Commissioner's Decision #1263
Décision du Commissaire #1263

TOPIC: FO1, O
SUJECT: FO1, O

Application No : 2,166,001
Demand no : 2,166,001

COMMISSIONER'S DECISION SUMMARY

C.D. 1263...Application No. 2,166,001

The examiner rejected this application on the basis that the invention claimed lacked novelty and was obvious, at the claim date, over cited prior art consisting of the Canadian patent application, a United States patent, a PCT patent application and several non-patent publications. The Board found that the applicant was claiming an invention which was novel and unobvious.

The application was returned to the examiner by the Commissioner of Patents.

IN THE CANADIAN PATENT OFFICE

DECISION OF THE COMMISSIONER OF PATENTS

Patent application 2,166,001 having been rejected under Rule 30(4) of the Patent Rules, the Applicant asked that the Final Action of the Examiner be reviewed. The rejection has consequently been considered by the Patent Appeal Board and by the Commissioner of Patents. The findings of the Board and the ruling of the Commissioner are as follows:

Agent for Applicant

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This decision deals with the Applicant's request for a review by the Commissioner of Patents of the Examiner's Final Action dated October 23, 2000, on application 2,166,001 (International Classification A61K-38/05), filed on December 22, 1995 and entitled "Stable Solid Formulation of Enalapril Salt and Process for Preparation Thereof". The inventor is Bernard Charles Sherman.

A hearing before the Patent Appeal Board was held on August 20, 2003. Appearing on behalf of the Applicant were Mr Harry Radomsky and Mr Ivor Hughes. Representing the Patent Office were Ms Holly Notman, the examiner in charge of the application and Mr Tony Neppel.

Prior to the hearing, Mr Alexander Macklin of the firm of Gowling Lafleur and Henderson, representing Merck & Co. and Merck Frosst Canada & Co. requested permission to intervene at the hearing on behalf of his clients. Permission to intervene was denied but the Board indicated that one observer could attend. Mr Emmanuel Manolakis of Gowling Lafleur and Henderson attended the hearing as an observer.

The application relates to a method of forming a stable formulation of an enalapril salt.

Claims 1 and 2 of the application read as follows:

> 1. A process of manufacture of a pharmaceutical solid composition comprising enalapril sodium, which process comprises the steps of:
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> i) a) mixing enalapril maleate with an alkaline sodium compound and at least one other excipient, adding water sufficient to moisten and mixing to achieve a wet mass, or
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> b) mixing enalapril maleate with at least one excipient other than an alkaline sodium compound, adding a solution of an alkaline sodium compound in water, sufficient to moisten and mixing to achieve a wet mass; thereby to achieve a reaction without converting the enalapril maleate to a clear solution of enalapril sodium and maleic acid sodium in water.
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> ii) drying the wet mass, and
>
> iii) further processing the dried material into a pharmaceutical solid composition.

> 2. A process of manufacture of a pharmaceutical solid composition comprising enalapril sodium, which process comprises the steps of:
>
> i) a) mixing enalapril maleate with an alkaline sodium compound and at least one other excipient, adding water sufficient to render the mass very moist and mixing to achieve a wet mass, or
>
> b) mixing enalapril maleate with at least one excipient other than an alkaline sodium compound, adding a solution of an alkaline sodium compound in water, sufficient to render the mass very moist and mixing to achieve a wet mass; thereby to achieve a complete reaction for converting enalapril maleate to sodium enalapril, without converting the enalapril maleate to a clear solution of enalapril sodium and maleic acid sodium in water.
>
> ii) drying the wet mass, and
>
> iii) further processing the dried material into a pharmaceutical solid composition.

