regulations up to the present date.

FACTORS SET OUT IN SUBSECTION 85 (1) OF THE *PATENT ACT*

7. Subsection 85(1) of the *Patent Act* (the "Act") sets out the factors the Board shall take into consideration in determining whether a medicine is being or has been sold at an excessive price in any market in Canada :

> In 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 prices 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; and
>
> (e) such other factors as may be specified in any regulations made for the purposes of this subsection

8. In accordance with the factors set out in subsection 85(1) of the Act, the Board, following considerable deliberation and consultation with all stakeholders pursuant to subsection 96(5) of the Act, published the Board's Compendium of Guidelines, Policies and Procedures (the "Guidelines"). Although the Guidelines are not binding on the Board, Board Staff submits that it is appropriate, in the case at bar, for the Board to give due consideration to its Guidelines to establish an approach and methodology in applying the factors set out in subsection 85(1) of the Act to determine if Neulasta is being or has been sold at an excessive price in Canada.

THE SCIENTIFIC REVIEW PROCESS

9. Following the procedures outlined in the Guidelines for new active substances, Board Staff referred Neulasta to the Human Drug Advisory Panel (the "HDAP") for its review. The HDAP provided its recommendation as to the categorization of the medicine, the appropriate comparable drug products and the comparable dosage regimens for the comparable drug products.

SEVERED

A. Category

10. Section 3 of Chapter 3 of the Guidelines - Scientific Review Procedures (the "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.

11. In a report dated October 6, 2004, the HDAP recommended that Neulasta be classified as a Category 3 new drug product as it represents a new DIN of a new chemical entity that provides moderate, little or no therapeutic advantage over comparable medicines (HDAP New Medicine Review, October 6, 2004, **Attachment 5**).

B. Comparable Drug Products and Dosage Regimens

12. With respect to the selection of comparable drug products, 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.

SEVERED

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.

9.5 For each comparable medicine identified, drug products of the same or comparable dosage form as the drug product under review will generally be selected. Schedule 7 lists the comparable dosage forms that the PMPRB uses to identify comparable drug products.

9.6 When comparable dosage forms cannot be identified, other dosage forms may be used if these dosage forms address the appropriate indication and have a clinically equivalent effect.

13. Based on the scientific information available to the HDAP at the time of its reviews and the above Scientific Review Procedures, the HDAP recommended Neupogen as the most appropriate comparator for Neulasta (HDAP New Medicine Review, October 4, 2004, **Attachment 5**). Neupogen is of the same 4th level ATC subclass as Neulasta, shares the same indication and is clinically comparable in addressing the approved indication according to clinical trials.

14. The HDAP recommended the following comparable dosage regimens for both drug products (HDAP New Medicine Review, October 9, 2007, **Attachment 6**):

Name	Comparable Dosage Regimen	Comparable Quantities Per Course of Treatment
Neulasta	A single 6 mg injection per chemotherapy cycle	A single 6 mg injection per chemotherapy cycle
Neupogen	Single daily injections of 5 mcg/kg	Single daily injections of 5 mcg/kg for 11 days (or 3.85 mg) per chemotherapy cycle*

* 70Kg adult used for comparison

THE MAXIMUM NON-EXCESSIVE ("MNE") PRICE FOR NEULASTA

15. The Guidelines set out various price tests that are used to determine the MNE price of the drug product under review. Drug products that are sold at a price that is above the MNE price are presumed to be excessive within the meaning of the Guidelines.

SEVERED

A. Prices at which Neulasta has been Sold in Canada

16. Subsection 85(1)(a) of the Act requires the Board to take into consideration the prices at which the medicine has been sold in the relevant market.

17. Based on the regulatory filings by the patentee, Board Staff calculated the Average Transaction Price ("ATP") of Neulasta in Canada for the introductory period (April 2004 to June 2004) and for each subsequent period to be as follows:

Reporting Period	Price/ 6 mg syringe
	ATP
Apr04-Jun04	**- SEVERED -**
Jul04-Dec04	**- SEVERED -**
Jan05-Dec05	**- SEVERED -**
Jan06-Dec06	**- SEVERED -**
Jan07-Dec07	**- SEVERED -**
Jan08-Dec08	**- SEVERED -**

B. Prices at which other Medicines in the Same Therapeutic Class as Neulasta have been Sold in Canada

18. Subsection 85(1)(b) of the Act requires the Board to take into consideration the prices at which other medicines in the same therapeutic class have been sold in the relevant market. The Therapeutic Class Comparison ("TCC") Test compares the price of the drug product under review with the price of drug products that are clinically equivalent and sold in the same market at prices that the PMPRB considers not to be excessive. Comparable drug products are first selected and then their prices are compared against the drug product under review.

