Commissioner’s Decision #1418

Décision du Commissaire #1418

TOPICS: O00 (Obviousness); K11 (Subject matter of applications - Treatment); J80 (Subject matter of applications – Professional skill)

SUJETS: O00 (Évidence); K11 (Objet des demandes - Traitement); J80 (Objet des demandes – Aptitudes professionnelles)

Application No.: 2,494,212

Demande n°.: 2,494,212

IN THE CANADIAN PATENT OFFICE

DECISION OF THE COMMISSIONER OF PATENTS

Patent application number 2,494,212 having been rejected under subsection 30(3) of the *Patent Rules*, has subsequently been reviewed in accordance with paragraph 30(6)(*c*) of the *Patent Rules*. The recommendation of the Patent Appeal Board and the decision of the Commissioner are to refuse the application.

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INTRODUCTION

[1] This recommendation concerns the review of rejected patent application number 2,494,212, which is entitled "Oral administration of calcitonin" and owned by Novartis AG. The outstanding defects to be addressed are whether the subject matter of the claims on file lies outside the definition of an invention and whether the subject matter of the claims on file is obvious. A review of the rejected application has been conducted by the Patent Appeal Board pursuant to paragraph 30(6)(*c*) of the *Patent Rules*. As explained in more detail below, our recommendation is that the application be refused.

BACKGROUND

The application

[2] Patent application 2,494,212 was filed in Canada on July 31, 2003 and laid open to the public on February 12, 2004.

[3] The application relates to the use of calcitonin (CT) in combination with one or more delivery agents for the treatment of disorders responsive to the action of CT (e.g., Paget's disease, hypercalcemia and osteoporosis). CT is a peptide hormone that is produced by the thyroid gland in humans. It acts to reduce blood calcium by inhibiting the activity of osteoclasts, which are cells that break down the bones and are involved in the maintenance, repair and remodeling of bones. In certain pathologies, there is an imbalance between bone resorption and bone formation, and bone loss is observed. Given the role played by osteoclasts in bone resorption and the inhibitory effect CT has on the activity of osteoclasts, CT has been indicated to be useful in the treatment of certain diseases wherein bone loss is observed.

[4] The description discloses that a pharmaceutical composition comprising CT and a delivery agent should be orally administered shortly prior to the consumption of food because food intake negatively impacts the bioavailability (i.e., the proportion of a drug that enters the systemic circulation when introduced into the body and so is able to have an active effect) of CT when CT is orally delivered in combination with a delivery agent.

History

[5] On August 19, 2014, a Final Action ("FA") was written pursuant to subsection 30(4) of the *Patent Rules*. The FA states that the claims on file do not comply with section 2 of the *Patent Act* because they encompass a method of medical treatment, subject matter that lies outside the definition of an invention as set out in section 2 of the *Patent Act*.

[6] In a response to the FA ("R-FA") dated February 18, 2015, the Applicant presented arguments as to why the claims on file are not directed to a method of medical treatment, citing the decision in *AbbVie Biotechnology Ltd. v. Canada (Attorney General)*, 2014 FC 1251 ("*AbbVie*") in support of its position. The Applicant also submitted an alternative claim set in response to the FA ("Proposed Claims Set-1") containing amendments that, according to the Applicant, "add additional physical structure to the claims, further distinguishing the claims from a method of medical treatment".

[7] As the Examiner considered that the application did not to comply with the *Patent Act* and was not convinced that the Proposed Claim Set-1 submitted by the Applicant in the R-FA would render the application allowable, the application was forwarded to the Patent Appeal Board ("the Board") for review, along with a Summary of Reasons ("SOR") that maintained the ground for rejecting the claims on file at the time of the FA. The SOR also concluded that the subject matter of proposed claims,

like the claims on file, is directed to a method of medical treatment. The SOR further identifies an alleged new defect concerning lack of clarity with respect to independent claims 1 and 7 of the Proposed Claim Set-1.

[8] In a letter dated October 2, 2015 (the "Acknowledgement Letter") the Board forwarded the Applicant a copy of the SOR and offered the Applicant an opportunity to make further written submissions and/or attend an oral hearing. In a response dated December 30, 2015, the Applicant expressed the wish to provide additional written submissions and to participate in an oral hearing.

[9] A Panel was formed to review the application under paragraph 30(6)(*c*) of the *Patent Rules* and to make a recommendation to the Commissioner as to its disposition. In a letter dated July 5, 2016 (the "Panel Letter"), we proposed a date for an oral hearing and we expressed our preliminary view that, based on the record before us, the claims on file are directed to subject matter that falls within the definition of an invention as set out in section 2 of the *Patent Act*. In the same letter, we also identified an additional defect (other than the one indicated in the FA) pursuant to subsection 30(6.1) of the *Patent Rules*. We expressed the preliminary view that the claims on file are obvious, contrary to section 28.3 of the *Patent Act*. We also expressed the preliminary view that the Proposed Claim Set-1 would not meet the requirements of a "necessary" amendment under subsection 30(6.3) of the *Patent Rules* because it does not overcome the obviousness defect relating to the claims on file, and because it introduces an indefiniteness defect.