In the Final Action, the Examiner cited the following references to reject all of the claims, as well as the application itself:

Canadian patent application

2,083,683	filed May 26, 1993	Merslavic et al

United States patent

4,743,450 May 10, 1988 Harris et al

P.C.T. application

WO 94/01093 January 20, 1994 Rork & Haslam

Non-patent publications

Remington's Pharmaceutical Sciences, 18th edition, page 1642

(A.R. Gennaro et al, editors). Mack Pub. Co. 1990

VASOTEC® Product Monograph; Merck Frosst Canada Inc., 1992

Federal Court of Canada, Trial Division, Court File No. T-2408-91

Merck & Co. et al v. Apotex Inc. March 28, 1994

In the Final Action, the Examiner also made reference to "Memorandum Opinion and Order of the United States Federal District Court Judge Matthew F. Kennelly, in case No. 96 C 7375, which was an action brought by Apotex USA, Inc. against Merck & Co., Inc. for infringement of a patent related to a process for the preparation of sodium enalapril.

In her Final Action, the Examiner stated, in part:

> Harris et al disclosed stable formulations of ACE inhibitors. Such formulations included; the ACE inhibitor, e.g. enalapril; an alkaline stabilizer, eg. a sodium salt; a saccharide, e.g. lactose; a disintegrating agent, e.g. starch; and a lubricant, e.g. magnesium stearate. The compounds were combined by the wet granulation method for the manufacture of tablets.
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> Merslavic et al discloses formulations of enalapril salt. Enalapril maleate was suspended in water, a solution of sodium hydroxide, sodium carbonate, or sodium hydrogen carbonate was added, and lactose was added to the resulting clear solution of enalapril sodium salt. For comparison, tablets were also prepared by premixing all the dry ingredients.. Both procedures resulted in production of enalapril sodium although the first method was found to produce a more stable tablet.
> Rork & Haslam disclosed an osmotic pump for the controlled release of enalapril. Example 1 described a process wherein enalapril maleate was mixed with a slurry of sodium bicarbonate and water and allowed to stir until neutralization was complete, whereupon other dry ingredients were added. Example 7 described a process wherein enalapril cores were prepared by a wet granulation process.
>
> Remington describes a general method of preparing tablets by wet-granulation.
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> The VASOTEC® product monograph listed the components of Merck Frosst's enalapril tablets.
>
> Court File T2408-91 comprises the proceedings of an infringement action brought by Merck & Co. et al against Apotex Inc. The transcript contains a description of the wet granulation process for making enalapril tablets (see pages 124 to 128, proceeding s of 28 March 1994).
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> .....
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> Claims 1 to 9 do not comply with Section 28.3 of the Patent Act because they would have been obvious on the claim date to a person skilled in the art to which they pertain, having regard to Harris et al, Merslavic et al, or Rork & Haslam, or in view of the disclosure made during the Court proceedings on 28 March 1994 in view of the Vasotec® product monograph.
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> Applicant has disclosed and claimed a process for preparing tablets of enalapril sodium using a wet granulation method. Both Harris et al and Rork & Haslam used an apparent wet granulation process to produce enalapril tablets. The ingredients of the Vasotec® tablets were known to the applicant through the Vasotec® product monograph. Thus it would have been obvious to one skilled in the art that enalapril tablets containing the ingredients published on the product monograph could be made by wet granulation.
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> .....
>
> Claims 1 to 9 also do not comply with Section 28.2(1)(b) of the Patent Act because the subject matter of these claims is anticipated by the formulations, use and sale of the Vasotec® tablets by Merck & Co. prior to filing of the instant application.
>
> Regarding the Applicant's claims to novelty of his claimed process; Applicant is claiming a process which comprises mixing

certain ingredients, subjecting them to a process of wet granulation, and obtaining tablets containing a stable sodium salt of enalapril. The ingredients are old and known. The wet granulation process is old and known. Sodium salts of enalapril are old and known (see Merslavic et al, cited above).

The Applicant has argued that the gist of the alleged invention is to have devised a method allowing for the formation of a stable formulation of enalapril sodium during the process of wet granulation. Applicant further argues that there is no teaching in the cited references that the wet granulation method allows for a reaction to occur between the enalapril and the alkalizing agent (sodium salt), or that a stable composition of enalapril can be obtained by reason of using the wet granulation method to obtain a reaction between drug and alkaline compound. Applicant claims that this process therefore differs from that used by Merck because Merck has stated that the Vasotec® tablets contain enalapril maleate. Applicant further states that this process is non-obvious in view of the cited art because one skilled in the art would not expect a chemical reaction to occur during the process of wet granulation. Applicant has provided affidavits from experts in the field of chemistry and pharmaceutics to support his arguments.

