Court File No. T-2411-14

FEDERAL COURT

B E T W E E N :

APOTEX INC.

Applicant

- and -

MINISTER OF HEALTH and
ATTORNEY GENERAL OF CANADA

Respondents

NOTICE OF APPLICATION

TO THE RESPONDENT:

A PROCEEDING HAS BEEN COMMENCED by the applicant. The relief claimed by the applicant appears on the following page.

THIS APPLICATION will be heard by the Court at a time and place to be fixed by the Judicial Administrator. Unless the Court orders otherwise, the place of hearing will be as requested by the applicant. The applicant requests that this application be heard at Toronto.

IF YOU WISH TO OPPOSE THIS APPLICATION, to receive notice of any step in the application or to be served with any documents in the application, you or a solicitor acting for you must prepare a notice of appearance in Form 305 prescribed

by the *Federal Courts Rules* and serve it on the applicant's solicitor, or where the applicant is self-represented, on the applicant, WITHIN 10 DAYS after being served with this notice of application.

Copies of the *Federal Courts Rules*, information concerning the local offices of the Court and other necessary information may be obtained on request to the Administrator of this Court at Ottawa (telephone 613-992-4238) or at any local office.

IF YOU FAIL TO OPPOSE THIS APPLICATION, JUDGMENT MAY BE GIVEN IN YOUR ABSENCE AND WITHOUT FURTHER NOTICE TO YOU.

November 24, 2014

Issued by: _____
Registry Officer

Address of local office: 180 Queen St. West
Suite 200
Toronto, Ontario M5V 3L6

TO: THE REGISTRAR
Federal Court of Canada
Application Division
180 Queen St. West
Suite 200
Toronto, Ontario M5V 3L6

AND TO: MINISTER OF HEALTH and ATTORNEY GENERAL OF CANADA
130 King Street West
Suite 3400, Box 36
Toronto, Ontario M5X 1K6

APPLICATION

THIS IS AN APPLICATION for judicial review by Apotex Inc. ("Apotex") for judicial review in respect of the refusal of the Respondent, Minister of Health ("Minister"), to issue a Notice of Compliance ("NOC") in respect of Apotex's submission for its Rasagiline 0.5 and 1 mg tablets ("Apo-Rasagiline") in accordance with Division C to the *Food and Drugs Act Regulations* ("*FDA Regulations*") notwithstanding that Apotex has met all requirements for the issuance of an NOC.

THE APPLICANT MAKES APPLICATION FOR:

1. An order quashing the decision of the Minister not to issue an NOC to Apotex for Apo-Rasagiline;

2. An Order in the nature of *mandamus* compelling the Minister to issue an NOC to Apotex for Apo-Rasagiline;

3. Costs of this application on a scale and in amount determined by this Honourable Court to be appropriate in all of the circumstances; and

4. Such further and other relief as this Honourable Court may deem just.

THE GROUNDS FOR THE APPLICATION ARE:

Overview

5. Apotex is a Canadian corporation that carries on business as a manufacturer of "generic" pharmaceutical products. A generic product is a product equivalent to an original product already on the market.

6. Apotex has filed with the Minister all necessary data to demonstrate the safety and efficacy of Apo-Rasagiline as required under the *FDA Regulations*.

7. Apo-Rasagiline tablets are manufactured at Apotex Research Private Limited ("ARPL"), a company related to Apotex based in India. The active pharmaceutical ingredient ("API") in Apo-Rasagiline is manufactured at Apotex Pharmachem India Pvt Ltd. ("APIPL"), another Indian company related to Apotex.

8. By letter dated April 15, 2013, Apotex was advised that its submission for Apo-Rasagiline was satisfactory and that the issuance of the NOC was on hold, awaiting the expiry of a market exclusivity period of another manufacturer and determination of applications for prohibition under the *Patented Medicines (Notice of Compliance) Regulations* (the *"PMNOC Regulations")* .

9. The market exclusivity period expired on August 17, 2014 and the last patent hurdle preventing issuance of an NOC pursuant to the *PMNOC Regulations* was overcome on November 13, 2014.

10. As c that date Apotex was entitled to an NOC in respect of Apo-Rasagiline.

11. On I ovember 17, 2014, Barbara Sabourin, Director General ("DG"), Therapeutic Produ :s Directorate ("TPD"), the Minister's delegate in charge of the issuance of NOCs, ' elephoned Apotex's President and CEO, Dr. Jeremy Desai ("Dr. Desai") and advise an NOC would not be issued to Apotex for Apo-Rasagiline.