[10] In a letter dated July 15, 2016, the Applicant confirmed its wishes to participate in an oral hearing and to provide written submissions addressing the issues raised in the Panel Letter. The Applicant also requested an extension of the deadline until January 5, 2017 for providing written submissions, and a new date for the oral hearing.

[11] In a letter dated July 19, 2016, we indicated to the Applicant that the deadline to provide written submissions in response to our letter dated July 5, 2016 was extended until January 5, 2017 and that the hearing was re-scheduled for January 12, 2017. In the same letter we also informed the Applicant that the Panel constitution was modified to the present Panel of two members as a result of the extension of time to provide written submissions. One of the members that participated in the preliminary review would not have been able to complete the review before leaving the Canadian Intellectual Property Office.

[12] On January 5, 2017 the Applicant replied to the Panel Letter ("Reply to the Panel Letter") and expressed the wish to proceed on the basis of the written submissions found in the letter and not participate in an oral hearing. In this letter, the Applicant acknowledged our preliminary view that the claims on file are directed to subject matter that falls within the definition of an invention as set out in section 2 of the *Patent Act* and provided written submissions to support its position that the subject matter of the claims on file is not obvious. In the same letter, the Applicant also submitted an alternative claim set in response to the Panel Letter ("Proposed Claims Set-2").

[13] In view of the Reply to the Panel Letter, an oral hearing was not held.

ISSUES

[14] There are two issues to address in this review:

1. whether the subject matter defined by the claims on file falls within the definition of an invention as set out in section 2 of the *Patent Act*; and

2. whether the subject matter defined by the claims on file is obvious, contrary to section 28.3 of the *Patent Act*.

LEGISLATION AND LEGAL PRINCIPLES

Purposive construction

[15] In accordance with *Free World Trust v Électro Santé Inc.*, 2000 SCC 66 essential elements are identified through a purposive construction of the claims done by considering the whole of the disclosure, including the specification and drawings (see also *Whirlpool Corp v Camco Inc.*, 2000 SCC 67 at paras. 49(f) and (g) and 52 ("*Whirlpool*"). In accordance with the *Manual of Patent Office Practice* §13.05 [revised June 2015; "MOPOP"], the first step of purposive claim construction is to identify the person of ordinary skill in the art ("POSITA") and the relevant common general knowledge ("CGK"). The next step is to identify the problem addressed by the inventors and the solution disclosed in the application. Essential elements can then be identified as those elements of the claims that are required to achieve the disclosed solution.

Statutory subject matter

[16] The definition of "invention" is set out in section 2 of the *Patent Act*:

> ***invention*** means any new and useful art, process, machine, manufacture or composition of matter, or any new and useful improvement in any art, process, machine, manufacture or composition of matter.

[17] Following the decision in *AbbVie*, the Office's practice was revised. This revision occurred between the sending of the FA and the SOR for the present application. The Office's practice with regard to the patentability of medical use claims is now guided by Practice Notice PN 2015-01, entitled *Revised Examination Practice respecting Medical Uses* ("PN 2015-01"), which provides:

> Section 2 of the *Patent Act* requires the subject-matter of an invention to fall within one of the categories of invention, *i.e.* an art, process, machine, manufacture, composition of matter, or an improvement in one of the foregoing.

> Medical inventions, in particular, have been subject to a number of jurisprudential interpretations whereby certain types of matter have been found to fall outside the scope of section 2. For instance, it is well established that methods of medical treatment and surgery are not statutory subject-matter and are excluded from the definition of *invention*.
>
> Medical use claims, however, are generally permitted as long as they do not equate to medical or surgical methods (*e.g.* do not include an active treatment or surgical step) and they satisfy all other requirements of patentability. The Federal Court has concluded, however, that inventions preventing physicians from exercising their skill and judgment in using a known compound for an established purpose effectively cover a method of medical treatment. [Citations omitted]

[18] According to PN 2015-01, medical use claims are generally permitted as long as they do not amount to a method of medical treatment. The determination of whether the subject matter of a claim is statutory is based on the essential elements of the claim as determined by a purposive construction as outlined above. Where an essential element only serves to instruct a medical professional "how" to treat a patient rather than "what" to use to treat the patient, it must be determined whether the essential element prevents, interferes with or requires the professional skill of a physician. If the answer is "yes", the claimed use will be considered to encompass a method of medical treatment that does not comply with section 2 of the *Patent Act*.

[19] However, PN 2015-01 also recognizes that there may be instances where essential elements serve to instruct a medical professional "how" to treat a patient but are not considered to prevent, interfere with or require the professional skill of a physician. For example, essential elements that narrow treatment to a fixed dosage, a fixed dosage regimen or to a patient sub-population are not considered to comprise a limitation of a physician's professional skill or judgment.

Obviousness

[20] Section 28.3 of the *Patent Act* sets out the statutory requirement that the claimed subject matter must not have been obvious to the POSITA:

> The subject matter defined by a claim in an application for a patent in Canada must be subject matter that would not have been obvious on the claim date to a person skilled in the art or science to which it pertains, having regard to
>
> (a) information disclosed more than one year before the filing date by the applicant, or by a person who obtained knowledge, directly or indirectly, from the applicant in such a manner that the information became available to the public in Canada or elsewhere; and
>
> (b) information disclosed before the claim date by a person not mentioned in paragraph (a) in such a manner that the information became available to the public in Canada or elsewhere.

