

**IN THE MATTER OF AN ARBITRATION UNDER CHAPTER ELEVEN OF
THE NORTH AMERICAN FREE TRADE AGREEMENT**

AND THE UNCITRAL ARBITRATION RULES (1976)

BETWEEN:

ELI LILLY AND COMPANY

Claimant/Investor

AND:

GOVERNMENT OF CANADA

Respondent/Party

(Case No. UNCT/14/2)

WITNESS STATEMENT OF KIMBY BARTON

JANUARY 26, 2015

Trade Law Bureau
Departments of Justice and
of Foreign Affairs, Trade
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I INTRODUCTION

My name is Kimby N. Barton. I am a citizen of Canada and reside in Ottawa, Ontario. I am currently Director, Bureau of Cardiology, Allergy and Neurological Sciences of the Therapeutic Products Directorate of Health Canada. I have been employed by Health Canada since 2002. A copy of my *curriculum vitae* is attached as Exhibit “KB-1”.

1. I obtained an Honours Bachelor of Science in 1992 in Marine Biology from the University of Guelph. I went on to obtain a Master of Science from the University of Guelph in 1996. My Master’s thesis focused on the effects of organic solutes on biological membranes.

2. From 1996 to 2000 I was enrolled in a Doctoral program in Biochemistry at the University of Toronto. I left this program in 2000 prior to obtaining my doctoral degree but after having finalized all my course work. My project focused on the structure of a transmembrane protein in skeletal muscle that is implicated in a particular type of muscular dystrophy. In 2000, another laboratory solved the structure of the protein that had been the focus of this thesis. Rather than restart my entire project after 4 years of research, I chose to leave my studies and pursue a position as an Associate Editor with a small medical publication in Toronto.

3. In my current position, I am responsible for the management and leadership of the Bureau of Cardiology, Allergy and Neurological Sciences. My role includes:

- a) recommending the approval or rejection of applications to market pharmaceuticals for human use in Canada;
- b) developing, evaluating, and continuously improving the policy framework for pharmaceutical products to maintain and enhance their safety, efficacy and quality;

- c) providing advice on the conduct of scientific and medical evaluation processes for suitability of pharmaceuticals for clinical trial;
- d) participating with other subject matter Directors in the assessment of product information and labelling for products to ensure optimal product use; and
- e) participating in the risk management of pharmaceuticals following their approvals for use in Canada.

4. Prior to my current position, I was the Manager of Scientific Section 2, of the Marketed Pharmaceuticals and Medical Devices Bureau of the Marketed Health Products Directorate of Health Canada. I held this position from 2002 to 2009.

5. The Bureau of Cardiology, Allergy and Neurological Sciences (BCANS) is responsible for the review and approval of any prescription pharmaceutical drugs for treatment or prevention of cardiovascular disease, renal disease, allergy and respiratory illnesses, and neurological disease (including Attention Deficit Hyperactivity Disorder treatments, anesthetics, antidepressants, antipsychotics, anti-epileptics, drugs for treating muscular dystrophy, drugs for treating multiple sclerosis, and anti-nauseants and anti-obesity drugs that have a neurological basis for their action). BCANS is responsible for the review of any clinical information that may be submitted by a sponsor, and also for coordinating the review of any other streams that may be necessary for a particular submission. More specifically, BCANS reviews drug submissions for ADHD drugs and atypical antipsychotics and reviewed the New Drug Submissions for both Zyprexa (Lilly's brand-name formulation of an olanzapine-based drug product) and Strattera (Lilly's brand-name formulation of an atomoxetine-based drug product).

II MANDATE

6. In its submission Eli Lilly and Company (Claimant) makes various references to Health Canada's approval of its olanzapine-based and atomoxetine-based drug products, suggesting that this was in some way material to the validity of its patents for uses of these same active ingredients. Claimant also makes various statements seeking to illustrate the state of its research at the time it filed the two patent applications, by suggesting that such studies were material to later Health Canada approval. With this in mind, I have been asked to explain the process that Eli Lilly and Company (Claimant) would have undergone to ensure Health Canada approval for the public sale of their atomoxetine and olanzapine-based drugs products, explaining the basis for Health Canada's decisions in that process, and to comment on the relationship between the Health Canada approval process and any prior grant of patents for these proposed pharmaceutical uses. I have also been asked to comment on what weight, if any, Health Canada would have ascribed to the scientific data the Claimant disclosed in its two patent applications (or, in the case of atomoxetine, had performed but not disclosed by the time it filed its patents), for purposes of issuing a Notice of Compliance (NOC). I have further consulted Health Canada's new drug approval files to determine whether in fact these same studies had any impact on the New Drug Submission approval process for either drug. Finally, I have been asked to respond to comments by some of Claimant's witnesses regarding the two drug products at issue.

III SUMMARY OF CONCLUSIONS

7. Health Canada's New Drug Submission process is a rigorous and lengthy administrative and technical review, which relies upon substantial clinical evidence regarding the safety and efficacy of proposed new drugs, together with a suite of related information regarding formulations, dosage, toxicology, secondary effects, and manufacturing, among other things. Its goal is to determine whether a proposed new drug product meets Health Canada standards of safety and efficacy, allowing it to be marketed in Canada.

8. Prior issuance of a patent for the same proposed new pharmaceutical use of the compound is of no weight or relevance to this determination: what matters is the data actually submitted to Health Canada in the New Drug Submission process.

