Commissioner=s Decision # 1343
Décision du Commissaire # 1343

TOPICS: B00, F01, K11, O00
SUJETS: B00, F01, K11, O00

Application No. : 2,365,923

Demande n^{o}. : 2,365,923

IN THE CANADIAN PATENT OFFICE

DECISION OF THE COMMISSIONER OF PATENTS

Patent application number 2,365,923 having been rejected under subsection 30(4) of the *Patent Rules*, has 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 ruling of the Commissioner are as follows:

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INTRODUCTION

[1] This decision deals with a review of the rejection of patent application number 2,365,923 entitled AMEDICAL PREPARATIONS FOR THE TREATMENT OF ALPHA-GALACTOSIDASE A DEFICIENCY.@

[2] The inventors are Marianne Borowski, Carol M. Kinoshita, Douglas A. Treco, Melanie D. Williams, Richard F. Selden, Thomas J. Schuetz and Peter Francis Daniel. The current owner is Shire Human Genetic Therapies Inc.

BACKGROUND

[3] The subject application relates to the use of a drug, in the form of a therapeutic human enzyme, to treat patients suffering from a rare genetic disease.

[4] An enzyme is a type of biochemical molecule that acts as a catalyst for specific biochemical reactions, converting a specific set of reactants into specific products. In the present case, the therapeutic enzyme is known as Aα-Gal A.@ Its natural role in the human body is to breakdown its reactant: Aceramide trihexoside.@

[5] In rare instances, a genetic defect leads to deficiency of the α-Gal A enzyme and causes AFabry@ disease. Fabry disease is a serious condition that affects the peripheral nervous system, causing episodes of agonizing, burning pain in the extremities, and accumulation of ceramide trihexoside within the blood vessels, tissues and organs leading to impairment of their proper function.

[6] The potential to treat Fabry patients by infusing them with α-Gal A had been suggested as a theoretical approach since the late 1970's. However, this type of enzyme replacement therapy did not become more of a practical reality until the large amounts of enzyme required for clinical experimentation could be readily obtained. By the 1990's that had been done. Using recombinant DNA technology, foreign cells, such as Chinese Hamster Ovary (CHO) cells, had been genetically engineered to produce the human enzyme in large amounts. Nonetheless, the enzyme still had not been formally approved for therapeutic use in treating Fabry disease.

[7] The claims of the present application focus on a specific dosage range of α-Gal A that may

be administered to Fabry patients. The inventors first engineered human cells to overproduce the enzyme. They then elucidated the glycosylation pattern of human α-Gal A when produced in human cells as compared to the glycosylation pattern of the enzyme when produced in foreign hamster cells. The Aglycosylation pattern@ of an enzyme refers to the arrangement of small sugar or carbohydrate chemical groups that are added to the much larger enzyme molecule after it is initially synthesized in cells. The pattern is an important biochemical property since it can affect the efficacy and pharmacokinetic profile of a therapeutic enzyme, and hence its appropriate dosage. In the present case, the applicant has asserted that the differences in glycosylation patterns that they observed factored into the dosages recited in the claims.

PROSECUTION HISTORY

[8] The application was filed on 09 March 2000. On 01 May 2007 the Examiner issued a Final Action in which: all of the claims were considered defective for lack of novelty under subsection 28.2(1) of the *Patent Act*; all of the claims were considered defective for being directed to non-statutory methods of medical treatment; and all of the claims were considered defective under subsection 27(4) of the *Patent Act*.

[9] In the Applicant=s response to the Final Action, dated 30 October 2008, former claims 1-24 were replaced with amended claims 1-75. In addition, new claims 76-91 defining a different dosage range were added to the application. The Examiner, not having reasonable grounds to believe that the application was compliant with the Act and Rules, forwarded the case to the Patent Appeal Board (the Board) for review. The Summary of Reasons dated 04 March 2009 indicated that claims 1-91 lacked novelty and were also considered to be directed to an unpatentable method of medical treatment. Claims 40-47 were considered to be indefinite under 27(4) of the *Patent Act*.