[21] In *Apotex Inc v Sanofi-Synthelabo Canada Inc*, 2008 SCC 61 at para. 67 ("*Sanofi*"), the Supreme Court of Canada stated that it is useful in an obviousness inquiry to follow the following four-step approach:

> (1) (a) Identify the notional "person skilled in the art";
> (b) Identify the relevant common general knowledge of that person;
>
> (2) Identify the inventive concept of the claim in question or if that cannot readily be done, construe it;
>
> (3) Identify what, if any, differences exist between the matter cited as forming part of the "state of the art" and the inventive concept of the claim or the claim as construed;
>
> (4) Viewed without any knowledge of the alleged invention as claimed, do those differences constitute steps which would have been obvious to the person skilled in the art or do they require any degree of invention?

[22] In the context of the fourth step, the Court in *Sanofi* accepted that it may be appropriate in some cases to consider an "obvious to try" analysis. For a finding that an alleged invention is "obvious to try", it must be more or less self-evident to try to

obtain the alleged invention in advance of routine testing. The mere possibility that something might work is not sufficient.

[23] The Court in *Sanofi* listed the following non-exhaustive factors to be considered in an "obvious to try" analysis:

> (1) Is it more or less self-evident that what is being tried ought to work? Are there a finite number of identifiable predictable solutions known to persons skilled in the art?
>
> (2) What is the extent, nature and amount of effort required to achieve the invention? Are routine trials carried out or is the experimentation prolonged and arduous, such that the trials would not be considered routine?
>
> (3) Is there a motive provided in the prior art to find the solution the patent addresses?

ANALYSIS

1. Claim Construction

The POSITA and the relevant CGK

[24] In the Panel Letter, we identified the POSITA as a team of persons practising in the fields of clinical pharmacology, pharmacokinetics and drug development, including a drug formulator knowledgeable in preparing, for example, solid pharmaceutical formulations by conventional methods.

[25] With regard to the relevant CGK possessed by the POSITA, we identified the following in the Panel Letter on page 4:

- The standard ways in which bioavailability of different pharmaceutical compounds (e.g., small molecules and peptide-based drugs such as

biologics) may be assessed and the established differences in general bioavailability that can exist among different types of pharmaceutical formulations (e.g., tablets, capsules, liquid or cream).

- The knowledge that the required dose of a given active agent to reach a desired therapeutic systemic concentration may vary according to the relative observed levels of bioavailability (i.e., reduction of the required dose of an active agent to reach therapeutic concentration is possible if the bioavailability is increased).

- The knowledge that co-administration of food with oral drug products may influence drug bioavailability and that food-effect bioavailability studies are common in a drug development process and of interest to regulatory authorities (see for example Li et al., "On the assessment of effects of food on the pharmacokinetics of drugs in early development", *Biopharm Drug Dispos*., May 2002, 23(4), pages 165-171 (*Li*); "Guidance for Industry, Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations", July 2002[1] (*Guidance for Industry 1)*; and "Guidance for Industry Food-Effect Bioavailability and Fed Bioequivalence Studies: Study Design, Data Analysis, and Labeling", draft guidance, October 2001[2], final version published December 2002[3] (*Guidance for Industry 2*).

- The general interest in enhancing the oral absorption of CT using different formulation strategies (see for example Lee and Sinko, "Oral delivery of salmon calcitonin", *Adv Drug Deliv Rev.*, August 2000, 42(3), pages 225-238).

[1]http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM154838.pdf
[2]http://www.fda.gov/ohrms/dockets/ac/02/briefing/3860b1_01_GFI-Food-effect.pdf
[3] http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126833.pdf

- The use of delivery agents 5-CNAC, SNAD or SNAC in oral formulations for increasing the bioavailability of biologically active peptides, including CT (see for example U.S. Patents No. 5,773,647, No. 5,866,536 and International Application WO 00/59863, all cited in the background section of the instant description on page 1 and WO 02/45754).

- The advantages and disadvantages of oral pharmaceutical compositions comprising peptides and the knowledge that bioavailability via this route is normally poor because peptides are susceptible to hydrolysis and modification at gastric pH levels, and they can be degraded by proteolytic enzymes in the gastrointestinal (GI) tract (see for example Niu and Chiu, "FDA perspective on peptide formulation and stability issues", *Journal of Pharmaceutical Sciences*, November 1998, 87(11), pages 1331-1334).

[26] The Applicant's Reply to the Panel Letter does not take issue with the above POSITA and CGK assessments.

The problem to be solved and the proposed solution

[27] In the Panel Letter on page 5, we expressed the view that the problem to be solved is the prevention of negligible plasma levels of CT (i.e., low bioavailability) that arise with administration of an oral formulation comprising CT and a delivery agent with a meal, and that the solution proposed by the application is to orally administer the pharmaceutical composition comprising CT and a delivery agent during a short time window prior to food intake.