9. Claimant has pointed to studies disclosed in its patent applications (or, in the case of atomoxetine, conducted by it prior to its application) and suggested that these studies were material to the ultimate granting of Health Canada approval in the New Drug Submission process. I examined the studies to which it refers. I can confirm that these studies were not of the quality or weight to have been of any relevance in Health Canada's New Drug Submission approvals process. Indeed, I specifically reviewed the New Drug Submission file for each of these drug products. In neither case were the referenced studies material to Health Canada approval.

10. The sufficiency of these same studies to support the grant of a patent is an issue beyond my remit. I understand that this issue has been the subject of extensive court proceedings (ultimately leading to the invalidation of the two patents at issue).

IV THE DRUG SUBMISSION PROCESS IN CANADA

11. In what follows I set out a brief description of the New Drug Submission approval process in Canada. This is the process through which applicants may seek authorization to market drug products to Canadians.

12. The Minister of Health is responsible for the review of drugs in Canada under the relevant provisions of the *Food and Drugs Act* [R.S., 1985, c. F-27] and associated regulations.¹ The term “drug” is defined in section 2 of the *Act*. Section 2 provides in relevant part that “drug” includes any substance or mixture of substances manufactured, sold or represented for use in (a) the diagnosis, treatment, mitigation

¹ *Food and Drugs Act* [R.S., 1985, c. F-27] (R-256); *Food and Drugs Regulations*, C.R.C., c.870, 15 December 2014 (“The Regulations”) (R-257).

or prevention of a disease, disorder or abnormal physical state, or its symptoms, in human beings or animals, or (b) restoring, correcting or modifying organic functions in human beings or animals.

13. Part C, Division 8 of the *Food and Drug Regulations*² is of particular relevance to the approval of Claimant’s drug products relying on the active ingredients olanzapine and atomoxetine, respectively. These two products fall under the definition of “new drug” set out in C.08.001. Specifically, because both drugs were composed of an active ingredient that had not been previously sold in Canada (*i.e.* a new active substance), they can be said to “contain or consist of a substance, whether as an active or inactive ingredient...that has not been sold as a drug in Canada for sufficient time and in sufficient quantity to establish in Canada the safety and effectiveness of that substance for use as a drug.”³ The “new drug” that is the subject of Health Canada approval is a formulation containing both active and inactive ingredients, as well as labeling information.

14. Section C.08.002 of the *Food and Drug Regulations* prohibits the sale or advertisement of a “new drug” unless the manufacturer has first obtained market authorization, referred to as a Notice of Compliance (NOC), from the Minister of Health. Accordingly, drug manufacturers who wish to advertise or sell a “new drug” in Canada must first obtain a NOC pursuant to Division 8 of the *Food and Drug Regulations* (the *Regulations*). They do so by filing a drug submission, of which there are several types.

15. The most relevant type of submission filed for a new drug product seeking an initial NOC is a New Drug Submission (NDS). An NDS is filed pursuant to section C.08.002 of the *Regulations*.⁴ The NDS usually contains voluminous clinical trial

² *The Regulations*, Division 8 (**R-257**).

³ *The Regulations*, C.08.002 (**R-257**).

⁴ *The Regulations*, C.08.002 (**R-257**).

data and detailed studies. For example, an NDS for a drug containing an active ingredient that had not been previously approved for sale on the Canadian market, such as olanzapine or atomoxetine, can range upwards to three hundred volumes of data. This provides the basis upon which the drug product is initially approved for sale on the Canadian market.

16. The purpose of the information in the NDS is to establish to Minister's satisfaction that the drug meets the regulatory requirements relating to the safety, efficacy and quality of the drug. The NDS therefore contains various sections, including clinical and non-clinical sections, chemistry and manufacturing sections, corresponding to each facet of the overall approval process.

17. The clinical section of the NDS comprises the majority of information generated by the applicant from all the studies conducted in humans, known as clinical trials. These include Phase I, II and III trials. In Phase I trials, the drug is typically given to healthy human volunteers, to determine initial tolerability and safety. Phase II trials include patients with the condition or disease that the drug is expected to treat, and can include hundreds of patients. Phase III trials are typically conducted world-wide, and usually include hundreds to thousands of patients with the disease or condition. They are intended to confirm efficacy and to give an initial picture of drug safety. All the data from each trial is provided in the NDS in both relatively unprocessed, and in summarized formats.

18. The non-clinical section of the NDS comprises all the information about the numerous experiments that the applicant has conducted in the lab setting in animals. These experiments are geared to test the action of the active ingredient on biological systems, and to test the toxicity of the active ingredient in these systems.

19. Additional sections of the NDS include the chemistry and manufacturing sections, through which the product quality and related manufacturing process are

evaluated. Also, the Literature Reference section may include published and unpublished articles that may provide additional support to the submission, beyond the studies upon which the NDS primarily relies.

20. A further element of the NDS is a Product Monograph (PM), which is a factual, scientific document that describes the properties, claims, indications and conditions of use for the drug. The Indications and Clinical Use section of the PM describes the condition, disorder or disease which the drug is authorized to treat, prevent or diagnose. This section also describes relevant clinical information and when the product is not recommended. The claims in this section are supported by scientific safety and efficacy data obtained from trials in the intended patient population. It also contains any other information that may be required for optimal, safe and effective use of the drug. The PM is reviewed during the NDS process, and is considered approved with NOC issuance.

