Commissioner=s Decision/Décision du Commissaire #1344

TOPIC/SUJET: O00

Application No./Demande nº:2,223,198

IN THE CANADIAN PATENT OFFICE

DECISION OF THE COMMISSIONER OF PATENTS

Patent application number 2,223,198 having been rejected under subsection 30(3) of the *Patent Rules*, has consequently been reviewed in accordance with subsection 30(6) of the *Patent Rules* by the Patent Appeal Board and the Commissioner of Patents. The findings of the Board and the decision of the Commissioner are as follows:

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INTRODUCTION

[1] Crohn=s disease is a severe, chronic disease that causes inflammation of the gastro-intestinal (GI) tract and has a profound impact on nutritional status and growth.

[2] In children, Crohn=s disease is of particular concern, causing stunted growth and poor weight gain, with the eventual need for surgery in up to 50% of cases. To this day, no cure exists.

[3] Patent Application no. 2,223,198, filed by Société des Produits Nestlé S.A., describes and claims nutritional compositions that have been shown to cause remission in children with Crohn=s disease. More generally, the application is directed to compositions for use in the treatment of inflammatory conditions of the gastro-intestinal tract.

[4] The application was rejected by a Patent Examiner in a Final Action as the Examiner found the claimed compositions and their uses to be obvious, largely in light of prior disclosures of the Applicant=s work in the same field. This is a review of the application under subsection 30(6) of the *Patent Rules*.

[5] Apart from a number of other minor defects, the Examiner maintained the rejection based on obviousness. Stated otherwise, the Examiner is alleging that the claimed subject matter does not comply with subsection 28.3 of the *Patent Act* as it lacks ingenuity.

[6] The Examiner argues that the claimed compositions are obvious in view of similar formulations tested for the same use in a prior study conducted with the assistance of Nestec Ltd.; see Beattie *et al.*, Aliment. Pharmacol. Ther. 1994: 8, 609-615. Moreover, the Examiner found that the claimed compositions do not produce an advantage over Beattie *et al.*, pointing out that the results of both treatments are in agreement.

[7] The Applicant submits that not only are the claimed compositions different, but they produce higher rates of remission for Crohn=s subjects when compared with Beattie *et al.* The Applicant also states that no one particular component of the claimed compositions can be

identified as the Amagic bullet@ that is responsible for the higher rate of remission; rather, the combination of differences give rise to the improvement.

[8] Additionally, though the point was not made during examination, the Applicant submits to the Board that the higher remission rate was obtained with substantially less transforming growth factor-beta 2 (TGF-β2) - what we perceive to be the active ingredient B than Beattie *et al.*

[9] Thus, to address the question of obviousness, the Board must resolve the following issues:

1. Do the Applicant=s compositions generate higher remission rates than the prior art?

2. Do the Applicant=s compositions comprise surprisingly low levels of TGF-β2?

PROCEDURAL HISTORY

[10] The Applicant provided written submissions to the Board, serving as the basis for the presentation at the hearing dated 15 February 2013.

[11] In its submissions to the Board, the Applicant requested consideration of two alternative sets of claims: a main set and an auxiliary set. These were presented in order to address a defect related to the polyunsaturated essential fatty acids (PUFA) levels recited in the claims that was identified in the Board=s preliminary review.

[12] As neither set of proposed claims improve the Applicant=s position in respect of the issues below, this review is conducted on the basis of the claims submitted in response to the Final Action.

BACKGROUND

[13] Prior to the filing of the present application, Crohn=s was treated in adults and children primarily by corticosteroid therapy. Though it would induce remission, the therapy had an adverse effect on growth in children.

[14] As an alternative, nutritional therapies were developed for the treatment or prophylaxis of Crohn=s. Though nutritional therapies proved to be just as effective, they were not without their

drawbacks; the compositions were expensive and unpalatable as they either contained amino acids and peptides in the case of Aelemental formulations,@ or hydrolyzed protein in the case of Asemi-elemental formulations.@

[15] As a more palatable and affordable alternative, attention shifted to the use of polymeric formulations that use whole protein rather than amino acids, peptides, or hydrolyzed protein.