[28] Although the Reply to the Panel Letter does not explicitly address the problem to be solved by the inventors and the solution disclosed in the application, the Applicant states on page 4 of its Reply to the Panel Letter that the inventors unexpectedly found that the oral administration of a solid CT formulation comprising CT and an oral delivery agent at a short interval prior to a meal greatly increases the oral absorption and the systemic bioavailability of CT in comparison to administration

with a meal. We consider that this statement is not inconsistent with our assessment of the problem to be solved and the proposed solution.

The essential elements of the claims that solve the identified problem

[29] Independent claims 1 and 7 read as follows:

> 1. Use of calcitonin in combination with one or more oral delivery agents selected from N-(5-chlorosalicyloyl)-8-aminocaprylic acid, N-(10-[2-hydroxybenzoyl] aminodecanoic acid or N-(8-[2-hydroxybenzoyl]amino) caprylic acid, or a disodium salt, hydrate or solvate thereof for the manufacture of a medicament for the treatment of a disorder responsive to the action of calcitonin, wherein said medicament is for oral administration to a human host from about 5 minutes to 2 hours prior to a meal.
>
> 7. A pharmaceutical composition comprising calcitonin in combination with one or more oral delivery agents selected from N-(5-chlorosalicyloyl)-8-aminocaprylic acid, N-(10-[2-hydroxybenzoyl] aminodecanoic acid or N-(8-[2-hydroxybenzoyl]amino)caprylic acid, or a disodium salt, hydrate or solvate thereof for use in the treatment of a disorder responsive to the action of calcitonin, wherein said composition is for oral administration to a human host from about 5 minutes to 2 hours prior to a meal.

[30] In the Panel Letter on page 6, we expressed the view that the POSITA would consider that i) CT, ii) oral delivery agent 5-CNAC, SNAD or SNAC, iii) treatment of a CT responsive disorder, iv) oral administration and v) 5 minutes to 2 hours prior to a meal are essential elements that contribute to solving the problem identified above.

[31] Regarding dependent claims 2-6 and 8-12 on file, which provide further limitations to the timing (claims 2, 3, 8 and 9), the nature of the oral delivery agent (claims 4 and 10), the amount of CT (claims 5 and 11) and the ratio of the amount of oral delivery agent to the amount of CT (claims 6 and 12), we expressed the view that these limitations do not comprise separate, additional elements, but further limit the identified essential elements.

[32] The Applicant's Reply to the Panel Letter does not take issue with our assessment of the essential elements of the claims on file.

The claims, purposively construed

[33] Based on the above, we expressed the view in the Panel Letter (page 7) that the POSITA would understand that the subject matter recited in claims 1 and 7 is directed to the use of an oral formulation comprising CT, in combination with one or more of the recited oral delivery agents, for the treatment of a disorder responsive to the action of CT according to a time-limited period of administration that consists of delivering the oral formulation from about 5 minutes to 2 hours prior to a meal.

[34] Once again, the Applicant's Reply to the Panel Letter does not take issue with our assessment.

2. Statutory subject matter assessment of the claims on file (section 2 of the *Patent Act*)

[35] According to the FA and the SOR, claims 1-12 on file encompass a method of medical treatment, subject matter that lies outside the definition of an invention. The subject matter analyses found in the FA and the SOR were conducted in view of two Office Practice Notices; the FA refers to Office's Practice Notice 2013-04 *Examination Practice Respecting Medical Uses* ("PN 2013-04") and the SOR refers to PN 2015-01.

[36] The FA concluded, based on PN 2013-04, that the subject matter of claims 1-12 amounted to a method of medical treatment because the essential element of timing the administration of the oral formulation pertains to "how" to treat a patient rather than "what" to use to treat the patient.

[37] Referring to PN 2015-01 and taking into account the Applicant's arguments in relation to the *AbbVie* decision, the SOR explained that when the problem to be solved relates to "how" or "when" it must be determined whether the essential

elements prevent, interfere with or require the professional skill of a physician. Although the subject matter analysis found in the SOR focused on the Proposed Claim Set-1 rather than the claims on file, the SOR on page 3 agreed with the Applicant that "once the physician has decided to prescribe the oral CT formulation shortly before a meal there is no further exercise of the physician's skill and judgment required".

[38] Likewise, we expressed the view in the Panel Letter (page 9) that the physician's skill and judgment are not expected to be exercised within the scope of the claims once the physician has decided to prescribe the oral CT formulation shortly before a meal in accordance with the claims on file. With respect to the essential element of timing the administration of the oral CT formulation, we considered that the POSITA would appreciate that any time during the recited time window would overcome the negligible plasma levels observed when administering an oral formulation of CT with a meal, so that no physician judgement is required in selecting a time within this range. We also considered that the physician could prescribe any dose of CT and still obtain the result of preventing the negligible plasma levels of CT that follow administration of an oral formulation comprising CT and a delivery agent with a meal if the recited timing of administration is respected. It follows, applying the practice described in PN 2015-01, that the subject matter of the claims on file does not amount to a method of medical treatment.

Conclusion on the lack of statutory subject matter

[39] In our view and for the reasons above, the subject matter defined by the claims on file falls within the definition of an invention as set out in section 2 of the *Patent Act*.

