Date: 20000629

Docket: T-857-99

Ottawa, Ontario, this 29th day of June, 2000

PRESENT: THE HONOURABLE MR. JUSTICE JOHN A. O'KEEFE

BETWEEN:

MERCK FROSST CANADA & CO., and
MERCK & CO., INC.

Applicants

- and -

THE MINISTER OF HEALTH and
THE ATTORNEY GENERAL FOR CANADA

Respondents

REASONS FOR ORDER AND ORDER

O'KEEFE J.

Factual Background

[1] This is an application for judicial review by Merck Frosst Canada & Co. and Merck & Co., Inc. ("applicants") in respect of a decision of the Therapeutic Products Programme, Submission and Information Policy Division of the respondent, The Minister of Health ("Minister") dated April 12, 1999.

[2] The decision of the Minister dated April 12, 1999 refused to list Canadian Patent No. 1,340,331 ("'331 Patent") against the medicine simvastatin on the Patent Register maintained by the Minister pursuant to the *Patented Medicines (Notice of Compliance) Regulations* (the "Regulations") because ". . . the patent only contains claims for metabolites of simvastatin and the use of simvastatin metabolites as medicine. These claims do not include a claim for the medicine or its use . . . Accordingly, Patent 1,340,331 will not be added to the Patent Register against simvastatin."

[3] The applicants made application for:

> (1) An Order quashing the decision of the Minister dated April 12, 1999, refusing

to add the ‘331 Patent to the Patent Register in respect of simvastatin.

(2) An Order directing the Minister and his agents to add the ‘331 Patent to the Patent Register in respect of simvastatin.

(3) Such further and other relief as to this Honourable Court may seem just.

(4) Its costs of the application.

[4] Merck Frosst Canada & Co. (“Merck”) filed a new drug submission with the Minister on July 14, 1988, seeking approval to market the drug ZOCOR in Canada, using the medicine simvastatin. In seeking approval to market ZOCOR, Merck filed many documents, including an expert’s report written by Dr. Gerson, Mr. Alberts and Dr. Vickers, dealing with the pharmacology and toxicology of using simvastatin. The documentation filed also included a memo from Mr. Schwartz to Dr. Stubbs which summarized studies profiling active metabolites of simvastatin found in dog and human plasma.

[5] Also included in the submission for the notice of compliance was an expert report on the pharmacology and toxicology of simvastatin. This report identifies the major metabolites of simvastatin. The notice of compliance included a product monograph of the tablets containing simvastatin.

[6] Merck received a notice of compliance on August 29, 1990 to market the drug ZOCOR using the medicine simvastatin in its lactone form. Simvastatin also refers to the conventional or generic name for this lactone. The notice of compliance gave Merck approval to market ZOCOR in strengths containing respectively, 5 mg, 10 mg, 20 mg and 40 mg of simvastatin. On June 21, 1999 Merck received a notice of compliance to market ZOCOR in a tablet strength of 80 mg of simvastatin.

[7] After the enactment in March, 1993 of the *Patented Medicines (Notice of Compliance) Regulations*, the applicants listed two patents, No. 1,199,322 and No. 1,161,380 on the Patent Register with respect to

the medicine simvastatin (No. 1,161,380 was referred to as 116,380).

[8] On February 22, 1999, the Minister received a request from Merck to list on the Patent Register with respect to simvastatin, a Patent List (Form IV) for the ‘331 Patent. Merck was granted the ‘331 Patent on January 26, 1999.

[9] The ‘331 Patent is entitled “HMG-COA Reductase Inhibitors”. ZOCOR tablets contain simvastatin in its lactone form which has a certain chemical structure, however, the medicine in this form is inactive against HMG-COA reductase, the target enzyme of simvastatin as hypocholesteremic agent. It is only after the ingestion of the simvastatin (ZOCOR tablet) that the medicine is metabolized in the liver and a new chemical structure results. It is this compound called a simvastatin metabolite that is claimed in the ‘331 Patent.