[10] The Board subsequently invited the Examiner to provide a Supplementary Summary of Reasons (SSOR) to address the issue of obviousness. This was done for several reasons. Firstly, in the response to the Final Action, the Applicant continued to maintain that one key issue to be decided in this case is the patentability of a narrowly claimed dosage range over

the prior disclosure of a broader range. In that regard, the Applicant submitted that the Federal Court of Appeal decision in *Hercules Inc. v. Commissioner of Patents,* 1985, 4 CPR (3d) 289 confirmed that the patentability of a narrower range within a broader range is a matter of obviousness, not novelty. Secondly, many of the Examiner=s arguments in the novelty analysis appeared to relate to the issue of obviousness. Upon further consideration, the Examiner concluded that claims 1-91 were also non-compliant with section 28.3 of the *Patent Act* for being obvious in view of the prior art on file. The Examiner also questioned the submission of new claims 76-91, saying that there appears to be a lack of unity of invention in the presently filed set of claims due to the definition of a different dose than that specified in claims 1-75.

[11] A hearing was held on 12 May 2010, at which time the Applicant was represented by Mr. David Schwartz and Mr. Brandon Reinhart of the firm Smart & Biggar. Also in attendance were Debora Fujimoto, the Examiner in charge of the application, and her acting Section Head, Steven Misener. In advance of the hearing, the Applicant presented written submissions for consideration by the Board to complement the Applicant=s oral arguments. In addition, the Applicant proposed to cancel claims 76-91 in an effort to advance prosecution in view of the Examiner=s concerns with respect to unity of invention.

ISSUES

[12] In the Final Action the Examiner maintained that the application was defective because the subject matter of all the claims was anticipated by the prior art. In their response to the Final Action, the Applicant acknowledged that the prior art discloses an α-Gal A preparation which inherently has the same pharmacokinetic properties as the α-Gal A preparation that is the subject of the present claims, as well as its use for the treatment of an α-Gal A deficiency. However, the Applicant emphasized that the broad dosage range described by the prior art cannot be considered a teaching or disclosure of the very specific dosage ranges presently claimed. Further, as indicated above, the Applicant

continued to argue that the patentability of a narrowly claimed dosage range over the prior disclosure of a broader range is a matter of obviousness and not novelty.

[13] The Examiner also considered the application to be defective on the grounds that the subject matter of all the claims was directed to non-statutory methods of medical treatment. The Examiner considered the dosage to be an essential element of the claims and held that the claims were directed to a method of medical treatment.

[14] Finally, the Examiner found the subject matter of claims 40-47 to be indefinite under 27(4) of the *Patent Act* for reciting a unit dose that can be varied or adapted in any manner.

[15] Since the Applicant has voluntarily proposed the cancellation of claims 76-91, the review will proceed on the basis of the remaining claims in dispute. Based on the above, the Board is faced with 4 questions:

1. Are claims 1-75 anticipated?
2. Are claims 1-75 obvious?
3. Do claims 1-75 fail to comply with section 2 of the *Patent Act* for being directed to a method of medical treatment?
4. Are claims 40-47 indefinite?

CLAIMS

[16] With respect to the claim set now on file, the Board notes that the Applicant made oral submissions explaining that these claims represent their last opportunity to submit additional or amended claims in the hopes that an allowable claim set might be obtained. The Board recognizes that it can be a challenge to draft acceptable claims that recite a dosage yet do not run afoul of the methods of medical treatment prohibition and still define novel and inventive subject matter. Although Aa single invention may be claimed in different ways@ (see *Wenzel Downhole Tools Ltd v. National-Oilwell Canada Ltd.*, 2012 FCA 333 at para. 48), that does not change the outcome of our analysis.

[17] The following claims are representative of the claims in dispute:

1. Use of a human α-Galactosidase A (α-Gal A) preparation wherein more than 50% of the total glycans of the preparation are complex glycans, in the treatment of α-Gal A deficiency, wherein the human α-Gal A preparation is for administration in a dose of between about 0.1-0.3 mg of the human α-Gal A preparation per kilogram of body weight of a subject.