3. Obviousness assessment of the claims on file (section 28.3 of the *Patent Act*)

[40] In the Panel Letter, we identified a defect other than the one indicated in the FA pursuant to subsection 30(6.1) of the *Patent Rules*. We expressed the preliminary view that the claims on file are obvious in view of WO 00/59863 (D1) and the CGK, contrary to section 28.3 of the *Patent Act*.

Identify the POSITA and the relevant CGK

[41] The POSITA and the CGK have been set out above as part of the purposive construction of the claims. As mentioned above, the Applicant's Reply to the Panel Letter did not take issue with our assessments.

Identify the inventive concept of the claim in question or if that cannot readily be done, construe it

[42] In the Panel Letter on page 11, we expressed our preliminary view that the inventive concept of the independent claims 1 and 7 on file is the use of an oral formulation comprising CT, in combination with one or more of the recited oral delivery agents, for the treatment of a human subject suffering from a disorder responsive to the action of CT, according to a time-limited period of administration that consists of delivering the oral formulation from about 5 minutes to 2 hours prior to a meal.

[43] The Applicant's Reply to the Panel Letter did not take issue with our determination of the inventive concept of independent claims 1 and 7 on file.

Identify what, if any, differences exist between the matter cited as forming part of the "state of the art" and the inventive concept of the claim or the claim as construed

[44] In the Panel Letter on page 11, we acknowledged that D1 does not disclose the effect of food on the bioavailability of the disclosed oral CT formulations and summarized

what we considered the difference between the "state of the art" and the inventive concept of the claims on file:

> In view of the above, our preliminary view is that the difference between the "state of the art" and the inventive concept of the claims is the recited time-limited schedule that limits the claimed use to a specific range of time prior to a meal to avoid the observed negative food effect.

[45] The Applicant's Reply to the Panel Letter did not take issue with our assessment of the difference between the matter cited as forming part of the "state of the art" and the inventive concept.

Viewed without any knowledge of the alleged invention as claimed, do those differences constitute steps which would have been obvious to the person skilled in the art or do they require any degree of invention?

[46] In the Panel Letter on page 11, we expressed our preliminary view that because the claimed subject matter relates to the delivery of pharmaceuticals, an area in which advances are often made by experimentation, it was appropriate to examine whether the difference between the "state of the art" and the inventive concept constitute steps which would have been "obvious to try" to a POSITA (see *Sanofi* at para 68).

[47] In the Panel Letter on pages 11-13, we expressed our reasons as to why the POSITA would consider independent claims 1 and 7, which recite a time-limited period of administration, would have been obvious to try:

- the POSITA knew that co-administration of food with oral drug products may influence drug bioavailability (CGK), that bioavailability of pharmaceutical compositions comprising peptides via oral route is generally poor (CGK), and that CT can be successfully delivered to the systemic circulation of fasting mammals by using an oral formulation comprising CT and one of the delivery agents recited in the claims on file (D1);

- the testing of food-effect on the bioavailability of an oral pharmaceutical formulation was a routine part of drug development practices at the claim date. Regulatory authorities recommended that such studies be conducted (see for example *Li*, and the *Guidance for Industry 1* and *Guidance for Industry 2* references) and there is nothing to suggest that the food-effect experimentations found in Example 7 would have been either prolonged or arduous. We considered that the negative impact of food on the bioavailability of oral CT formulations would inevitably have been determined as a result of these routine studies; and

- the POSITA, who knew from D1 that the oral delivery of CT in combination with the disclosed delivery agents can be successfully delivered to mammals in a fasted state, would have been motivated to optimize the timing of administration of oral CT formulations in relation to meals not only because it was routine to do so in the field, but also because of the known relatively poor bioavailability of oral pharmaceutical compositions comprising peptides (i.e., optimizing bioavailability by acquiring knowledge of factors that negatively impact the bioavailability is particularly important when the bioavailability of oral peptide formulations is low to start with and constitutes a commonly known problem).

[48] Although the Applicant did not take issue with the appropriateness of an "obvious to try" analysis in the present context, the Applicant submitted the following on pages 3 and 4 of the Reply to the Panel Letter with respect to the "obvious to try" test:

> In the terminology of the "obvious-to-try" test, the test becomes whether it was "more or less self-evident to try to obtain the invention. Mere possibility that something might turn up is not enough": *Sanofi-Synthelabo Canada Inc v Apotex Inc*, 2008 sec 61 at para 66. Rothstein J also held in *Sanofi* at para 65, "the 'obvious to try' test will work only where it is very plain or ... more or less self-

> evident **that what is being tested ought to work**" (emphasis added). Notably, the test is not "whether the skilled person had good reason to pursue predictable solutions or solutions that provide a 'fair expectation of success'": *Eli Lilly Canada Inc v Mylan Pharmaceuticals ULC,* 2015 FCA 286 at para 4.