12. The purported basis for the refusal to issue the NOC was that the DG is not willing or is not being permitted to issue NOCs for products manufactured at APRL or manufactured using API from APIPL. ARPL and APIPL have been subject to an import ban in respect of certain products since September 30, 2014 (the "Import Ban"). Apotex asserts that the Import Ban is unlawful and on October 29, 2014 commenced a separate judicial review proceeding challenging the legality of the Import Ban.

13. Regardless of the lawfulness of the Import Ban, neither the fact of the Import Ban nor any purportedly underlying issue, if any exists, are relevant considerations for the issuance of an NOC to Apotex for Apo-Rasagiline. The matters are unrelated.

Regulatory Regime

14. The Minister controls the approval of new drugs in Canada through exercise of statutory powers under the Food and Drugs Act, (Canada) and the FDA

Regulations. No person may advertise or sell a new drug in Canada unless and until the Minister grants that person an NOC in respect of that drug.

15. Section C.08.004 of the *FDA Regulations* directs that a drug manufacturer may obtain an NOC in respect of a new drug only after filing a submission. The Minister has the statutory duty to receive and process submissions in accordance with the FDA Regulations. If a submission is compliant with the FDA Regulations, the FDA Regulations direct that the Minister shall issue an NOC. The decision as to acceptability of submissions is delegated by the Minister to the DG of TPD.

16. A submission must contain sufficient information to enable TPD to assess the safety and effectiveness of the new drug in question. The submission may be either a New Drug Submission ("NDS") which is a submission including the results of clinical trials, or it may be an Abbreviated New Drug Submission ("ANDS"), which is a submission demonstrating equivalence to a reference product already approved and sold in Canada.

17. Typically, an ANDS will include one or more "comparative bioavailability studies" or "bioequivalence studies" to establish equivalence to a reference product already marketed and sold in Canada. These are studies in which the product is compared to the reference product by administering the drugs to human subjects, and measuring blood levels over a period after ingestion. A

statistical analysis is then performed on the results to demonstrate that both products are absorbed to a comparable extent and at a comparable rate.

Apo-Rasagiline Tablets

18. Rasagiline is the generic name for a drug product used as a monotherapy in early Parkinson's disease or as an adjunct therapy in more advanced cases. Rasagiline is marketed in in Canada by Teva Pharmaceutical Industries Ltd. ("Teva") under the brand name Azilect.

19. Apotex submitted to TPD a submission for its Apo-Rasagiline tablets demonstrating bioequivalence to Azilect tablets on August 23, 2012.

20. At the time of the submission, Teva was entitled to market exclusivity pursuant to the data protection provisions of the *FDA Regulations* until August 17, 2014. Teva also had two patents listed on the Patent Register pursuant to the *PMNOC Regulations.*

21. By letter dated April 15, 2013, the DG advised Apotex that its submission for Apo-Rasagiline met the requirements for the issuance of an NOC pursuant to the *FDA Regulations.* However, the issuance of the NOC was placed on hold pending the expiration of Teva's market exclusivity period and until the requirements of the *PMNOC Regulations* were met.

22. On August 17, 2014, Teva's market exclusivity period for Azilect expired. On October 12, 2014, the first of Teva's registered patents expired. On

November 13, 2014, Apotex successfully resisted a prohibition proceeding brought by Teva in respect of Teva's other registered patent. Accordingly, as of November 13, 2014, Apotex had met all requirements necessary for the issuance of an NOC for Apo-Rasagiline, namely:

(a) Apotex had demonstrated, to the satisfaction of Health Canada, the product to be safe and effective pursuant to the *FDA Regulations;*

(b) No exclusivity period remained; and

(c) Apotex had met all requirements *PMNOC Regulations.*

23. Pursuant to section C.08.004 of the FDA *Regulations*, the Minister was under a statutory duty to issue Apotex an NOC for Apo-Rasagiline as of that date.

The Import Ban

24. In late January 2014, the United States Food and Drug Administration ("FDA") conducted an inspection of APIPL's manufacturing plant and advised APIPL of alleged observations with respect to "data reliability" and laboratory procedures. This was done via the issuance of a "Form 483" notice to APIPL under U.S. law.