21. Section C.08.004 of the FDR requires the Minister to examine an NDS and, if satisfied that the NDS meets the safety and efficacy requirements set out in the *FDR*, issue an NOC.⁵

V APPLICATIONS FOR A PATENT AND NDS ARE SEPARATE PROCESSES

22. I have been asked to comment on the relation between the granting of a patent for the invention based on a particular use of an active ingredient, and the granting of Health Canada approval for a drug product containing that same active ingredient for the same indicated use. I can confirm that the two processes are entirely distinct.

⁵ *The Regulations*, C.08.004 (**R-257**).

23. As described above, prior to receiving an NOC, a manufacturer must present substantive scientific evidence that satisfies the Minister of a product's safety, efficacy and quality as required by the *Regulations*. Prior issuance of a patent based upon the alleged invention of that same specific proposed pharmaceutical use is irrelevant for purposes of the Minister's determination. Health Canada's approval process instead depends upon the actual scientific and related data submitted to it, in fulfillment of *FDR* requirements.

24. It is my understanding that patents are by contrast issued, and the grant of such patents ultimately reviewed, based upon the statutory criteria set out in the *Patent Act*, as interpreted and applied by the Federal Court. This is a separate legislative process, and in my experience determinations by the Patent Office or the courts form no part of Health Canada's approval process.

25. At certain instances in its submissions, Claimant suggests that the scientific information it disclosed in its two patent applications (or, in the case of atomoxetine, that otherwise had in hand when it filed its patent application), was somehow material to Health Canada's ultimate NOC issuance. To the contrary, my review confirms that the referenced data was preliminary, and not the sort that Health Canada would take into account as the basis for granting such approval. Moreover, having reviewed Health Canada's approval files for these two drug products, I found no evidence that such data in fact was of any consequence to Health Canada approval. I discuss these points in further detail below.

VI The Atomoxetine Patent Specification Contains No Scientific Support for the Asserted Use

26. I have reviewed Claimant's patent specification for the invalidated patent for the use of atomoxetine to treat Attention Deficit-Hyperactivity Disorder (ADHD).⁶ I can confirm that it contains no relevant scientific data of the kind that Health Canada typically relies upon when issuing an NOC.

27. The atomoxetine patent provides some high level assertions regarding the benefits of atomoxetine over other approved therapies. However, it fails to provide any data in support of such assertions. Further, the patent makes no reference to any non-clinical, chemistry or manufacturing data concerning atomoxetine, as would be required to be included in a New Drug Submission. For example:

- Page 2, line 28 of the patent specification states that atomoxetine is a “notably safe drug” and its use is “superior” because of its improved safety. No data are provided to support this point.
- The patent specification asserts on page 3, lines 13 to 15, that atomoxetine is readily orally absorbed and that therefore, there is no reason to administer it any other way than orally. Again, no supporting data are provided.
- The specification includes several pages (pages 3, line 31 to page 6 line 10) referencing diagnostic criteria for ADHD. It then asserts on page 6, lines 15 to 17, that treatment with atomoxetine is effective in patients who are primarily suffering from either component or from the combined disorder. Again, no data are provided in support of that point.

⁶ Patent specification CA 2,209,735 for Claimant's new proposed use for atomoxetine (**R-026**). I note that in the patent specification, the active ingredient atomoxetine is referred to as “tomoxetine”. I understand that the technical name for this active ingredient was subsequently changed to “atomoxetine” to avoid confusion with another active ingredient. For the sake of consistency, I refer throughout my witness statement to this active ingredient as “atomoxetine”.

- The specification cites one reference article on page 6, line 24, as evidence that many ADHD patients continue to suffer from the disorder as they grow through adolescence into adulthood. This may be evidence of the existence of the disorder, but on its face provides no support for the asserted use of atomoxetine.
- The specification states on page 6, lines 33 to page 7, line 2, that psychiatric comorbidity is quite common in ADHD patients and that atomoxetine is effective in treatment of ADHD, even though the situation of the treated patient may be complicated by comorbidity with one or more additional disorders. However, it fails to provide any source data for atomoxetine's effect in this patient population.
- Page 7 of the patent specification sets out reference to the seriousness of ADHD, and the damage it does to the patient. It asserts that it is readily apparent that an improved treatment of ADHD is needed. However, the preceding section appears to reference characteristics of an untreated patient with ADHD, not characteristics of a patient who may be controlled by another already approved medication. Thus, the statement seems of limited relevance. In any event, it again provides no support to the asserted use of atomoxetine *per se*.
- Also on page 7, the patent specification refers to atomoxetine being effective in the treatment of patients who are children, adolescents or adults, asserting there is no significant difference in treatment among patients of different ages. Again, no data are provided for this statement. The patent references both "effective" and "preferred" doses of the product in children and adults but provides no source of clinical data upon which to base any dosing information. In contrast, as explained in more detail below, the recommended dosing information referenced in the approved Product

Monograph was based on evidence obtained from clinical studies that are referenced in the Product Monograph for which a statistically significant response was observed.

28. In light of its limited contents, I can confirm that nothing in the atomoxetine patent specification supported Health Canada's later NDS approval process.

VII THE MGH STUDY WAS OF NO RELEVANCE TO HEALTH CANADA NEW DRUG APPROVAL

29. I understand that at the time Claimant filed its patent for the use of atomoxetine to treat ADHD, it was relying on a study that had been conducted by the Massachusetts General Hospital (the MGH study) that was later published in the *American Journal of Psychiatry*.⁷ I have been asked to consider the MGH study and determine what, if any, weight the study had in the NDS approval process.