14. Use of a human α-Galactosidase A (α-Gal A) preparation wherein more than 50% of the total glycans of the preparation are complex glycans, in the manufacture of a medicament for the treatment of α-Gal A deficiency, wherein the medicament is for administration of a dose of between about 0.1-0.3 mg of the human α-Gal A preparation per kilogram of body weight of a subject.

27. A human α-Galactosidase A (α-Gal A) preparation wherein more than 50% of the total glycans of the preparation are complex glycans, for use in the treatment of α-Gal A deficiency in a dose of between about 0.1-0.3 mg of the human α-Gal A preparation per kilogram of body weight of a subject.

40. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a human α-Galactosidase A (α-Gal A) preparation wherein more than 50% of the total glycans of the preparation are complex glycans, the pharmaceutical composition being in a unit dosage form comprising a unit dose of between about 0.1-0.3 mg of the human α-Gal A preparation per kilogram of body weight of a subject.

50. The pharmaceutical composition according to any one of claims 40 to 49 comprising polysorbate 20, sodium chloride, sodium hydroxide, sodium phosphate monobasic, and water for injection.

51. The pharmaceutical composition according to any one of claims 40 to 50, for use in the treatment of an α-Gal A deficiency in a subject.

52. The pharmaceutical composition according to any one of claims 40 to 50, for use in the treatment of typical or atypical Fabry disease in a subject.

53. A pharmaceutical composition in the form of a solution for injection, the pharmaceutical composition comprising a pharmaceutically acceptable carrier and a human α-Galactosidase A (α-Gal A) preparation wherein more than 50% of the total glycans of the preparation are complex glycans, the pharmaceutical composition comprising an amount of the human α-Gal A preparation sufficient to provide a dose of between about 0.1-0.3 mg of the human α-Gal A preparation per kilogram of body weight of a subject when the pharmaceutical composition is administered to the subject in a single dose.

63. The pharmaceutical composition according to any one of claims 53 to 62 comprising polysorbate

20, sodium chloride, sodium hydroxide, sodium phosphate monobasic, and water for injection.

64. The pharmaceutical composition according to any one of claims 53 to 63, for use in the treatment of an α-Gal A deficiency in a subject.

65. The pharmaceutical composition according to any one of claims 53 to 63, for use in the treatment of typical or atypical Fabry disease in a subject.

68. Use of a human α-Galactosidase A (α-Gal A) preparation in the manufacture of the pharmaceutical composition according to any one of the claims 40 to 50.

70. A commercial package comprising the pharmaceutical composition according to any one of claims 40 to 50, together with instructions for use of the pharmaceutical composition in the treatment of α-Gal A deficiency in a subject.

74. A commercial package comprising a human α-Galactosidase A (α-Gal A) preparation wherein more than 50% of the total glycans of the preparation are complex glycans, together with instructions for use of the human α-Gal A preparation for making a pharmaceutical composition according to any one of claims 40 to 50.

CLAIM CONSTRUCTION

[18] Purposive construction is performed to objectively determine where the person skilled in the art would, as of the date of publication of the patent application and on the basis of the particular words or phrases used in the claim, have understood the applicant to have intended to place the fences around the monopoly claimed: *Free World Trust v. Electro Sante Inc.*, 2000 SCC 66 [*Free World Trust*]. During purposive construction, the elements of the claimed invention are identified as either essential or non-essential.

The Skilled Person and Common General Knowledge

[19] The exercise begins with the identification of the notional person skilled in the art and the relevant common general knowledge of that person.

[20] In the SSOR, the Examiner defined the skilled person in the art as a clinician with training in molecular biology and experience in clinical trials.

[21] In its submissions to the Board, the Applicant argued that the Examiner provided no evidence to support this characterization of the person skilled in the art and that the only evidence on record on this issue is the affidavit from Dr. Carol M. Kinoshita dated 03 November 2005. Dr. Kinoshita is an inventor both in the present application and the cited prior art by Selden et al.