[10] The structure of the metabolite is commonly referred to as simvastatin in its “ring

> opened" form due to the visual representation of the changes undergone in chemical structure from simvastatin in its lactone form. It is the medicine in the ring opened form which inhibits the production of certain enzymes and acts as a counter-agent to the formation of cholesterol.

[11] The basic difference between simvastatin and its metabolites is that simvastatin

> has a methyl group at the "6' position". The metabolites have a different identity at the 6' position. It is these metabolites that have an active therapeutic effect in inhibiting HMG-COA reductase and thereby prevent and treat hypercholesterolemia. These active metabolites also have a therapeutic effect in preventing and treating coronary heart disease.

[12] In order to comply with the *Food and Drug Regulations*, Merck was required to

> supply considerable material establishing the safety and utility of the medicine simvastatin and its proposed drug ZOCOR. Part of these submissions included a memo describing the identification and effects of the above mentioned metabolites on human and dog plasma. The memo describes hydroxymethyl simvastatin,

dihydroxy-acid, carboxy simvastatin and the activity of these compounds against the HMG-COA reductase–the target enzyme.

[13] On January 26, 1999, Merck was granted the ‘331 Patent which contained both product claims and use claims. The product claims include claims for the novel compounds 6'-CH_2OH-simvastatin (hydroxymethyl simvastatin) and 6'-COOH-simvastatin (carboxy simvastatin) and their ring opened dihydroxy acids. The remaining claims deal with the use of these compounds in the treatment of various diseases and as HMG-COA reductase inhibitors.

[14] From the information provided, Merck indicates that simvastatin enters the body in its 6' methyl form. Simvastatin is then metabolized in humans to form the active compounds claimed by the ‘331 Patent. The active metabolites are used as therapeutic agents by the body to inhibit HMG-COA reductase.

[15] The Patent List, the ‘331 Patent and the United States Pharmacopeia chemical

structure for simvastatin were reviewed by Therapeutic Products Programme employee, Ms. Bowes. Ms. Bowes decided that the patent was ineligible for inclusion on the Patent Register since the '331 Patent contained no claims for the medicine simvastatin *per se*, only for its metabolites. Therefore, the '331 Patent did not contain a "claim for the medicine itself".

[16] Merck was notified of the decision and filed further submissions, however, by letter dated April 12, 1999, the original objection to inclusion of the '331 Patent was maintained:

> The patent does not contain a claim for the medicince itself, namely simvastatin, nor does the patent contain a claim for the use of the medicine. As you have pointed out on page 2 of your representations, the patent only contains the claims for metabolites of simvastatin and the use of simvastatin metabolites as medicines. These claims do not include a claim for the medicine simvastatin or its use. Therefore, paragraph 4(2)(d) [sic] of the Regulations has not been satisifed.

[17] Merck commenced this application on May 14, 1999.

Issue

[18] Was the Minister correct in refusing to add the ‘331 Patent to the Patent Register in respect of simvastatin for reason of non-compliance with paragraph 4(2)(b) of the Regulations?

Law

[19] Section 2 of the *Patented Medicines (Notice of Compliance) Regulations* (“Regulations”) read:

2. In these Regulations,	2. Les définitions qui suivent s'appliquent au présent règlement.
"claim for the medicine itself" includes a claim in the patent for the medicine itself when prepared or produced by the methods or processes of manufacture particularly described and claimed or by their obvious chemical equivalents;	«revendication pour le médicament en soi» S'entend notamment d'une revendication, dans le brevet, pour le médicament en soi préparé ou produit selon les modes du procédé de fabrication décrits en détail et revendiqués ou selon leurs équivalents chimiques manifestes.
"claim for the use of the medicine" means a claim for the use of the medicine for the diagnosis, treatment, mitigation or prevention of a disease, disorder or abnormal physical state, or the symptoms thereof;	«revendication pour l'utilisation du médicament» Revendication pour l'utilisation du médicament aux fins du diagnostic, du traitement, de l'atténuation ou de la prévention d'une maladie, d'un désordre, d'un état physique anormal, ou de leurs symptômes.
"medicine" means a substance intended or capable of being used for the diagnosis, treatment, mitigation or prevention of a disease, disorder or	«médicament» Substance destinée à servir ou pouvant servir au diagnostic, au traitement, à l'atténuation ou à la prévention d'une

abnormal physical state, or the symptoms thereof;	maladie, d'un désordre, d'un état physique anormal, ou de leurs symptômes.