30. I have reviewed the file for Health Canada's NDS approval of Claimant's atomoxetine product. I found no reliance on the MGH study. The MGH study was very preliminary in nature and therefore, at best, was incidentally referred to among additional literature relevant to the NDS.

31. The NDS for Claimant's atomoxetine-based product was filed with Health Canada on July 30, 2002. Health Canada ultimately issued a notice of compliance (NOC) for the new drug on December 24, 2004. Lilly Canada continues to hold a valid NOC for this drug.

32. The atomoxetine-based drug, which Claimant marketed under the brand name "Strattera", is a capsule formulation which contains atomoxetine along with non-

⁷ Article from the *American Journal of Psychiatry* entitled "Effectiveness and Tolerability of Tomoxetine in Adults with Attention Deficit Hyperactivity Disorder", *AM J Psychiatry* 155:5, May 1998 (R-258).

medicinal ingredients. It a selective norepinephrine reuptake inhibitor and is authorized in Canada as a treatment for attention-deficit/hyperactivity disorder (ADHD) in children 6 years of age or older, for adolescents and adults. Strattera capsules were initially approved in 10, 18, 25, 40 and 60 mg strengths. Its therapeutic effect in ADHD is thought to be related to its potential inhibition of norepinephrine transporters; thereby increasing levels of norepinephrine in the brain (see ACTION and CLINICAL PHARMACOLOGY section of the PM).⁸

33. The NDS initially contained 138 volumes of information, with an additional 15 volumes submitted to address issues raised by the Health Canada reviewer during the NDS. For the clinical section of the submission, 9 trials conducted in children and adolescents and 2 trials conducted in adults were included in the NDS as pivotal support for the safety and efficacy of the drug for the sought indication.⁹ Also, additional supportive safety studies were provided to contribute to the safety and efficacy of the drug. A total of 2725 patients were included in these trials.

34. Additional clinical (human pharmacokinetic and bioavailability) and non-clinical (toxicology, carcinogenicity, and mutagenicity) trials were submitted, along with chemistry and manufacturing information to support approval.

35. The MGH study is a small, very preliminary proof-of-concept study of adults with ADHD, following only 22 patients. The objective of the MGH study was to evaluate the tolerability of atomoxetine, indicative of a preliminary study for which efficacy has not yet been established.

⁸ Product Monograph, Strattera: Selective Norepinephrine Reuptake Inhibitor for Attention-Deficit/Hyperactivity Disorder (ADHD), “Action and Clinical Pharmacology”, 22 December 2004 (**R-259**).

⁹ Product Monograph, Strattera: Selective Norepinephrine Reuptake Inhibitor for Attention-Deficit/Hyperactivity Disorder (ADHD), “Clinical Trials”, 22 December 2004 (**R-260**).

36. Each applicant for an NDS must signal which studies they deem to be pivotal to their application to Health Canada.

37. In my review of the NDS file for atomoxetine, I determined that the MGH Study was not submitted by Claimant as a pivotal clinical trial. Claimant instead included the study under “published / unpublished clinical articles” as a literature reference, and in the proposed Product Monograph as a reference. The MGH Study as submitted to Health Canada was indeed merely a summary of a clinical trial that *could* be submitted as part of the NDS, but was not in fact submitted in seeking that approval. While the article describes the trial (that is the objective, methods used, results, *etc.*), reports of clinical trials that Health Canada receives in new drug submissions are much more descriptive. Instead of a summary article, they are often thousands of pages long, and include all data and results that were obtained during the course of the trial.

38. Applicants submit literature references to provide further support to the safety and efficacy data upon which the NDS primarily relies. Literature references are not pivotal, which means they are not relied on by Health Canada in granting its approval. Pivotal studies are typically large scale, well-controlled Phase III studies, which play the greatest role in establishing the safety and efficacy of the product. For example, actual Health Canada approval of Claimant’s atomoxetine drug was based on nine separate pediatric studies involving a total of 2189 children/adolescents, and two adult studies with 536 subjects. These two adult studies had 280 and 256 patients, respectively and did not include the MGH study.

39. Moreover, I determined that following Health Canada’s review process, the MGH study was not even referenced in the “References” section of the approved

Product Monograph.¹⁰ In my experience, this indicates that the study did not even merit listing.

40. Overall, based upon my review of the file and knowledge of the Health Canada drug approvals process, including the MGH study as a “literature reference” in the NDS for atomoxetine had negligible relevance to the ultimate drug approval.

41. I will also respond to a specific comment by Claimant in its Memorial concerning the MGH Study. Paragraph 129 of Claimant’s Memorial states that the MGH Study: “...was cited in a 2003 Canadian government publication on atomoxetine as one of “three randomized, double blind, placebo controlled trials conducted in adults with ADHD,” and summarized as having “demonstrated a statistically significant decrease in ADHD [symptoms] in the [atomoxetine] group compared to placebo.” I have reviewed a copy of the “Canadian government publication” to which Claimant refers.¹¹ This document was generated by the Canadian Coordinating Office for Health Technology Assessment (CCOHTA), now referred to as the Canadian Agency for Drugs and Technologies in Health (CADTH).