[16] Indeed, a particular whole-protein suitable for such treatments was the subject of patents obtained by Nestlé in Europe and in the United States (US). The patents are EP 527 283 (AEP >283@) to Huggett *et al.*, cited by the Examiner in the Final Action; and its US counterpart, US 5,461,033 (AUS >033@), cited in the present description at pg.4.

[17] These patents teach that a milk protein called casein is associated with high levels of TGF-β2. They demonstrate that TGF-β2 can suppress inflammatory response in cells of the GI tract and claim the use of nutritionally balanced enteral products containing TGF-β2 for treatment of inflammatory bowel diseases, including Crohn=s.

[18] Subsequently, the inventors listed in the EP and US patents conducted the Beattie *et al.* study jointly with St. Bartholomew=s Hospital (London, England) demonstrating the efficacy of a specific polymeric nutritional composition comprising TGF-β2 in inducing remission in children with Crohn=s. The children were treated with Nestle-Clintec infant formula enriched with the TGF-β2-rich casein that was disclosed in EP >283.

[19] Like the formulation disclosed in Beattie *et al.*, the nutritional compositions described and claimed in the present application also include casein rich in TGF-β2. Claim 1 of the application reads as follows:

An enteral, nutritional composition for the treatment or prophylaxis of inflammatory conditions of the gastro-intestinal tract, the composition comprising:

casein rich in TGF-β2;

a lipid source providing about 35% to about 50% of energy and containing a mixture of medium and long chain triglycerides, wherein the medium chain triglycerides provide at least 20% by weight of the lipid source, and the lipid source comprises less than 10% of lipid energy from polyunsaturated essential fatty acids; and

a carbohydrate source;

the composition having an energy content of at least 800 Kcal/[L]; and wherein the casein provides about 10% to about 14.5% of the energy of the composition and the casein contains about 1.2 μg to about 2.0 μg of TGF-β2 per g of casein.

OBVIOUSNESS PRINCIPLES

[20] Obviousness, or the ingenuity requirement, is judicially recognized as being integral to the definition of Ainvention@ under section 2 of the *Patent Act*. Section 28.3 of the Act now provides that claimed subject matter must not be obvious to the person skilled in the art or science to which the subject matter pertains in light of information disclosed before the relevant date.

[21] To provide an objective framework in which to assess obviousness, a four-step approach was endorsed by the Supreme Court in *Apotex Inc v Sanofi-Synthelabo Canada Inc*, 2008 SCC 61, as follows:

(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 present case, the main disagreement between the Examiner and the Applicant lies in step 4 of the *Sanofi* framework; there is no material disagreement regarding the identification of the skilled person, the common general knowledge, or regarding the differences over the cited prior art.

[23] The answer to step 4 in this case is provided by addressing the issues set out at para. 9. Before turning to the issues, it is helpful to set out the differences between the claimed compositions and Beattie *et al.*

DIFFERENCES BETWEEN THE CLAIMED COMPOSITIONS AND BEATTIE *ET AL.*

[24] The claimed compositions are new; the Examiner acknowledges that the claimed compositions differ from that disclosed in Beattie *et al.*

[25] The composition disclosed in Beattie *et al.* differed from the present claims as the former had a lower caloric content (700 Kcal/L in Beattie *et al.* vs. Aat least 800 Kcal/[L]@ in the present application), did not appear to include any medium chain triglycerides, and contained more TGF-β2 (although it is unclear whether Beattie *et al.*=s composition contained 24 µg or 160 µg of TGF-β2).

[26] Although in its response to the Final Action the Applicant had presented the PUFA content as a difference as well, the Applicant later conceded that this limitation did not correspond to what the Application describes, and offered to strike the reference to the PUFA content in its set of claims proposed as a AMain Request.@ As such, we do not take the PUFA content to be a difference.