[20] Section 4 of the Regulations states:

4. (1) A person who files or has filed a submission for, or has been issued, a notice of compliance in respect of a drug that contains a medicine may submit to the Minister a patent list certified in accordance with subsection (7) in respect of the drug.	4. (1) La personne qui dépose ou a déposé une demande d'avis de conformité pour une drogue contenant un médicament ou qui a obtenu un tel avis peut soumettre au ministre une liste de brevets à l'égard de la drogue, accompagnée de l'attestation visée au paragraphe (7).
(2) A patent list submitted in respect of a drug must	(2) La liste de brevets au sujet de la drogue doit contenir les renseignements suivants:
(a) indicate the dosage form, strength and route of administration of the drug;	a) la forme posologique, la concentration et la voie d'administration de la drogue;
(b) set out any Canadian patent that is owned by the person, or in respect of which the person has an exclusive licence or has obtained the consent of the owner of the patent for the inclusion of the patent on the patent list, that contains a claim for the medicine itself or a claim for the use of the medicine and that the person wishes to have included on the register;	b) tout brevet canadien dont la personne est propriétaire ou à l'égard duquel elle détient une licence exclusive ou a obtenu le consentement du propriétaire pour l'inclure dans la liste, qui comporte une revendication pour le médicament en soi ou une revendication pour l'utilisation du médicament, et qu'elle souhaite voir inscrit au registre;

[21] The definition of the term drug is not defined in the Regulations, but it is defined

in section 2 of the *Food and Drug Act*, R.S.C. 1985, c. F-27:

"drug" includes any substance or mixture of substances manufactured, sold or represented for use in	«drogue» Sont compris parmi les drogues les substances ou mélanges de substances fabriqués, vendus ou présentés comme pouvant servir_:
(a) the diagnosis, treatment, mitigation or prevention of a disease, disorder or abnormal physical state, or its symptoms, in human beings or animals,	a) au diagnostic, au traitement, à l'atténuation ou à la prévention d'une maladie, d'un désordre, d'un état physique anormal ou de leurs symptômes, chez l'être humain ou les animaux;
(b) restoring, correcting or modifying organic functions in human beings or animals, or	b) à la restauration, à la correction ou à la modification des fonctions organiques chez l'être humain ou les animaux;
(c) disinfection in premises in which food is manufactured, prepared or kept;	c) à la désinfection des locaux où des aliments sont gardés.

Analysis and Decision

[22] After the applicants were granted their Patent No. 1,340,331 on January 26, 1999, they applied to the Minister to have the ‘331 Patent added to the Patent List. The Minister refused on the grounds that the ‘331 Patent made no “claim for the medicine itself or a claim for the use

of the medicine." as required by paragraph 4(2)(b) of the Regulations.

[23] The applicants stated in their letter to the Minister dated March 24, 1999 that

"after oral ingestion in humans simvastatin is converted to its corresponding metabolites including hydroxymethyl simvastatin and carboxy simvastatin and their corresponding ring opened dihydroxy acids". It is the metabolites that lower blood cholesterol.

[24] As the NOC was issued for the medicine simvastatin, the Minister takes the

position that there is no claim for the medicine itself or a claim for the use of the medicine in the '331 Patent. A study of the '331 Patent shows that, for the purpose of this application, the patent contains claims to novel compounds having pharmacological activity as antihypercholesterolemic agents and these compounds are hydroxymethyl simvastatin and carboxy simvastatin and their corresponding ring opened dihydroxy acids.