The examiner has carefully considered the affidavits supplied by the Applicant. The expert witnesses consulted by the Applicant all state that in the references cited in this and previous Office Actions, no mention is made of a reaction occurring between enalapril maleate and the sodium compound during the wet granulation process. The witnesses also state that one skilled in the art would not expect a chemical (as opposed to a physical) reaction to occur during wet granulation. The witnesses again state that Merck & Co. describe their Vasotec® tablets as containing enalapril maleate, not enalapril sodium.

The examiner does not dispute these conclusions by the Applicant's expert witnesses. However, the examiner does not believe these conclusions to be relevant to the prosecution of the instant application, for reasons outlined below.

If the wet granulation process described by Mr McLeod in his testimony of 28 March 1994 (Merck v Apotex, Court File T-2408-91) and used by Merck actually resulted in tablets of enalapril maleate, then Applicant's manipulation of the process to produce tablets of enalapril sodium would indeed be inventive. However, the Applicant has gone out of his way to show that the process used by Merck actually does produce tablets of enalapril sodium, not enalapril maleate.

The Applicant has made reference to his Statement of Facts which he prepared for the Canadian Federal Court Trial (Merck v Apotex, 1994) and also submitted to the U.S. District Court for the Northern District of Illinois in Apotex U.S.A. v. Merck & Co. Inc. In this statement he asserts that

(1) he first saw the Vasotec® product monograph on March 30 1994;
(2) he knew that Vasotec® tablets were made by a wet granulation process;
(3) it immediately occurred to him that the enalapril maleate and sodium bicarbonate used by Merck would react with each other in the wet granulation process, so that the final product would contain not enalapril maleate and sodium bicarbonate but rather sodium enalapril;
(4) to confirm the forgoing, he carried out a series of experiments which showed that one mole of enalapril maleate underwent the expected acid-base reaction with 3 moles of sodium bicarbonate;
(5) Vasotec® tablets were analysed and shown to contain no unreacted enalapril maleate or unreacted sodium bicarbonate, and an independent analysis of the sodium content of Vasotec® tablets confirmed that approximately 3 moles of sodium bicarbonate were used per mole of enalapril maleate;
(6) infrared spectral analysis of Vasotec® tablets showed that the tablets contained sodium enalapril rather than enalapril maleate.

The Applicant has thus demonstrated that Merck's Vasotec® tablets are identical to the tablets Apotex produces by the process disclosed in the instant application. As Applicant has used enalapril maleate and sodium bicarbonate (with other non-reactive compounds) in a wet granulation process, it appears that Applicant's process is identical to that of Merck. As Merck was using this process long before the filing of the instant application, and as both the ingredients and the process of wet granulation were disclosed by Merck prior to the filing of the instant application, it follows that the process claimed in the instant application in not inventive because it was anticipated by Merck.

On April 23, 2001, the Applicant replied to the Final Action. In that reply, the Applicant proposed cancellation of the set of 9 claims which were before the Examiner and submitted a new set of 12 claims. The claims remain the same, however the Applicant has added 3 additional claims. Proposed new claim 3 reads as follows:

A process of manufacture of a pharmaceutical solid composition comprising enalapril sodium, which process comprises the steps of:

i) a) mixing solid enalapril maleate with a solid alkaline sodium compound and at least one other excipient, adding water sufficient to moisten, and mixing to achieve a wet mass, or

b) mixing solid enalapril maleate with at least one excipient other than an alkaline sodium compound, adding a solution of an alkaline sodium compound in water, sufficient to moisten and mixing to achieve a wet mass;

thereby to achieve a complete reaction without converting the enalapril maleate to a clear solution of enalapril sodium and maleic acid sodium in water.

ii) drying the wet mass, and

iii) further processing the dried material into tablets.