[27] Finally, in its written submissions to the Board, the Applicant appears to have erroneously identified the casein content as a difference over Beattie *et al.* We say erroneously because, by our calculations, Beattie *et al.* provide almost 12% of total energy from casein, falling within the range of 10-14.5% recited in claim 1. Casein content was not previously identified as a

difference during examination and was possibly introduced in the Applicant=s submissions to the Board in error.

[28] Thus it is accepted that the composition disclosed by Beattie *et al.* differs from what is recited in the present claims by the caloric content, the inclusion of medium chain triglycerides, and the TGF-β2 content. We will address the significance of the TGF-β2 levels below.

[29] Identifying the differences only answers step 3 of the *Sanofi* approach. As set out above, step 4 asks: A...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?@ The Applicant submits that ingenuity of the present compositions is indicated by the higher remission rates, as compared to Beattie *et al*.

ISSUE 1: DO THE APPLICANT=S COMPOSITIONS GENERATE HIGHER REMISSION RATES THAN THE PRIOR ART?

[30] If the present formulations give rise to an advantage, it may indicate an inventive step in the obviousness assessment, which is to be conducted from the perspective of the person of ordinary skill in the art (POSITA).

[31] In this review, we will adopt the Applicant=s characterization of the POSITA as a clinician or dietician with experience in treating GI diseases who would work with a patient to meet the patient=s nutritional needs. The POSITA would be well versed in the dose ranges of therapeutic dietary components such as proteins, as well as the nutritional requirements of a patient with an inflammatory condition of the GI tract.

Remission

[32] Full remission from the inflammatory conditions of the intestinal tract is the ultimate goal in treating Crohn=s, states the Applicant.

[33] According to the Applicant=s submissions, a formulation within the scope of claim 1 was administered to children with Crohn=s disease, resulting in remarkably higher remission rates compared to those observed in Beattie *et al.* If higher rates of remission were indeed obtained, it could indicate that the claimed compositions provide a nonobvious advance in the art.

[34] To quantify the rate of remission obtained in each, the Applicant states that complete (or full) remission was achieved in 8 of 9 patients who consumed the claimed composition, whereas only 2 of 7 patients achieved full remission in Beattie *et al.* In order to conduct a useful comparison between the performance of the two compositions, it is necessary to use the same standard.

[35] What does the Applicant mean by Afull remission?@ The Applicant did not define the term in its submissions, nor is it defined in the present application. At the hearing, the Applicant submitted that, in general, remission is based on a holistic assessment, taking into account many factors. To understand what was meant by Afull remission@ in the present application, we turn to the description.

Remission in the present description

[36] It is clear from reviewing the present description that a patient in Afull remission@ can still have some degree of inflammation in the bowel.

[37] Example 2 in the present description sets out a study of 11 children suffering from Crohn=s disease. The claimed composition is administered to the children as a sole source of nutrition for 8 weeks. A table on pg.10 of the description provides endoscopic assessments of the children, both at the start of the study and at eight weeks. For each child, inflammation observed in different areas of the bowel is rated on a score of 0 to 3 (0 = normal, 1 = mild inflammation, 2 = moderate inflammation, and 3 = severe inflammation). A second table on pg.11 sets out the outcome for each of the patients, describing for each patient whether the treatment was completed, whether full remission was achieved, or whether the patient relapsed.

[38] When the outcomes listed in the second table are compared with the endoscopic assessments at eight weeks shown in the first table, it is evident that Afull remission,@ in the context of the application, does not require the complete absence of inflammation. Indeed, two of the patients characterized as being in Afull remission@ (patient 5 in group 1 and patient 4 in group 2) showed no change in inflammation (observed endoscopically); in two others (patients 3 in both groups) mild inflammation was observed in a part of the bowel where no inflammation was initially observed; and all but one of the patients in full remission (patient 1, group 2) still had at least mild inflammation in at least one part of their bowel.