42. As confirmed by disclosure on its website¹², CADTH is neither a Canadian Federal Government Department, nor an agency of the Federal Government. It is funded by the federal, provincial and territorial governments, and is an independent not-for-profit agency. CADTH delivers a Common Drug Review, providing

¹⁰ Product Monograph, Strattera: Selective Norepinephrine Reuptake Inhibitor for Attention-Deficit/Hyperactivity Disorder (ADHD), “References”, 22 December 2004 (**R-261**).

¹¹ “*Issues in Emerging Health Technologies: Atomoxetine for Attention Deficit / Hyperactivity Disorder*”(the “CCHOTA Document”) (**R-262**).

¹² CCOHTA Announces New Corporate Name, 3 April 2006 available online: www.cadth.ca/en/cadth (**R-263**).

participating drug plans with clinical and economic reviews of new drugs, and recommendations about whether or not they should be provided as a benefit. Its analysis is therefore a pharmaco-economic analysis, as opposed to a determination of a product's safety, efficacy and quality as performed by Health Canada in the NDS and related processes.

43. Typically, CADTH reviews a drug to determine whether or not it recommends reimbursement, after a drug has received market authorization in Canada.¹³ To the extent CADTH may have commented on the MGH study, this in no way reflected the views of the Government of Canada, nor does it change the fact that the MGH study played no part in the approval of Claimant's atomoxetine drug product in Canada.

VII THE OLANZAPINE PATENT SPECIFICATION CONTAINED INSUFFICIENT SCIENTIFIC SUPPORT OF THE ASSERTED USE

44. I have also been asked to consider the scientific evidence referenced in Claimant's patent specification relating to olanzapine, to determine the extent to which such references would have led to successful market authorization for Claimant's related drug product.¹⁴ To recall, in the above-described *FDR* process under the Regulations, Health Canada is essentially seeking to ensure that a proposed drug formulation will safely achieve its purported health effects, and that the description of the drug (*e.g.* for the proposed label) corresponds accurately to the drug's actual effects.

45. From a clinical perspective, the information contained in Claimant's patent specification for olanzapine would not meet the requirements to establish safety, efficacy and quality for an NOC in Canada.

¹³ From my personal experience.

¹⁴ Patent Specification CA 2,041,113 entitled "Thienobenzodiazepine Derivatives and Their Use as Pharmaceuticals" (the 'olanzapine patent') (**R-030**)

46. Page 5 of the olanzapine patent specification refers to an open study of olanzapine in eight patients, as well as preliminary results from three ongoing clinical trials. Data from an open label,¹⁵ very small study, and preliminary data from three trials, would be insufficient for Health Canada's purposes and would provide at best marginal additional support. As mentioned above, the clinical section of the NDS comprises information generated by the applicant from all the studies conducted in humans, known as clinical trials. As a general rule, open label trials would not be considered sufficient to establish efficacy. Indeed, the actual clinical section for Claimant's olanzapine NDS comprised five randomized, double-blinded,¹⁶ multicenter clinical trials involving over 2500 patients.

47. The olanzapine patent specification further contains a single sentence on page 5, describing one dog toxicity study of another substance that led to cholesterol increases. It compares that study to olanzapine, stating that olanzapine did not lead to cholesterol increases. However, no data were provided to support this statement. As such, this would not be sufficient in establishing the safety and efficacy of olanzapine. To support market authorization, companies generally conduct a comprehensive battery of non-clinical tests to establish toxicity, carcinogenicity, genotoxicity and mutagenicity of drug products prior to market approval. For instance, the PM for Claimant's olanzapine-based drug product states in the Toxicology section that an extensive series of acute, subchronic, chronic, reproduction and genetic toxicity as well as oncogenicity studies have been conducted to support clinical trials with olanzapine. This non-clinical information is included in the non-clinical section of the NDS submission.¹⁷

¹⁵ An open label study is one in which the investigator and the trial participant know which treatment a patient is receiving. Because of this design, results are subject to bias.

¹⁶ A double-blind study is one in which neither investigator nor the trial participants are aware of the treatment received, eliminating the potential for bias.

¹⁷ Product Monograph, Zyprexa: Antipsychotic Agent, "Toxicology", 23 October 1996 (**R-264**)

48. The balance of the patent specification provides high level information on chemistry and manufacturing that also would not be sufficient to meet requirements for drug approval.

49. Overall, the scientific data disclosed in the olanzapine patent specification would have been of only marginal relevance to Health Canada's approval for Claimant's olanzapine drug product.

VIII CLAIMANT'S STUDIES CONTEMPORARY TO ITS PATENT FILINGS WERE OF NO RELEVANCE TO HEALTH CANADA'S ULTIMATE APPROVALS PROCESS

50. I have also reviewed the contents of the NDS file for Claimant's olanzapine drug, to consider to what extent the studies referenced in Claimant's patent application had any actual impact on Health Canada's approval. I found no reference to the studies in the NDS file. Even to the extent they had been included, as I noted above, the studies would at best be of marginal relevance.

51. Claimant's olanzapine-based product, which it marketed under the trade name "Zyprexa", is a tablet formulation containing olanzapine along with non-medicinal ingredients. It is an antipsychotic agent of the thienobenzodiazepine class. It was initially approved by Health Canada for use as an acute and maintenance treatment of schizophrenia and related psychotic disorders.¹⁸ The drug product has subsequently been approved for use in bipolar disorder. Intramuscular olanzapine has also been more recently approved for the acute treatment of agitation in patients with schizophrenia and related psychotic disorders and bipolar disorder.. Tablets were initially approved in 2.5, 5, 7.5, 10, 15, and 20 mg strengths. The New Drug Submission (NDS) was filed with Health Canada on October 3, 1995. The Notice of

¹⁸ Product Monograph, Zyprexa: Antipsychotic Agent, "Indications and Clinical Uses", 23 October 1996 (R-265).