25. The alleged observations did not suggest any problem with actual product quality. The issuance of a Form 483 with observations requiring improvements is very common and occurs with most inspections. Moreover, unlike what happens in the U.S., Apotex fully retests all dosage forms and ingredients

imported into Canada before release for use or sale, regardless of testing done at the manufacturing plants. Hence, even if there were deficiencies in testing at the plants, same would have no relevance to quality of goods for sale in Canada.

26. The FDA has different operating guidelines for its inspection when auditing foreign facilities. Those guidelines are such that non-U.S. plants are subject to more frequent and more stringent inspections by the FDA than U.S. plants. As a result, FDA often issues Form 483s, and then warning letters and/or import alerts, on the basis of observations that would not result in equivalent actions against plants in the United States.

27. The differential nature of the FDA's foreign plant inspection procedure is such that many of the Form 483s, warning letters and import alerts that are issued by the FDA generally result in no action by agencies of other countries, who rely on their own inspections of such facilities or on the inspections of other countries' regulatory bodies.

28. On April 2, 2014, the FDA issued an import alert in respect of APIPL products (i.e., APIs) entering the United States (the "APIPL Import Alert"). This was done solely on the basis of the Form 483 issued in January 2014, and without regard for Apotex's responses explaining that the observations were minor, partially erroneous, and already addressed, such that there was no reasonable basis of concern. The effect of the import alert was to refuse entry into the United States of

all drug products originating from material made at APIPL except for riluzole which was deemed to be medically necessary.

29. From April to August 2014, Apotex regularly communicated with Health Canada in respect of APIPL (and ARPL), including providing copies of materials submitted to the FDA as part of the FDA's ongoing investigations. Health Canada did not bring any concerns to the attention of Apotex or APIPL in this period.

30. Between August 7, 2014 and August 14, 2014, Health Canada, supported by the Australian Therapeutic Goods Administration ("TGA"), Health Canada's counterpart regulatory agency in Australia, inspected APIPL. Neither Apotex nor APIPL was advised of any significant concerns by Health Canada or the TGA inspectors regarding compliance with Good Manufacturing Practices ("GMP") at that time, this despite them being cognizant of the FDA's alleged data reliability and laboratory procedure concerns.

31. On September 25, 2014, Health Canada provided Apotex with confirmation that APIPL would be assigned a Compliant (C) rating, and that no observations had been made of issues related to data integrity (which had purportedly been found by the FDA).

32. A similar inspection had been carried out in February, 2014 by the United Kingdom Medicines and Healthcare Products Regulatory Agency ("MHRA"), Health Canada's counterpart regulatory agency in the U.K., supported by Health

Canada, at the ARPL facility. At the time of this inspection, MHRA and Health Canada were fully cognizant of the FDA's alleged data reliability and laboratory procedure concerns relating to APIPL. Following the February 2014 inspection, on May 6, 2014, the MHRA issued a GMP Certificate of Compliance for ARPL. The GMP Certificate of Compliance is valid for 3 years.

33. On or about May 6, 2014, Health Canada similarly recognized that ARPL was GMP compliant pursuant to the above joint MHRA/Health Canada inspection.

34. During the month of September, 2014 the Toronto Star published several articles impugning Indian pharmaceutical manufacturing facilities generally and Apotex's Indian facilities specifically. In the days which followed these publications, the Minister was compelled to respond to vigorous questioning in Parliament in respect of the content of the articles.

35. Then, on September 30, 2014, Apotex was advised by Health Canada that the Canadian Border Services Agency ("CBSA") had been instructed to restrict importation of active pharmaceutical ingredients ("APIs") from Apotex Pharmachem India Pvt Ltd. ("APIPL") and finished product from ARPL, and that the CBSA would defer to Health Canada to make a determination of action. At the same time, similar action was taken with respect to only one other plant, an API plant called IPCA Laboratories ("IPCA").

36. This came as a complete surprise to Apotex because at all times up to September 29, 2014, there had been no indication from Health Canada of any significant concern about GMP compliance at either APIPL or ARPL. To the contrary, as result of inspections carried out jointly with other regulatory agencies after the inspections by US FDA, and with full knowledge of them, Health Canada had explicitly confirmed that both plants were and are compliant.