Comparing remission in Beattie *et al.*

[39] A different standard appears to have been applied by the Applicant when assessing the remission rate in Beattie *et al.* When endoscopic observations are compared, Beattie *et al.* show comparable remission rates.

[40] In Beattie *et al.*, a similar study of seven children with Crohn=s disease is described. All were fed a casein-based, polymeric feed rich in TGF-β2 for a period of 8 weeks as their sole source of nutrition. All were assessed at the start of the study and at 8 weeks.

[41] Consistent with the Applicant=s submissions, complete remission did occur in 2 of 7 children in the Beattie *et al.* study, however these children were in Acomplete histological remission.@ Histological remission B assessed by inspecting biopsies B was not the standard applied by the Applicant when assessing performance of the present application.

[42] It is not possible to compare results on the basis of histology. Though the present description states that histological assessments were performed, again using a score of 0 to 3 similar to that used to quantify endoscopic observations, no such data is reported.

[43] On the other hand, when endoscopic assessments are compared instead, Beattie *et al.* showed that 3 of 5 had complete endoscopic remission with partial remission in the other two, results that are comparable to or better than those reported in Table 2 of the present application.

[44] However, as the Applicant stated, Afull remission@ is typically based on a holistic assessment. With this in mind, we turn to the other measurements of inflammatory and disease activity common to the present application and Beattie *et al.*

Other measurements

[45] Several other common measurements were taken to assess the efficacy of the treatment in both the present application and Beattie *et al.*, namely, Lloyd Still Index (LSI), Erythrocyte Sedimentation Rate (ESR), and serum albumin levels. Results from these measurements in the present application are illustrated in Figures 1a, 1b (LSI); Figures 2a and 2b (ESR); and Figures 3a and 3b (serum albumin).

[46] Performance across every one of these indicators shows that Beattie *et al.* appears to be at least as effective as the claimed compositions, when compared to the results shown in the Figures of the present application. In its submissions to the Board, the Applicant acknowledges that both Beattie *et al.* and the present application show approximately the same LSI score; that Aimprovement is evident@ in the ESR values of both studies; and, Acomparable improvements@ are shown with respect to the serum albumin parameter.

[47] One additional parameter was reported in the present description, IL-1β B an indicator of down-regulation of inflammation. Figure 4 of the present application illustrates that IL-1β measurements for the present application confirm that the children treated with the claimed composition experienced a down-regulation of inflammation across the board.

[48] Though this parameter wasn=t reported by Beattie *et al.*, they did report remission in biochemical markers of inflammation in all children. Given that the results related to inflammation published in Beattie *et al.* were at least as strong as those given in the present application, the Board is satisfied that the IL1-β marker doesn=t help to distinguish the two studies.

Conclusion B remission rates

[49] The Board does not accept the Applicant=s principal argument that the present compositions are inventive over Beattie *et al.* on account of a higher rate of remission. While the claimed compositions appear to produce significant results in treating children with Crohn=s, the results are in agreement with those published by Beattie *et al.*

[50] However, the composition could nonetheless be inventive if these results were achieved with substantially less TGF-β2 than what would have been expected by the skilled person.

ISSUE 2: DO THE APPLICANT=S COMPOSITIONS COMPRISE SURPRISINGLY LOW LEVELS OF TGF-β2?

[51] The Applicant submits that the level of TGF-β2 provided in the composition used by Beattie *et al.* was significantly higher than what is required by the present claims and what was used in Example 2 of the application.

[52] Though the Applicant submits that Athere is no magic bullet,@ the prior art strongly suggests that TGF-β2 is principally responsible for the reduction in inflammation in the intestinal tract (see e.g., the Applicant=s EP >283 patent and Beattie *et al.* at pg. 614). Thus, if the Applicant has discovered that significantly less TGF-β2 is required to produce results comparable to Beattie *et al.*, it might indicate an inventive step. However, merely comparing with Beattie *et al.* would be insufficient; the *Sanofi* approach (see para 21, above), consistent with prior case law, requires that obviousness be assessed in light of the state of the art as a whole.