[49] We note that Applicant's arguments are focused on Proposed Claim Set-2 (discussed in detail below), but we consider that the following submissions found on pages 5-7 of the Reply to the Panel Letter are also relevant to the claims on file. In summary, the Applicant submits that:

- D1 does not disclose anything about the food effect on the bioavailability of the disclosed oral CT formulations. Therefore, D1 can neither teach nor suggest that delivering CT within the recited time would enhance the oral delivery and bioavailability of CT;

- the bioavailability studies in the fasted state described in Dl (ten hours fasting followed by CT/5-CNAC administration, followed by 4-6 hours of further fasting) would not have suggested the surprising results for the subject matter of the claims;

- optimizing oral administration of peptide formulations was not routine and very little was known about the food effect on peptide formulations and optimized oral delivery of peptide formulations; and

- the timing of CT administration recited in the claims is also inventive because the POSITA would have been aware that: (i) CT exerts anti-resorptive effects; and (ii) there is a strong circadian variation in bone resorption with peak bone resorption occurring during the night. Therefore, prior to the present invention, in order to ensure maximum effect, CT was recommended to be administered at night (i.e., with or after a meal). Therefore, the invention of the claims would also have been counterintuitive to the POSITA.

[50] Regarding these arguments, our first observation is that a significant portion of the submission is based on the contention that an unexpected enhancement of bioavailability of CT when it is delivered in accordance with the recited time-limited period of administration supports the inventiveness of the claimed subject matter over D1. However, we consider that the information included in the specification does not support the view that the recited time-limited period of administration enhances oral absorption and bioavailability of CT in comparison to the fasting conditions of D1, but rather that it enhances oral absorption and bioavailability of CT in comparison to administration with a meal. In our view, the results presented in Table 1 of the instant description (reproduced below) indicates that the oral administration of the CT formulations under fasting conditions and at any pre-meal time point lead to similar total amount of CT absorbed (as determined by the area under the curve (AUC)) and similar maximum mean plasma levels of CT (mean C_{max}):

Table I. Effect of meal administration on sCT bioavailability

Treatment group	Time of administration	Mean AUC ± SD (pg•h/mL)	Mean C_{max} ± SD (pg/mL)
A	After overnight fast	66.3 ± 42.2	139.3 ± 74.3
B	1 hour pre-meal	63.4 ± 37.9	135.9 ± 64.7
C	30 minutes pre-meal	79.0 ± 79.3	161.7 ± 141.8
D	15 minutes pre-meal	72.1 ± 45.1	161.9 ± 67.9
E	5 minutes pre-meal	60.4 ± 67.4	149.5 ± 150.7
F	With meal	12.6 ± 18.5	24.0 ± 26.7
G	2.5 hours post-meal	61.1 ± 114.2	79.8 ± 133.5

[51] The statistical significance of the observed differences is not disclosed. Further, we note the high level of variability among the different groups of subjects tested (denoted by the high standard deviation values). In any event, based on the record before us, we consider that the POSITA would not find anything "surprising" about the results obtained with the recited time-limited period of administration in comparison to the fasting state and to what has been disclosed in D1; CT can be successfully delivered to the systemic circulation of mammals by using an oral

formulation comprising CT and one of the delivery agents recited in the claims on file if orally administered on an empty stomach.

[52] As noted above, the Applicant also submits on pages 6 and 7 of the Reply to the Panel Letter that the timing of CT administration recited in the claims would have been counterintuitive to the POSITA prior to the instant invention because CT was recommended to be administered at night (i.e., with or after a meal) to ensure maximum effect, citing a passage of Karsdal et al., "Influence of food intake on the bioavailability and efficacy of oral calcitonin", *Br J Clin Pharmacol*., April 2009, 67(4), pages 413-420 ("*Karsdal*") to support this view. Having reviewed *Karsdal*, we do not consider that the cited passage establishes that CT was generally recommended to be administered at night with or after a meal at the claim date. The relevant passage of *Karsdal* reads:

> Because of the short half-life of calcitonin in serum, **one potential path** to optimizing the clinical benefits of calcitonin **could be** to administer treatment when bone resorption reaches maximal levels, i.e. during the evening [9, 29, 36]. Diurnal variation is a principal parameter of bone turnover, in which postprandial decreases in bone resorption are observed [36]. Bone resorption during the night may account for >75% of total resorbed calcium. However, evening dosing, rather than morning dosing in the fasting state, may introduce the potential for food–drug interactions. Presently, it is unknown how food intake may affect the pharmacokinetics and pharmacodynamics of sCT. [Emphasis added]

[53] In our view, the POSITA would understand from the above passage, including the citations[4], that in April 2009, almost seven years after the claim date, it was hypothesized that evening dosing could optimize the clinical benefits of CT.

[4] A review of the citations revealed that two of the three cited documents disclose information with regard to the circadian variation of bone resorption (see Gertz et al., "Application of a new serum assay for type I collagen cross-linked N-telopeptides: assessment of diurnal changes in bone turnover with and without alendronate treatment", *Calcif Tissue Int*., 1998, 39, 172-179 and Schlemmer et al., "Marked diurnal variation in urinary excretion of pyridinium cross-links in premenopausal women", *J Clin Endocrinol Metab*., 1992, 74, 476-480), and that none discloses or suggests that calcitonin was recommended to be administered at night with or after a meal.