19. Based on the HDAP's recommendation that Neupogen is the most appropriate comparator for Neulasta, Board Staff conducted a Therapeutic Class Comparison ("TCC") Test using Neupogen as the comparator for Neulasta in accordance with subsection 8.5 of Chapter 1 of the Guidelines - Excessive Price Guidelines (the "Excessive Price Guidelines") -, which provides as follows:

> 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).

20. With respect to the price of Neupogen, the comparable drug product, section 2 of Schedule 2 of the Excessive Price Guidelines provides as follows:

> Ordinarily, the introductory price of the new drug product and the Ontario Drug Benefit Formulary price of the comparable drug products, if available, will be used for the comparison. If the ODB price is not available, or the PMPRB considers it inappropriate,

other prices may be used for the comparison. For example, when an identified comparable drug product is patented and marketed by the same patentee as the drug product under review, the comparable drug product's average price based on the patentee's submission to the PMPRB (or, if outside the Guidelines, its maximum non-excessive price) may be used for the comparison.

21. Neupogen is also marketed by Amgen. Accordingly, the TCC Test was applied as follows for the date of first sale of Neulasta (April 12, 2004):

Drug Product	Dosage Regimen per Course of Treatment	Price per Course of Treatment in Canada (ATP)
Neulasta	**6 mg (1 syringe)**	**- SEVERED -**
Neupogen	**5 mcg * 70 kg * 11 days = 3,850 mg**	**- SEVERED -**
Price Review Result: Fail		

22. Pursuant to section 8.5 of the Excessive Price Guidelines, the price per course of treatment of Neupogen sets the MNE price for Neulasta. The result of the TCC Test indicated that in its introductory period, the price of Neulasta exceeded its MNE price of **- SEVERED -** by **- SEVERED -** (TCC Test 2004, **Attachment 7**).

23. Although not provided for by the Guidelines, Board Staff also conducted a TCC Test for the period from January to December 2008. The results of that test indicate that the price of Neulasta (**- SEVERED** -) continued to exceed the price per course of treatment of its sole comparator, Neupogen (**- SEVERED -**) (TCC Test 2008, **Attachment 8**).

C. Prices at which Neulasta and other Medicines in the Same Therapeutic Class as Neulasta have been Sold in Countries other than Canada

24. Subsection 85(1)(c) of the Act requires the Board to take into consideration the prices at which the medicine has been sold in countries other than Canada.

i) International Prices of Neulasta

25. The Excessive Price Guidelines set out the Highest International Price Comparison (the "Highest IPC") Test for new and existing drug products 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*.

SEVERED

26. Section 2.1 of Schedule 3 of the Guidelines provides that:

> 2.1 Whenever possible, the price of the drug product under review will be compared with the simple average of the ex-factory prices of the same strength and dosage form for each country listed in the Regulations (France, Germany, Italy, Sweden, Switzerland, the United Kingdom and the United States).

27. The ex-factory prices of Neulasta in the countries listed in the Regulations and the ATP of Neulasta in Canada, for the introductory period, are as follows:

Country	**Introductory Period**	**Introductory Period**
	Jan04-Jun04 Patentee Sources Price per syringe (CDN $)	**Jan04-Jun04 Board Staff Sources (for verification purposes) Price per syringe (CDN $)**
France	**- SEVERED -**	$1,702.7461
Germany	**- SEVERED -**	$1,820.1198
Italy	**- SEVERED -**	$1,622.5688
Sweden	**- SEVERED -**	$1,977.9559
Switzerland	**- SEVERED -**	$1,807.2082
UK	**- SEVERED -**	$1,661.2287
US	**- SEVERED -**	$3,300.4930
Highest International Price	**- SEVERED -**	**$3,300.4930**
Median International Price	**- SEVERED -**	$1,807.2082
ATP (in Canada)	**- SEVERED -**	
Price Test Result: Pass		