Compliance was issued on October 28, 1996. . Lilly Canada continues to hold a valid NOC for this drug.

52. At the time of filing, the clinical section of the NDS contained 260 volumes of information. The clinical section included four pivotal clinical trials that ran from 1991 to 1995 (HGAD, E003, HGAP, HGAJ) to support the safety and efficacy of olanzapine in the treatment of schizophrenia. All were six- week, randomized double-blind, well-controlled, multicenter studies with double blind or open label extensions. An additional eight-week double-blind trial from May, 1994 to January, 1995 (HGAO) was also submitted and contributed to the safety database. In these five studies, that ran from 1991 – 1995, including blinded and open label extensions, approximately 2500 patients were exposed to at least one dose of olanzapine. Additional support for the safety of olanzapine was obtained from data from other clinical trials included in the submission which consisted of over 600 patients or healthy subjects.¹⁹ The non-clinical components of the submission consisted of multiple pharmacology and toxicology studies, along with chemistry and manufacturing data.

53. None of the above studies are those disclosed in Claimant’s patent application. Moreover, I did not find reference to these studies in the literature references. This simply confirms that they played no part in NDS approval.

IX COMMENTS ON CLAIMANTS WITNESS STATEMENTS

54. I have been asked to read the Witness Statements of Armitage, Nobles, Postlethwaite and Stringer filed by Claimant and provide my comments. None of these Statements contain any information explaining the basis for the approval of Claimant’s atomoxetine or olanzapine drug products in Canada. More generally, none of the witnesses seem familiar with the Canadian drug approval system.

¹⁹ Product Monograph, Zyprexa: Antipsychotic Agent, “Clinical Trials”, 23 October 1996 (**R-266**). .

55. Beyond these general remarks, I have noted specific misstatements in their evidence relevant to the weight to be given to scientific work on the two drug products.

56. Mr. Armitage notably refers to the fact that “peer reviewed clinical work” had “confirmed” the usefulness of Claimant’s atomoxetine drug product. I presume here he is referring to the MGH Study, discussed above.²⁰ Publication of an article on a very small study of 22 adult patients would not be considered sufficient to merit market authorization. In my experience, many studies that may be published in peer-reviewed journals fall short of achieving the bar that is necessary to support market authorization. For example, there may well be methodological flaws in the study that are not apparent to peer reviewers who do not themselves analyze the statistical data in a study, but usually look at the overall design and accept or not the authors’ interpretations of the data. This is very different from a regulatory review in which we may consult with biostatisticians and ask for them to re-analyze the data and/or for the company themselves to re-analyze data based on concerns regarding methodology.

57. Mr. Armitage makes several other statements which leave a misleading impression of the conclusions that could be drawn, from a scientific point of view, from the MGH study. For example, based on my experience, the MGH study would not be sufficient to demonstrate the “advance state of clinical development of the drug” and provides insufficient data to show “real world usefulness of atomoxetine”.

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²⁰ Armitage Statement, para. 23

²¹ Armitage Statement, para. 8.

58. With respect to olanzapine, Mr. Armitage makes reference to “unusually extensive testing on Zyprexa prior to our patent filing, including clinical studies in both healthy volunteers and patients suffering from schizophrenia.”²² Mr. Armitage also suggests that Claimant's olanzapine patent had already been shown “to have utility in human clinical trials”.²³ However, as explained above, the disclosed studies were in one case a very small open-label study conducted on only eight patients, and the others were preliminary. In any event, my understanding is that Claimant for purposes of its patents was obliged to show the relative merits of olanzapine as a treatment, as compared with other members of the class of compounds to which it belonged.

59. I also take issue with Ms. Nobles’ statement that stimulants are among the most abused prescription drugs, and therefore Claimant’s atomoxetine drug product has particularly benefitted those patients at risk for substance abuse.²⁴ The Product Monograph for Claimant’s atomoxetine drug product does not provide any information that the drug has benefitted patients at risk for substance abuse and no explicit claim to that effect has been allowed. On page 20 of the PM, there is reference to the fact that atomoxetine is neither a controlled substance nor a stimulant and was not associated with stimulant or euphoriant properties.²⁵ In addition, the PM states that in preclinical studies, atomoxetine did not show a behavioural profile or stimulant properties associated with drugs that have abuse liability. However, there are no statements in the PM that assert that the drug has particularly benefitted those at risk for substance abuse. Moreover, the Claimant failed to provide any data to support that statement in the patent specification.

²² Armitage Statement, para. 16.

²³ Armitage Statement, para. 8.

²⁴ Nobles Statement, para. 6

²⁵ Product Monograph, Strattera: Selective Norepinephrine Reuptake Inhibitor for Attention-Deficit/Hyperactivity Disorder (ADHD), “Drug Abuse and Dependence”, 22 December 2004 (**R-267**).