In his reply, the Applicant stated, in part:

> Applicant respectfully submits that the Examiner's above analysis is legally and factually flawed for the following reasons:
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> 1. The Examiner has applied a subjective standard rather than an objective standard to the test of anticipation as required by the *Patent Act*;
> 2, the Examiner has mosaiced the prior art; and
> 3. The Examiner has misinterpreted the teachings of the prior art.
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> Initially, the Applicant would like to clarify a point with respect to the protest filed by Merck & Co., a competitor of the Applicant's in the enalapril market. Merck & Co. has tried to create the impression that the subject-matter of the Sherman Patent Application has been misappropriated from them and that they are allegedly the first inventors and as such all others are disentitled to a patent for this subject-matter. From the reasoning of the Examiner's Final Action the Applicant believes that the Examiner has been swayed by Merck's reasoning. However, Applicant would like to point out that the current *Patent Act* is no longer based on a first to invent principle but is based on the principle of first to file. Section 27(1)(a) of the old Patent Act (Pre Oct 1/89), which disentitled an applicant to an invention if he was not the first to invent it, no longer applies. Case law based on the old patent system, in particular *Fox* and cases from the Supreme Court of Canada decided in 1933, must be read with caution and in light of the changes to the patent system. Therefore, allegations, assumptions and innuendoes of what the Applicant 'knew or ought to have known' or allegations of Merck being the first to use or invent are irrelevant. The only relevant question under s,28.2(1)(b) is whether the subject matter was available to the public prior to the filing of the Sherman Patent Application. The Applicant respectfully submits and maintains that the answer to this question is "no".
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> .....
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> It is clear from the wording of subsection 28.2(1)(b) of the *Patent Act* that this test for anticipation is not addressed to "what the inventor knew" (a subjective standard), but is addressed to "what was publicly available in Canada or elsewhere" (objective standard).
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> The Applicant again asserts that the March 28, 1994 trial testimony of Mr McLeod does not constitute a piece of prior art since the publication was not available to the public at the relevant time. Neither Merck nor the Examiner has provided any record of the transcript being publicly available before the claim date of the Sherman Application. In addition, it would not be logical to presume that the notional person skilled in the art of pharmaceutical formulation would have been present in the courtroom on the date of March 28, 1994 or would have been appraised of this Court proceeding. In fact the Examiner admits that such a publication would not constitute prior art against any other applicant.
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> The Examiner has stated that the formulation, use and sale of the Vasotec® tablets by Merck & Co. constitutes an anticipation. Applicant disagrees with this conclusion for the following reasons.
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> Mosaic of prior art
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> From the reasoning of the Examiner it is clear that she has created a mosaic of the prior art by combining the formulation (the making) with the use and sale.
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> .....
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> Since Mr McLeod never identified the presence of sodium bicarbonate in a Vasotec® tablet during his testimony and the Vasotec® Product Monograph does not disclose the process by which the tablet is prepared, it is clear that the Examiner has combined a misconstruction of the teaching of the ingredients of the Vasotec® tablet from the Product Monograph with the testimony of Mr McLeod which discloses that Vasotec® is made *via* wet granulation. The Vasotec® Product Monograph teaches that enalapril maleate is present in the tablet and not an ingredient used in a process to make the tablet. Even if the Product Monograph mentioned enalapril sodium (which it does not) it is not permissible under Canadian Law to combine references to find anticipation. Such an approach is not permitted under Canadian Patent Law. In this regard the Examiner is referred to the leading case (a decision of the House of Lords) with regard to mosaicing and anticipation - *Pope Appliances Corporation v. Spanish River Pulp and Paper Mills Ltd.* [1929] 46 R.P.C.26:
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> .....
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> The Examiner has stated that the use and sale of the Vasotec® (enalapril maleate) tablets amounts to an anticipation of the Applicant's process for making enalapril sodium tablets. The Examiner has further made reference to the excerpt from *Fox* which states: "Where an article would show its method of manufacture by means of dissection or examination, the making and selling of such an article would amount to anticipation."
>
> Applicant disagrees with the Examiner's conclusion that from an analysis of the composition of a Vasotec® tablet one can deduce the process by which that tablet was prepared. Although an analysis of a Vasotec ® tablet may disclose the contents or composition of that tablet, it would not disclose the process by which the tablet was prepared or that a reaction occurred during the processing.
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> .....
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> The Examiner has also erroneously applied the teachings of the prior art on this point. The Examiner has arrived at the conclusion that the Vasotec® tablets actually contain sodium enalapril and not enalapril maleate. However, there is absolutely no prior art publication that the Examiner is able to point to which discloses that (a) a Vasotec® tablet is anything other than what it claims to be, an enalapril maleate tablet; (b) an analysis of a Vasotec®tablet