[54] We maintain our view expressed in the Panel Letter that determining whether food has an effect on the bioavailability of an oral pharmaceutical formulation comprising CT in combination with one or more oral delivery agents by performing bioavailability studies in fasted and fed states was a routine step of the accepted drug development practices for the POSITA to take and did not constitute either prolonged or arduous experimentations. We acknowledge Applicant's submission that the potential the food-effect on the bioavailability of oral peptide formulations in particular has not necessarily been systematically investigated as of the claim date. However, we consider that the testing of food-effect on the bioavailability of orally administered drug products in general was a routine part of the drug development practices at the claim date and that the regulatory authorities recommended that such studies be conducted (see the CGK set out above).

[55] In its Reply to the Panel Letter on pages 5, second paragraph and page 7, fourth paragraph, the Applicant submits that, in the context of the "obvious to try" test, it must have been more or less self-evident that an oral formulation comprising CT in combination with one or more of the recited oral delivery agents delivered shortly prior to a meal would enhance oral absorption and bioavailability of CT for the present invention to have been obvious. As explained above, we are of the view that the POSITA would not take Table 1 as showing that the time-limited period of administration recited in the claims enhances oral absorption and bioavailability of CT in comparison to the fasting state of D1.

[56] Accordingly, we consider that the question is whether it would have been more or less self-evident to the POSITA, based on the disclosure of D1 and the CGK, that an oral formulation comprising CT in combination with one or more of the recited oral delivery agents delivered about 5 minutes to 2 hours prior to a meal ought to work. Given that it was known from D1 that an oral formulation comprising CT in combination with one of the recited oral delivery agents can successfully deliver CT to the systemic circulation in fasted subjects, we consider that it would have been more or less self-evident to the POSITA that delivering the same oral formulation

prior to a meal according to the time-limited period recited in the claims ought to also work.

[57] Therefore, we are of the view that independent claims 1 and 7 of the claims on file would have been obvious to the POSITA at the claim date.

[58] With respect to dependent claims 2-6 and 8-12 on file, we expressed the view on page 13 of the Panel Letter that the limitations to the timing (claims 2, 3, 8 and 9), the nature of the oral delivery agent (claims 4 and 10), the specific amount of CT (claims 5 and 11), or the ratio of the amount of oral delivery agent to the amount of CT (claims 6 and 12) do not provide an unexpected or surprising effect and would also have been obvious to try in view of D1 and the CGK.

[59] In the Reply to the Panel Letter, the Applicant provided no submissions or arguments specifically addressing the inventiveness of these dependent claims on file.

Conclusion on obviousness

[60] In our view, and for the reasons provided in the Panel Letter and the reasons above, the subject matter defined by the claims on file would have been obvious to the POSITA in view of D1 and the CGK and, therefore, the claims on file do not comply with section 28.3 of the *Patent Act*.

ANALYSIS OF THE PROPOSED CLAIMS

[61] Since we consider that the claims on file are obvious, we will consider the Proposed Claim Set-2. The Proposed Claim Set-2 was submitted on January 5, 2017 with the Reply to the Panel Letter in order to address the issues raised in the Panel Letter with respect to the claims on file and the Proposed Claim Set-1. Accordingly, we consider Proposed Claim Set-2 to be a replacement of the Proposed Claim Set-1. As a result, there is no need to address the lack of clarity issue raised in the SOR with respect to the Proposed Claim Set-1.

[62] Claims 1, 2, 4, 5, 6 and 8 of the Proposed Claim Set-2 correspond to claims 1, 4, 6, 7, 10 and 12 of the claims on file respectively. Independent claims 1 and 5 of the Proposed Claim Set-2 define the time period of administration as from about 5 to 15 minutes prior to a meal and define the amount of CT as about 0.1-2.5 mg. Moreover, the references to "medicament" have been amended to "solid pharmaceutical composition". Finally, new claims 3 and 7 further define the "solid pharmaceutical composition" as a capsule, soft-gel capsule, tablet or caplet.

Statutory subject matter

[63] As the claims of the Proposed Claim Set-2 are narrower in scope than the corresponding claims on file, we consider that the subject matter of the Proposed Claim Set-2 falls within the definition of an invention as set out in section 2 of the *Patent Act* for the reasons provided previously with respect to the claims on file.

Obviousness

[64] We have presented our view above that the limitations to the time period of administration prior to a meal and the specific amount of CT are not associated with

an unexpected or surprising effect and that such limitations would not require any degree of invention from the POSITA.

[65] In its Reply to the Panel Letter, it appears that the Applicant submits that 5 to 15 minutes prior to a meal is a short time period of administration that is particularly effective in comparison to other time periods of administration and thus indicates inventiveness for the subject matter of the Proposed Claim Set-2.