[25] Hydroxymethyl simvastatin and carboxy simvastatin are derivatives of

simvastatin which differ from simvastatin at the 6' position of the polydydronaphthyl group by inclusion of either hydroxymethyl or carboxyl group at that position. Simvastatin has a methyl group at the 6' position.

[26] Hydroxymethyl simvastatin and carboxy simvastatin and their corresponding ring

opened dihydroxy acids are made after oral ingestion in humans of simvastatin i.e. after the ZOCOR tablet is ingested. The simvastatin in the tablet is converted to its corresponding metabolites including hydroxymethyl simvastatin and carboxy simvastatin and their corresponding ring opened dihydroxy acids.

[27] The applicants have admitted that hydroxymethyl simvastatin and carboxy

simvastatin have different chemical structures than simvastatin. The examination in chief of Dr. Michael Dobrinska, the executive director, Drug Metabolism-Clinical with the applicants and an expert in the area of drug metabolism contains the following at pages 123-124:

Q. Okay. Now, do you agree that to be different medicines you require a different chemical structure?

A. Different medicines require a different chemical structure? Yes, that is a truism. Otherwise, it would be the same thing.

Q. Now I am going to refer you to paragraph two of your affidavit. In paragraph two you have there the chemical structure of simvastatin, is that correct, the first - -

A. Yes.

Q. The following page, page three, you have the chemical structure of the other two; the ones that are at play here: the carboxyl-simvastatin, and also the hydroxymethyl-simvastatin. Do these have the same chemical structure?

A. No, they do not.

Q. I am sorry?

A. No.

Q. They do not?

A. They do not.

[28] The applicants submitted that hydroxymethyl simvastatin and carboxy simvastatin

are medicines that have therapeutic effects and were mentioned in the New Drug Submission ("NDS") for ZOCOR using the medicine simvastatin and are therefore covered by the NOC that

was issued for ZOCOR. The applicants thus claim that there is a claim for the use of the medicine itself.

[29] The evidence establishes that the NOC was issued for ZOCOR using simvastatin as a medicine and that two documents filed with the NDS for ZOCOR did discuss hydroxymethyl simvastatin and carboxy simvastatin.

[30] In essence, the applicants have submitted before me that hydroxymethyl simvastatin and carboxy simvastatin are medicines and that there is a claim for their use as medicines in the '331 Patent. Then, since they are compounds of simvastatin, they should be added to the Patent List for simvastatin.

[31] The applicants have admitted that hydroxymethyl simvastatin and carboxy simvastatin are metabolites of simvastatin. It is agreed that after oral ingestion in humans, simvastatin is converted to its corresponding metabolites (degradation products of the drug resulting from metabolism in the liver).

[32] This Court has traditionally taken a less than broad approach to defining the words "the medicine itself" (see *Hoffman-LaRoche Ltd.* v. *Canada (Minister of National Health and Welfare)* (1999) 86 C.P.R. (3d) 187 (F.C.A.)). This approach may be changing with the remarks made by Rothstein J.A. in *Apotex Inc. and NovoPharm Limited* v. *The Minister of National Health and Welfare and The Attorney General of Canada*, Unreported, December 16, 1999, Docket A-473-98 (see paragraphs 17 and 18).

[33] The standard of review to be applied to the Minister's decision to add patents to the Register is discussed in *Apotex Inc. and Novopharm Limited* and *The Minister of National Health and Welfare and The Attorney General of Canada, ibid*, at pages 7-8:

> What this then leaves is the question of whether the Minister was unlawfully exercising or declining to exercise his discretion to refuse to add or to delete patents from the Register. Arguably, *mandamus*, injunctive or even declaratory relief might be available in such circumstances. In *Baker* v. *Canada (M.C.I.)* (1999), 174 D.L.R. (4th) 193, at para. 53, L'Heureux-Dubé J. observes that traditionally, discretionary decisions can only be reviewed on limited grounds such as the bad faith of the decision-maker, the exercise of discretion for an improper purpose or the use of irrelevant considerations. A general doctrine of unreasonableness had also sometimes been applied to discretionary decisions. She continues that discretionary decisions must be made within the bounds of jurisdiction conferred by the statute but that considerable deference will be afforded to decision-makers by the courts in