60. Mr. Postlethwaite for his part refers to Claimant's olanzapine drug being a 2nd generation antipsychotic, with a lower incidence of side effects.²⁸ While the drug may be associated with a lower incidence of extrapyramidal symptoms (EPS) and agranulocytosis, it has significant side effects, which are outlined in the PM.²⁹ Most notably, since coming to market, Claimant's "Zyprexa" is recognized for causing the secondary effects of weight gain and metabolic syndrome.

Date: 2015-01-26

[signed]

Kimby Barton

²⁸ Postlethwaite Statement, para. 13

²⁹ Product Monograph, Zyprexa: Antipsychotic Agent, "Contraindications and Warnings", 23 October 1996 (R-268)

Appendix A

Kimby N. Barton, MSc
Interim Director, Bureau of Cardiology, Allergy and Neurological Sciences
Therapeutic Products Directorate
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EDUCATION

1996-2000 **Doctor of Philosophy**, Biochemistry, University of Toronto (undefended)
1993-1996 **Master of Science**, Zoology Department, University of Guelph
1988-1992 **Bachelor of Science**, Marine Biology, University of Guelph

OVERVIEW OF EMPLOYMENT HISTORY

2009-present Director, Bureau of Cardiology, Allergy and Neurological Sciences
(BCANS), Therapeutic Products Directorate (TPD), Health Canada
2013 Interim Senior Executive Director, TPD
Sept/Oct
2003-2009 Manager, Scientific Section 2, Marketed Pharmaceuticals and Medical
Devices Bureau (MPMDB), Marketed Health Products Directorate
(MHPD), Health Canada
2002-2003 Scientific Evaluator, Marketed Pharmaceuticals Division, MHPD
2001-2002 Head, Strategic Development *and* Associate Editor, Geriatrics and Aging
2000-2001 Associate Editor, Geriatrics and Aging

WORK-RELATED AWARDS

- Assistant Deputy Minister's Award: Openness and Transparency
- Therapeutics Products Directorate: Two TPD Awards for Excellence
- Marketed Health Products Directorate Award: Contributions to Biologist
Development Programme Promotion Assessment Boards
- Marketed Health Products Directorate Award: Contributions to
Pharmacovigilance Planning

WORK EXPERIENCE

Health Canada, Health Products and Food Branch, Therapeutic Products Directorate,
Bureau of Cardiology, Allergy and Neurological Sciences

September 2009-present
Director (EX-02)

Context: The Therapeutic Products Directorate is the Canadian federal authority that regulates pharmaceuticals drugs and medical devices for human use. The Bureau of Cardiology, Allergy and Neurological Sciences is responsible for approval of products in these therapeutic areas. The Bureau consists of over 40 staff and a budget of approximately \$4.5 million dollars. As Director, I have had the responsibility for overseeing the recommendations for approval of all products in this area, managing the bureau budget, managing staffing, contributing to updates to regulations and legislation and representing the Bureau at multiple different forums, including at Directorate and Branch management committee meetings and interdepartmental and international discussions.

Accountabilities and Experience:

- Ensuring performance standards are met for cost-recovered authorizations and other submission types
- Timely management of emerging health risks, including health risk assessments, and drug shortages
- Managing a bureau budget of \$4.7M
- Responsible for staffing, training, rewards and labour relations
- Chaired BI staffing initiative that led to hiring of over 50 new biologist staff to the Branch
- Eliminated backlog of bureau submissions and contributed to reduction of backlog in generic submissions
- Participate as a Directorate representative on Directorate and Branch committees, providing advice to, and participating in discussions with the Assistant Deputy Minister, Deputy Minister, Minister's Office and Parliamentary committees
- Direct supervision of bureau staff and ensuring compliance with PDPs and PMPs
- Manage relationships with diverse stakeholder groups, including industry, health care professionals, patient groups, other Canadian and international Governments
- Defending and representing the Government in ongoing litigation
- Representation of the Bureau and/or Branch in external functions, international relations and stakeholder negotiations
- Provided subject matter expertise in support of litigation management strategies for several files.
- Media spokesperson: conducted interviews with national news media

Health Canada, Health Products and Food Branch, Therapeutic Products Directorate, Director General's Office

September-October 2013
Interim Senior Executive Director (EX-02)

Context: The Director General's Office is responsible for sign-off on all market authorizations for pharmaceuticals and medical devices. The Senior Executive or Medical Director is responsible for ongoing briefing of upper management, participating in Branch level discussions, supervision of certain Directors and managing activities within the Directorate to ensure performance and cost-savings measures are realized. The Directorate has approximately 540 employees and an annual budget of \$62M.

Accountabilities and experience:

- Timely approval of cost-recovered submissions
- Acting for Director General during absences
- Advancing regulatory and program initiatives within the TPD and across the Branch (Commercial Compound Manufacturing, Drug Shortages)
- Representing the Directorate at interactions with industry and other external stakeholders (Province and Territories)
- Responsible for briefing upper management on politically sensitive files (e.g. Heroin release through Special Access Programme)

Health Canada, Health Products and Food Branch, Marketed Health Products Directorate,

January 2003-September 2009
Manager, Scientific Section 2 (BI-05)

Context: The Marketed Health Products Directorate works to assure that HPFB programs take a consistent approach to post-approval safety surveillance, assessment of signals and safety trends and risk communications concerning all regulated marketed health products. The Marketed Pharmaceuticals and Medical Devices Bureau (MPMDB) is responsible for these activities with respect to pharmaceuticals and medical devices. As Manager I was responsible for direct supervision of a team of 8 scientific staff, managing staffing, contributing to updates to regulations and legislation and representing the Bureau at multiple different fora, including at Directorate and Branch management committee meetings and interdepartmental and international discussions. I did not manage a budget.