[66] In support for its submissions, the Applicant relies on the results presented in Table 1 (discussed above at paras [50] and [51]) and *Karsdal*, a scientific article which post-dates the filing date:

> Karsdal, M. et al., (April 2009) "Influence of food intake on the bioavailability and efficacy of oral calcitonin" *J. Clin Pharmacol.* 67(4):413-420 (attached hereto), which post-dates the filing date of the present application, also provides additional, statistically significant data confirming the data of the present application. Page 3 of Karsdal, M. et al., describes the statistical analysis performed using SAS software package (release 9.1; SAS Institute Inc., Cary, NC USA). A difference was considered significant if the P-value was <5 %.
>
> Using the SAS software package, Karsdal, M. et al. were able to determine that a predose meal at 18.00 and 21.00 hour (4 hours before dosing and 1 hour before dosing, respectively) significantly **decreased** relative oral bioavailability of sCT to 26%, P = 0.009 and P = 0.01, respectively, compared to that of the dose in the fasting state. The predose meal at 20 hours (2 hours before dosing) decreased relative oral bioavailability to 35%, P = 0.06. The meal consumed at 22.10 h **(10 minutes after dosing, which falls within Applicant's dosing range of 5 to 15 minutes prior to a meal of the Proposed Claims)** only decreased oral bioavailability of sCT to 59%, P = 0.48. *See* pages 3 and Tables 1 and 3 of Karsdal, M. et al. As acknowledged by the Board, D1 does not disclose anything about the food effect on the bioavailability of the disclosed oral calcitonin formulations. Therefore, D1 can neither teach nor suggest that delivering calcitonin within the time period of 5 minutes to 15 minutes recited in the Proposed Claims would enhance the oral delivery and bioavailability of calcitonin. Indeed, ***based on Dl, the skilled person would not know whether there was a food effect at all***. [Emphasis in the original]

[67] We have expressed our view that the results presented in Table 1 of the instant description indicates that the oral administration of the CT formulations under fasting conditions and at any pre-meal time point lead to similar maximum plasma levels of CT. Further, we note that the results of Table 1 show a higher maximum plasma level of CT for the 30 minutes pre-meal time point than for the 5 minutes pre-meal time point. Accordingly, we are of the view that the results of Table 1 do not disclose or suggest that a time period of administration from about 5 to 15 minutes prior to a meal is associated with an enhancement of the oral absorption and bioavailability of CT in comparison to the fasting state or any other reported time period of administration prior to a meal.

[68] Moreover, we consider that the disclosure of *Karsdal* published in 2009 is of no assistance in determining the obviousness of the claims of Proposed Claim Set-2 as the inquiry is concerned with the state of the art as of August 1, 2002 (the claim date) and the invention described in the patent application as originally filed. A relevant case touching on this point is *Johnson & Johnson Inc. v. Boston Scientific Ltd.*, 2008 FC 552 at paras 316 and 317, citing *Janssen-Ortho Inc. v. Novopharm Ltd*., 2007 FCA 217:

> More importantly, the Parodi article is dated 1991 (some eight years after the date of the invention of the '505 Patent). This inquiry (whether the invention of the '505 Patent was obvious in view of the Ersek Patent) is concerned with the state of affairs at the relevant time (May 18, 1983). In *Janssen-Ortho*, Madam Justice Sharlow stated, at paragraph 26:
>
> > …I find it difficult to envisage a situation where a subsequently recognized advantage to a claimed invention would be of any assistance in determining whether inventive ingenuity was required to make it. I can imagine a situation where the commercial success of an invention is attributable to a subsequently recognized advantage, but that would not assist the inquiry as to inventive ingenuity. I recognize that it is impossible to imagine every possible situation, but given the

> current state of the jurisprudence I would be inclined to give this factor no weight except in the most extraordinary case.
>
> I find that reasoning to be apposite to this issue and I subscribe to Justice Sharlow's view. The Parodi article does not assist me in determining the obviousness of the '505 Patent and I accord no weight to it in that regard.

[69] In any event, and having reviewed *Karsdal*, we consider that its disclosure does not support that a time period of administration from about 5 to 15 minutes prior to a meal is associated with an enhancement of the oral absorption and bioavailability of CT in comparison to the fasting state or any other time period of administration prior to a meal. Only a single pre-meal time of administration (10 minutes prior to a meal) has been tested in *Karsdal*, and all the other tested time points were post-meal time points.

[70] Therefore, we maintain our view that the limitations to the time period of administration prior to a meal and the specific amount of CT, including the ones recited in the claims of the Proposed Claim Set, are not associated with an unexpected or surprising effect and that such arbitrary limitations would not require any degree of invention from the POSITA. Accordingly, we are of the view that the claims of the Proposed Claim Set-2 would have been obvious in view of D1 and the CGK.

CONCLUSIONS

[71] In our view, the subject matter defined by the claims on file falls within the definition of an invention as set out in section 2 of the *Patent Act* but is obvious, contrary to section 28.3 of the *Patent Act*.

[72] We consider that claims 1-8 of the Proposed Claim Set-2 do not overcome the obviousness defect of the claims on file.

RECOMMENDATION OF THE BOARD

[73] The Panel recommends that the application be refused because the claims on file do not comply with section 28.3 of the *Patent Act*.

[74] Further, the proposed claims do not overcome this defect and therefore do not constitute specific amendments that are "necessary" under subsection 30(6.3) of the *Patent Rules*.

Marcel Brisebois
Member

Paul Fitzner
Member

DECISION

[75] I concur with the findings and the recommendation of the Board and its recommendation that the application should be refused because the claims on file do not comply with section 28.3 of the *Patent Act*.

[76] Accordingly, I refuse to grant a patent on this application. Under section 41 of the *Patent Act*, the Applicant has six months within which to appeal my decision to the Federal Court of Canada.

Johanne Bélisle
Commissioner of Patents
Dated at Gatineau, Quebec,
this 10th day of March, 2017