28. The results of the Highest IPC Test indicate that, from the date of first sale (April 12, 2004) until the end of 2008, Neulasta was sold in all 7 of the countries listed in the Regulations and the price of Neulasta in Canada ranked second highest of the said comparator countries (IPC Test, **Attachment 9**; Verification of Foreign Patented Drug Prices, **Attachment 10**).

ii) <u>International TCC</u>

29. Subsection 85(1)(c) also requires the Board to take into consideration the international prices of other medicines in the same therapeutic class as Neulasta (the “International TCC Test”), a factor not addressed in the Guidelines.

SEVERED

30. Board Staff submits that in conducting an International TCC Test the following criteria must be satisfied :

a) The comparators included in an International TCC Test must be those identified in the domestic TCC Test; and

b) The price of the drug product under review will be deemed excessive if it exceeds the median price of the International TCC Test or if it exceeds the median of the ratios. The ratio of the price of the drug product under review relative to the prices of comparable drug products in the countries listed in the Regulations is calculated. The median ratio is then applied to the price of the drug product under review in Canada.

31. In its introductory period and in 2008, the price of Neulasta was higher than the median international TCC price and the ratio of the Canadian price of Neulasta and the Canadian price of the comparable drug product (Neupogen) was higher than the median of the ratios for the countries listed in the Regulations. As a result, Neulasta failed both international TCC tests (International TCC Test 2004, **Attachment 11**; International TCC Test 2008, **Attachment 12**).

D. Changes in the Consumer Price Index ("CPI")

32. Subsection 85(1)(d) of the Act requires the Board to take into consideration changes in the CPI.

33. The Excessive Price Guidelines set out the appropriate CPI-Adjustment methodology to be applied to all existing drug products as follows:

9.1 In addition to the Guideline applicable to all patented drug products detailed in Section 7, the price of an existing DIN will be presumed to be excessive if it exceeds the benchmark price of the DIN adjusted for the cumulative change in the Consumer Price Index (CPI) from the benchmark period to the pricing period under review (CPI-adjusted price). Schedule 4 provides detailed definitions and examples of the PMPRB's CPI-adjustment methodology.

9.2 Regardless of the above, and in addition to the Guideline applicable to all patented drug products detailed in Section 7, one-year price increases in the current pricing period may not exceed 1.5 times the forecast change in the annual CPI. In periods of high inflation (over 10%), the limit will be five percentage points more than the forecast change in the CPI.

34. Commencing in July 2004, Board Staff reviewed the price of Neulasta, an existing drug product, by applying the PMPRB's CPI-Adjustment methodology, in accordance with the Guidelines.

SEVERED

35. The ATP of Neulasta in Canada, from July 2004 to December 2008, continued to exceed the MNE price:

Reporting Period	Price/syringe		
	ATP	MNE	% Over
- SEVERED -	**- SEVERED -**	**- SEVERED -**	**- SEVERED -**
- SEVERED -	**- SEVERED -**	**- SEVERED -**	**- SEVERED -**
- SEVERED -	**- SEVERED -**	**- SEVERED -**	**- SEVERED -**
- SEVERED -	**- SEVERED -**	**- SEVERED -**	**- SEVERED -**
- SEVERED -	**- SEVERED -**	**- SEVERED -**	**- SEVERED -**

36. By letter dated March 7, 2008, Board Staff informed Amgen that it had completed its investigation and that the price of Neulasta exceeded the Guidelines during the benchmark period and in subsequent reporting periods up to December 31, 2007, resulting in accumulated excess revenues of **- SEVERED -** (Board Staff's investigation letter sent to Geoffrey Sprang, Director, Reimbursement at Amgen Canada Inc., **Attachment 13**)**.**

37. According to publicly available information, Amgen was selling Neulasta at a price of $2,252 per syringe in 2004, 2005 and 2006; $2,375.23 per syringe in 2007; and at a price of $2,380 per syringe in 2008 (Liste des médicaments de l'Association québécoise des pharmaciens propriétaires, 2004-2007, **Attachment 14**; Liste des médicaments de l'Association québécoise des pharmaciens propriétaires, February 2008, **Attachment 1**).