> would teach the subject-matter if the Sherman Patent Application; and (c) an analysis of a Vasotec® tablet disclosing it to be enalapril sodium was ever publicly disclosed on the prior art.
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> .....
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> The Examiner appears to have taken the position that a person skilled in the art would have simply arrived at the subject-matter of the Sherman Patent Application by taking the list of ingredients from the Vasotec® product monograph and combining them by the well-known process of wet granulation. That is, that if one were to simply combine enalapril maleate with sodium bicarbonate in a wet granulation process it is inevitable and appreciated that a reaction will occur to give enalapril sodium. Applicant disagrees with this conclusion for three reasons.
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> Firstly, and most importantly, Applicant stresses that the prior art specifically teaches that to combine the ingredients of Vasotec® tablet in a wet granulation process does not result in a reaction and therefore does not produce enalapril sodium tablet.
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> Secondly, the essence of the process of the Sherman Patent Application is the occurrence of a chemical reaction during the wet granulation process. Implicit in this is the fact sodium base (eg. sodium bicarbonate) is present to react properly with the enalapril maleate. Missing from the Examiner's combination of the prior art teachings is any reference that a reaction will occur during a wet granulation process. This element is required in the claimed process of the Sherman Patent Application and is specifically claimed in all claims. Without the required disclosure that a chemical reaction will occur during the wet granulation it cannot be said that the prior art leads "directly and without difficulty" to the Sherman Process.
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> ...
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> Thirdly, the Examiner's approach to obviousness (her obviousness analysis) fails to explain why a person skilled in the art looking to make a sodium enalapril tablet would use a list of ingredients that relate to an enalapril maleate tablet. The prior art (Merslavic, Harris, Rork, Gu and the McKay, J. decision) each teach that a reaction does not occur during the wet granulation process, but must be effected prior to the wet granulation. There is not a single piece of prior art which teaches the occurrence of a reaction during the wet granulation process. Therefore, if a person skilled in the art was to use the Vasotec® ingredients to make a sodium enalapril tablet he would know that he must effect a reaction in order to convert the enalapril maleate into sodium enalapril. The Applicant respectfully submits, that such a person would have simply done what the prior art had previously taught in order to effect such a reaction, that is, carry out the reaction under solution conditions prior to the wet granulation and not during the wet granulation.

There are two questions before the Board: 1. Is the method which is set out in the claims anticipated by the cited prior art? and 2. Is the method which is set out in the claims obvious in view of the cited prior art?

With respect to the first question, one of the many tests for anticipation was set out in *Reeves Bros. Inc. v. Toronto Quilting & Embroidery Ltd.*, 43 C.P.R. (2d), 145 at 157 by Gibson J. . It is as follows:

> As I understand it, in order that there may be a finding of anticipation, the prior art must (1) give an exact prior description; (2) give directions which will inevitably result in something within the claims; (3) give clear and unmistakable directions; (4) give information which for the purpose of practical utility is equal to that given by the subject patent; (5) convey information so that a person grappling with the same problem must be able to say "that gives me what I wish"; (6) give information to a person of ordinary knowledge so that he must at once perceive the invention; (7) in the absence of explicit directions, teach an "inevitable result"which "can only be proved by experiments"; and (8) satisfy all these tests in a single document without making a mosaic.

The Examiner has taken the position that the claimed method lacks novelty in view of the formulation, use and sale of Vasotec® tablets, as demonstrated by the Vasotec® product monograph. It is the Board's understanding that Vasotec® tablets contain enalapril maleate, as is shown in the Vasotec® Product Monograph. The fact that sodium enalapril is a known compound but that it is not shown in the printed material related to Merck's product means that the rejection based on lack of novelty does not meet criterion # 8 in the above stated test for anticipation. None of the cited references shows a process which includes all of the following steps: mixing input ingredients enalapril maleate, an alkaline compound and water in a wet granulation process to form a wet mass, drying the wet mass and forming it into tablets containing sodium enalapril.