37. Even when the Import Ban was issued, Health Canada issued a statement advising consumers that "no specific safety issues have been identified with products...". There was no recall of product already on the market made by APIPL or ARPL. It was clear that there was no safety issue.

38. In the two years prior to September 30, 2014, approximately 40 foreign plants, including plants in Canada, had been subject to similar Warning Letters and/or Import Alerts by the US FDA. Yet, Health Canada had never previously announced an import ban with respect to any, apparently in recognition that the US actions are often unreasonable and discriminatory, instead relying on Health Canada's own inspections, in accordance with Canadian regulations and policies. The only apparent basis of distinguishing the plants of APIPL, ARPL and IPCA from all others was that only these plants were cited in the Toronto Star articles, which asserted that the Minister was negligent to not also ban these three plants.

39. Apotex has filed a judicial review asserting, *inter alia,* that the Import Ban is unlawful, is outside the scope of authority of the Minister and was implemented for an ulterior purpose.

Unlawful Decision not to Issue NOC

40. Notwithstanding that Apotex has met all lawful requirements for the issuance of an NOC, the Minister, through the DG, has refused to comply with her statutory obligation to issue an NOC.

41. Without warning and without providing any opportunity for Apotex to respond, in a telephone call from the DG on November 17, 2014, Dr. Desai was advised that the DG was not willing to grant or was not being permitted to grant NOCs for products that have been made at ARPL or products using API made from APIPL due to the Import Ban imposed by the Minister. Dr. Desai was told that the affected products, including Apo-Rasagiline would be put on hold.

42. There is no lawful basis upon which the decision not to issue the NOC for Apo-Rasagiline was made. More particularly:

(a) all requirements for the issuance of an NOC have been met;

(b) there is currently no legitimate safety concern related to Apo-Rasagiline, nor has one been offered by the Minister;

(c) no safety (or efficacy) concern was identified during the review of Apotex's submission for Apo-Rasagiline;

(d) Heath Canada has acknowledged in both its words and actions that there is no safety concern with respect to products originating from ARPL or products using API made from APIPL;

(e) the Import Ban is unlawful and was implemented for an unlawful purpose;

(f) the Import Ban has no bearing on the requirements for the issuance of an NOC; and

(g) Health Canada's guidance entitled: *Post-Notice of Compliance (NOC) Changes - Quality Guidance* permits a manufacturer to change the manufacturing site of a drug substance (API) or drug product (finished dosage form) after receipt of an NOC without requiring the prior approval of Heath Canada, confirming that the site of manufacture is an irrelevant consideration for the issuance of an NOC.

43. The decision not to issue the NOC was made contrary to facts known to the DG and Minister that Apo-Rasagiline submission met all lawful requirements for the issuance of an NOC. Accordingly, the decision was made for some ulterior, improper, irrelevant or arbitrary reason. Moreover, Apotex was afforded no opportunity to be heard in advance of the decision being made.

44. Apotex states that it was only as a result of the publicity of the Toronto Star articles, rather than any genuine concern about safety, that the Import Ban was issued. Apotex states that this was arbitrary, discriminatory and unfair and, as such, the reliance on the Import Ban in making the decision not to issue an NOC for Apo-Rasagiline was also arbitrary, discriminatory and unfair.

45. As Apotex has met all lawful requirements for the issuance of an NOC, the Minister is obligated to now issue an NOC. The Minister has no discretion to do otherwise. The withholding of the NOC in the face on the Minister's statutory duty to issue same is unlawful and a denial of natural justice, and compels this Court's intervention.

46. The Minister and her delegates have treated Apotex unfairly, unlawfully, arbitrarily, discriminatorily and contrary to its legitimate expectations such that this Honourable Court should intervene.

THE APPLICANT REQUESTS, PURSUANT TO RULE 317, THE FOLLOWING MATERIAL IN THE POSSESSION OF THE MINISTER BE PRODUCED:

47. All documents relating to:

(a) the decision to not to issue the NOC for Apo-Rasagiline; and

(b) communication between TPD and the Minister's Office in respect of Apo-Rasagiline.

THIS APPLICATION WILL BE SUPPORTED BY THE FOLLOWING MATERIAL:

1. The Affidavits to be affirmed;

2. Such further and other material as counsel may advise and this Honourable Court may permit.

November 24, 2014

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