E. Other Factors

38. Subsection 85(1)(e) of the Act requires the Board to take into consideration such other factors as may be specified in any regulations made for the purposes of this subsection. There are currently no such regulations.

CONCLUSION

39. Board Staff respectfully submits that, when considering the applicable factors in subsection 85(1) of the Act, there are grounds for the Board to conclude that, pursuant to section 83 of the Act, Amgen is selling or has sold the medicine known as Neulasta in any market in Canada at prices which are or were excessive.

ORDER REQUESTED

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

SEVERED

a) The MNE prices of Neulasta in Canada for the period April 12, 2004 to December 31, 2008 inclusive shall be as follows:

Reporting Period	Price/mL
	MNE
Apr04-Jun04	**- SEVERED -**
Jul04-Dec04	**- SEVERED -**
Jan05-Dec05	**- SEVERED -**
Jan06-Dec06	**- SEVERED -**
Jan07-Dec07	**- SEVERED -**
Jan08-Dec08	**- SEVERED -**

b) The MNE prices of Neulasta for future years shall be calculated in accordance with the Guidelines.

c) In accordance with subsection 83(1) of the Act, Amgen shall cause the maximum price at which it sells Neulasta in Canada to be reduced to the MNE price effective on or before 30 days from the date of the Board's Order.

d) In accordance with subsection 83(2) of the *Patent Act*, Amgen shall offset the amount of excess revenues estimated to have been derived by Amgen from the sale of Neulasta at excessive prices from April 12, 2004 until the date on which the price reduction referred to in paragraph c) above comes into effect as follows:

i) With respect to the period from April 12, 2004 to December 31, 2008, Amgen shall pay to Her Majesty in right of Canada, within 30 days of the date of the Board's Order, **- SEVERED -** (Calculation of Excess Revenues, **Attachment 15**); and

ii) With respect to the period from January 1, 2009 to the date on which the price reduction referred to in paragraph c) comes into effect, Amgen shall pay to Her Majesty in right of Canada, a further amount equal to the amount of excess revenues estimated by the Board to have been derived by Amgen from the sale of Neulasta at an excessive price 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 e) below.

e) Amgen 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 decrease as required by the Board's Order (a copy of which shall be included in such notifications) and the effective date of such price decrease;

SEVERED

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 Neulasta sold and either the average price per package or the net revenue from sales of Neulasta in Canada, in the same form as required by subsection 4(1) of the Regulations for the period January 1, 2009 to the date on which the price reduction referred to in paragraph c) comes into effect.

OTHER

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

42. Pursuant to section 86 of the 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 Neulasta should be held in public and, subject to orders of the Board, all information and documents filed should form part of the public record.

Dated at Ottawa this 5th day of March 2009.

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SEVERED

LIST OF ATTACHMENTS

Attachment 1	Public price of Neulasta according to the Liste des médicaments de l'Association québécoise des pharmaciens propriétaires, February 2008
Attachment 2	Product monograph for Neulasta (Date of Revision: September 14, 2006)
Attachment 3	Notice of Compliance for Neulasta dated March 12, 2004
Attachment 4	Canadian Patents No. 2,178,752; No. 1,297,004; No.1,339,071; No. 1,312,569; No. 1,297,005; and, No. 1,341,537
Attachment 5	HDAP New Medicine Review dated October 6, 2004
Attachment 6	HDAP New Medicine Review dated October 9, 2007
Attachment 7	Therapeutic Class Comparison Test for Neulasta as of its date of first sale (April 12, 2004)
Attachment 8	Therapeutic Class Comparison Test for Neulasta, 2008
Attachment 9	International Price Comparison Test for Neulasta
Attachment 10	Verification of Foreign Patented Drug Prices (Board Staff Sources)
Attachment 11	International Therapeutic Class Comparison Test for Neulasta as of its date of first sale (April 12, 2004)
Attachment 12	International Therapeutic Class Comparison Test for Neulasta, 2008
Attachment 13	Investigation letter from Board Staff to Amgen dated March 7, 2008
Attachment 14	Public price of Neulasta according to the Liste des médicaments de l'Association québécoise des pharmaciens propriétaires (2004 - 2007)
Attachment 15	Calculation of Excess Revenues for Neulasta (2004 - 2008)