In *Reeves Bros. Inc. v. Toronto Quilting & Embroidery Ltd.*, 43 C.P.R. (2d), 145 at 157 , Gibson J. also set out the following test for obviousness:.

> As I understand it also, in order for the prior defence of obviousness to succeed because there must be a finding that there is no inventive step, the defence evidence must establish that the solution sought which gave rise to the alleged invention was "very plain", evident to an unimaginative technician, and must not be based on *ex post facto* analysis.

A test for obviousness was also set out by the Court in *Beloit Canada Ltd. v. Valmet OY*, 8 C.P.R. (3d), 289 at 294:

> The test for obviousness is not to ask what competent inventors did or would have done to solve the problem. Inventors are by definition inventive. The classic touchstone for obviousness is the technician skilled in the art but having no scintilla of inventiveness or imagination; a paragon of deduction and dexterity, wholly devoid of intuition; a triumph of the left hemisphere over the right. The question to be asked is whether this mythical creature (the man in the Clapham omnibus of patent law) would, in the light of the state of the art and of common general knowledge as at the claimed date of invention, have come directly and without difficulty to the solution taught by the patent. It is a very difficult test to satisfy.

With respect to the rejection based on obviousness, the Board notes that claim 1 sets out a process of manufacturing sodium enalapril including the following steps: mixing ingredients including enalapril maleate, an alkaline sodium compound and water to form a wet mass, drying the wet mass and forming the resulting material into a solid composition comprising sodium enalapril.

The Examiner has included a very good analysis of the prior art in her final action and that analysis is quoted above. To recap:

Harris et al, USP 4,743,450, discloses stable formulations of enalapril; an alkaline stabilizer, a saccharide, a disintegrating agent, and a lubricant, all of which are combined in the wet granulation method. There is no mention of sodium enalapril being formed as the result of a chemical reaction during the mixing step.

Merslavic et al discloses a stable formulation of enalapril salt. Enalapril maleate is suspended in water, a solution of sodium hydroxide, sodium carbonate, or sodium hydrogen carbonate is added and lactose was added to the resulting clear solution of enalapril sodium salt. There is no mention of the wet granulation process .

The Rork & Haslam patent application discloses an osmotic pump for the controlled release of enalapril. In one of the methods given in the application, sodium enalapril is formed from enalapril maleate when disolved in water and in another example, the ingredients are mixed before any water is added. There is no mention of converting enalapril maleate into sodium enalapril during the wet granulation process.

Remington describes a general method of preparing tablets by wet-granulation and is not specific to the compositions of the instant application.

The VASOTEC® product monograph listed the components of Merck Frosst's enalapril tablets. Throughout this document, the product is described as being composed of enalapril maleate. There is no mention sodium enalapril.

Throughout the court proceedings in Merck & Co. v Apotex Inc., and in the decision of the Federal Court, the product in question is referred to as being enalapril maleate. There is no mention of sodium enalapril.

Each of the steps of the method set out in the instant application is shown to be known in at least one of the references. However, each of these references is missing at least one essential feature of the method which has been disclosed and claimed in the instant application and there is no direction given in any of the references which would make the combination of these references very plain or evident to an "unimaginative technician"

The Board therefore, concludes that the method which is disclosed and claimed in the instant application is novel and unobvious in view of the references.

The Board therefore recommends that the Examiner's rejection of the application be reversed and that the application be returned to the Examiner for further prosecution consistent with these recommendations.

Michael Gillen	John Cavar	M. Wilson
Chairman	Member	Member

I concur with the recommendation of the Board that the Examiner's rejection of the application be reversed and return the application to the Examiner for further prosecution consistent with the Board's recommendation.

David Tobin

Commissioner of Patents

Dated at Gatineau, Quebec

this 13th day of July, 2005