> reviewing the exercise of that discretion and the scope of the decision-makers' jurisdiction.
>
> We are not satisfied that there are grounds in this case for the Court interfering with the exercise of discretion by the Minister. There are two reasons for our coming to this conclusion. The first is based on the evidence and the second relates to the scheme of the Regulations.

[34] I will now review the Minister's refusal to add the '331 Patent to the Patent Register against this standard of review. The Minister had before him, an application to add the '331 Patent which is a patent for, among other things, hydroxymethyl simvastatin and carboxy simvastatin which are medicines in their own right. It was the finding of the Minister that hydroxymethyl simvastatin and carboxy simvastatin are different chemical compounds than simvastatin and hence, a claim for these compounds is not a claim for the medicine itself (simvastatin) or the use of the medicine (simvastatin). I agree that the decision of the Minister is correct.

[35] My reasons for coming to this conclusion are as follows:

1. The medicine in the ZOCOR pill is simvastatin.

> 2. The ZOCOR tablet does not contain hydroxymethyl simvastatin or carboxy simvastatin as these metabolites of simvastatin are derived from the simvastatin, in the tablet, by the liver, after the ingestion of the ZOCOR tablet.
>
> 3. If hydroxymethyl simvastatin and carboxy simvastatin are medicines, they are not the medicine simvastatin.
>
> 4. The '331 Patent makes no claim for the medicine simvastatin itself or the use of the medicine simvastatin.

[36] The Minister can only add a patent to the Patent List pursuant to paragraph 4(2)(b) of the *Patented Medicines (Notice of Compliance) Regulations*, a patent that contains a claim "for the medicine itself or a claim for the use of the medicine". Paragraph 4(2)(b) in its entirety states:

4(2) A patent list submitted in respect of a drug must	4(2) La liste de brevets au sujet de la drogue doit contenir les renseignements suivants :
. . .(b) set out any Canadian patent that is owned by the person, or in respect of which the person has an exclusive licence or has obtained the consent of the owner of the patent for the inclusion of the patent on the patent list, that contains a claim for the medicine itself or a claim for the use of the medicine and that the person wishes to have included on the register;	. . . b) tout brevet canadien dont la personne est propriétaire ou à l'égard duquel elle détient une licence exclusive ou a obtenu le consentement du propriétaire pour l'inclure dans la liste, qui comporte une revendication pour le médicament en soi ou une revendication pour l'utilisation du médicament, et qu'elle souhaite voir inscrit au registre;

[37] It is my conclusion that since hydroxymethyl simvastatin and carboxy simvastatin

are different chemical compounds and medicines which are not contained in the ZOCOR tablet, therefore, the ‘331 Patent does not contain a claim for the medicine simvastatin itself or the use of the medicine simvastatin. As a consequence, the ‘331 Patent cannot be added to the Patent List for ZOCOR tablets.

[38] I therefore find that:

1. The Minister was correct in refusing to add the ‘331 Patent to the Patent Register

in respect of simvastatin for reason of non-compliance with paragraph 4(2)(b) of the Regulations.

2. The Minister did not refuse to exercise his jurisdiction.

3. The Minister did not err in law or act contrary to the law.

4. The Minister did not base his decision on an erroneous finding of fact made without regard to the material before him.

[39] The application for judicial review is dismissed.

[40] The respondent shall have its costs to be taxed.

ORDER

[41] **IT IS ORDERED that** the application for judicial review is dismissed.

[42] **IT IS FURTHER ORDERED that** the respondent shall have its costs to be taxed.

"John A. O'Keefe"

J.F.C.C.

Ottawa, Ontario
June 29, 2000