Accountabilities and experience:

- Advancing regulatory and program initiatives within the MHPD and across federal departments and agencies
- Staffing, training, rewards and labour relations
- Met with industry associations, NGOs, and provinces, presented at conferences
- Leading on implementation of Risk Management Planning (RMP) at Health Canada and international harmonization.
- Advising on post-market requirements for the proposed new Food and Drugs Act and Regulations.
- Coordinated input from multiple government departments and agencies, and provided strategic advice and briefing to upper management.
- Helped developing multiple guidance documents (hepatotoxicity, the summary basis of decision document, risk communication).
- Wrote SOPs for RMP and assisted process development for signal detection and prioritization.
- Regularly developed briefings and strategic position papers for upper management on programme issues.
- Provided second review and advice on management or drug safety issues on numerous pharmaceuticals post-authorization, including involvement in several high profile safety files that led to drug withdrawal.

COMMITTEES AND MEMBERSHIP

Current

HPFB lead, World Dementia Council Dementia Integrated Development Regulators' Party
Member, Advisory Council for North America for the Drug Information Association (DIA)
HPFB lead, ACSS consortium Project on Benefit/Risk Assessment
Co-Chair, Health Portfolio Risk Management Planning Working Group
Member, Prescription Drug Abuse Tripartite Group
Member, Clinical Safety and Efficacy Committee
Member, Acetaminophen Working Group
HPFB lead, Tamper-resistance working group
Member, Subject Matter Experts Group, C-17
Member, Directorate Management Committees (several)

Previous

Health Canada Invited Panelist, Legislative and Regulatory Modernization Sessions (October, November 2010 and January 2011)
Co-Chair, Drug Information Association 8th Annual Canadian Conference
Chair, Market Authorization Holder Submitted Information Signal Detection Working Group (MPMDB)
Marketed Health Products Directorate Lead, Cough and Cold Working Group
Member, Hepatotoxicity Working Group
Member, Post-DIN Guidance document Working Group
Alternate Member, Summary Basis of Decision Working Group
Member, Industry issued Health Professional and Public Communication Working Group (development of SOP and Guidance)
Lead, Canadian delegation to North American Regional Task Force on Lindane
Member, Biologist Development Programme Management Working Group

LANGUAGE PROFILE

E/C/C

SECURITY CLEARANCE

Secret

RESEARCH AWARDS

- Medical Research Council of Canada Doctoral Research Award
- Charles H. Best Studentship
- Ontario Graduate Scholarship
- Scholander Award for Best Student Poster (First Runner Up), American Physiological Society
- Samuel E. Gruber Award for Best Student Paper (Third prize), American Elasmobranch Society

SELECT PRESENTATIONS

Barton KN. Health Canada Regulatory Considerations for Functional Outcomes in Depression. CANMAT Consensus conference, February 2011.

Barton KN. Towards Comprehensive Risk Management Planning: Health Canada's Proposed Approach. CAPRA Education Day, June 2009.

Barton KN. Signal detection, prioritization and assessment. Presentation to the inaugural meeting of Health Canada's Paediatric Expert Advisory Committee, February 2009.

Barton KN. Towards Comprehensive Risk Management Planning: Health Canada's Proposed Approach. DIA 6th Annual Canadian Meeting, November 2008.

Barton KN. Health Canada's utilization of post-market data (detection, and analysis of signals). DIA 4th Annual Canadian Meeting, October 2006.

Barton KN. Status of lindane in Canada: The Pharmaceutical Perspective and the Pesticide Perspective. Presentation to the Commission for Environmental Cooperation Lindane Task Force at the Alaska Forum on the Environment, February 2004. (Similar presentations were given in Guadalajara, Mexico and Washington DC, USA in 2003).

SELECT PUBLICATIONS

Barton, KN and MacLennan, DH. The proteins of the sarco(endo)plasmic reticulum system. *In*. Myology, Volume 2. (Franzini-Armstrong, C Ed). McGraw Hill Incorporated, 2004.

Barton, KN and MacLennan, DH. The sarco(endo)plasmic reticulum system. *In* Disorders of Voluntary Muscle, Eds. Karpati, G, Hilton-Jones, D and Griggs, R.C. Cambridge University Press., Cambridge UK. 7th Edition, 2001.

Odermatt A., Barton KN, Khanna V et al. The mutation of Pro789 to Leu reduces the activity of the fast-twitch skeletal muscle sarco(endo)plasmic reticulum Ca²⁺ ATPase (SERCA1) and is associated with Brody disease. *Human Genetics* 2000; 106: 482-91.

Barton KN. Unknown Cause, Unknown Cure: Mechanisms of insulin resistance, *Geriatrics & Aging*, 2001; 4 (1).

Barton KN. What is better for my elderly cardiovascular patient: Surgery or Pharmaceutical Intervention? *Geriatrics & Aging*, 2000; 3 (8).

Barton KN. Reversal of Fortune: The Fate of Huntington's Disease. *Geriatrics & Aging*, 2000; 3 (5).

Barton KN, Buhr MM and Ballantyne JS. Effects of urea and trimethylamine N-oxide on fluidity of liposomes and membranes of an elasmobranch. *Am J. Physiol*, 1999; 276: R397-406.