TGF-β2 levels in Beattie *et al.*

[53] Turning to Beattie *et al.*, it isn=t entirely clear how much TGF-β2 is contained in the polymeric formula. However, by any interpretation, the composition used by Beattie *et al.* appears to have contained significantly more TGF-β2 (either 24 μg or 160 μg) than the present claims require.

[54] This might suggest an inventive step if read in isolation, however the single formulation taught by Beattie *et al.* is not on its own representative of the skilled person=s understanding of how much TGF-β2 would have been required to provide an effective treatment. From our reading of Beattie *et al.*, the purpose of their study was not to explore the range of TGF-β2 that is effective in bringing about a reduction in inflammation. For this, the skilled person would have regard to the Applicant=s EP >283 patent and its US equivalent, US >033. Indeed, Beattie *et al.* cited the EP >283 patent as guidance on the preparation of casein rich in TGF-β2.

TGF-β2 levels in US >033

[55] Irrespective of whether the composition taught by Beattie *et al.* contained more TGF-β2 than is recited in the present claims, the levels recited in the present claims would come as no surprise to the POSITA in light of US >033. It follows that the present claims are not inventive on account of the recited levels of TGF-β2.

[56] The present description cites US >033 to teach the skilled reader how to produce TGF-β2 enriched casein - the component that contains the TGF-β2; see description at pg. 4, line 18. The description states that, at the levels of casein and TGF-β2 recited in the claims, casein provides about 10 μg to about 40 μg of TGF-β2 per 100g of the composition, on a dry basis. That is, casein supplies 0.1 to 0.4 μg/g of the composition.

[57] Similarly, the US >033 patent discloses 0.1 to 20 μg TGF-β2 per gram of dry matter of a nutritionally balanced enteral product for treating Crohn=s disease, with 0.1 to 0.5 being the preferred levels of TGF-β2; see Example 2 of US >033.

Conclusion - TGF-β2 levels

[58] Thus, the Board finds that the levels of TGF-β2 recited in the present claims are within the levels the POSITA would have expected to be effective in a nutritional formulation for the treatment of inflammatory bowel diseases, including Crohn=s.

REMAINING CLAIMS

[59] The findings above apply equally to the remaining claims, namely claims 2-17. Certain of these claims recite more specific amounts of various elements, while others restate the composition for use claim as use of composition claims.

[60] The Applicant did not make any submissions to the Board regarding any of the remaining claims, but instead focused on the subject matter of claim 1.

[61] Regarding claims 4, 9, and 14 in particular, these claims recite certain levels of sodium. The Examiner cited a further reference (Sanderson) that shows similar sodium levels used in nutritional products for Crohn=s patients. Again, the Applicant made no further submissions on this point and we agree that the sodium levels recited in these claims are consistent with those taught for Crohn=s formulations in Sanderson.

CONCLUSION

[62] The Board finds that the subject matter of claims 1-17 would have been obvious to a POSITA.

[63] The claimed compositions, though different, do not provide higher remission rates than the Beattie *et al.* study, as the Applicant submits.

[64] Moreover, the levels of TGF-β2 recited in the present claims, though lower than the amounts contained in the Beattie *et al.* formulation, are within the range that would have been expected by the POSITA, in light of the US= 033 patent referred to in the present description.

RECOMMENDATION OF THE BOARD

[65] In view of the above findings, the Board recommends refusal of the application under

section 40 of the *Patent Act*.

Mark Couture | Christine Teixeira | Paul Sabharwal

Member | Member | Member

DECISION OF THE COMMISSIONER

[66] I concur with the Patent Appeal Board=s findings and their recommendation that I uphold the Examiner=s rejection of the application due to the claims being obvious in view of the cited prior art.

[67] 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.

Sylvain Laporte

Commissioner of Patents

Dated at Gatineau, Quebec,

this 15th day of May 2013