[22] We find that Dr. Kinoshita is not adequately representative of the skilled person because her main area of expertise appears to be limited to protein purification and characterization. The Board finds that there is more to the understanding of the present patent application than possessing the skill of a pharmaceutical chemist. The patent application also addresses the use of enzyme preparations for the treatment of certain rare diseases. We also find the Examiner=s characterization of the skilled person as a clinician with training in molecular biology and experience in clinical trials to be too general as it omits relevant skills and knowledge, e.g. knowledge of protein biochemistry.

[23] We identify the skilled person as a team comprising a molecular biologist, a protein biochemist, a pharmachemist and a clinician familiar with treating diseases related to enzyme deficiencies. This team=s collective common general knowledge would therefore include: knowledge of the recombinant expression, purification and characterization of therapeutic proteins; knowledge of the preparation of drug formulations; and knowledge of how to conduct clinical trials to assess the safety and efficacy of potentially useful therapeutics.

Grouping of the Construed Claims Into Two Categories

[24] The next step in the exercise involves a consideration of the claims themselves.

[25] As a preliminary matter, it is apparent that B after having done a purposive construction of all of the claims at issue B each claim can be placed into one of two general categories: claims related to medical uses and claims related to pharmaceutical compositions.

[26] In arriving at these groupings, the Board has kept in mind the principle of issue-driven analysis in the context of purposive construction. Claim analysis and purposive construction should focus on narrow, determinative, points of dispute B not on areas where there is mutual agreement; i.e., purposive construction should be focussed on Awhere the shoe pinches@: *Laboratoires Servier v. Apotex*, 2008 FC 825; *Shire Biochem Inc. v. Canada (Minister of Health)*, 2008 FC 538.

[27] As explained more fully below, a key point of dispute in this case revolves around the mention of a specific dosage range in the claims and the effect this feature has on determining whether a claim is related to a medical use or to a pharmaceutical composition. We have found that the claims within each group are Arelated@ even if their preambles might suggest otherwise and even if claim scope within a group may be similar or variable. The manner of claim grouping focusses the analyses which follow.

First Claim Category: Claims Related to Medical Uses (claims 1-39, 51, 52, 64, 65 and

70-73)

[28] The present claim set contains the three different forms of second medical use claims that are considered allowable: claims 1-13 are in the form of a direct use claim; claims 14-26 are in the form of a ASwiss-type@ medical use claim; claims 27-39, 51, 52, 64 and 65 appear in the form of a Amedical composition for use@ claim.

[29] Although claims 70-73 reference commercial packages that contain a pharmaceutical composition they additionally contain instructions for use of the pharmaceutical composition in the Atreatment of α-Gal A deficiency in a subject@. Therefore, for the purposes of this decision, claims 70-73 will be treated as related to medical uses because they all reference a human α-Gal A preparation along with an indication that the composition is for Atreatment of α-Gal A deficiency.@ They also all, either directly or indirectly, refer to a dosage range.

[30] Representative claims 1, 14, 27, 51, 52, 64, 65 and 70 are each construed to have the following essential elements:

(i) human α-Gal A having at least 50% complex glycans
(ii) for use in the treatment of an α-Gal A deficiency [typical or atypical Fabry disease in the case of claims 52 and 65]
(iii) at a dose of 0.1-0.3 mg/kg of body weight of a subject.

Second Claim Category: Claims Related to Pharmaceutical Compositions (claims 40-50, 53-63, 66-69, 74 and 75)

[31] Claims 40-50, 53-63, 66-69, 74 and 75 relate to pharmaceutical compositions. There are

no explicit limitations in these claims that the compositions are for a particular medical use, i.e., for Atreating an α-Gal A deficiency@ as indicated in the claims related to medical uses.

[32] Claim 40 defines a pharmaceutical composition in a unit dosage form suggesting that it is intended to be in a fixed, unique, form. Further, the claim makes reference to a Aunit dose@, a term which is neither mentioned nor defined in the description, but which is considered a standard of measurement which contains a *fixed* quantity of drug. However, the remainder of the claim language indicates that the amount of the drug in the Aunit dose@ of the composition can be *varied* according to the weight of a subject (i.e., on a mg per kg basis). The reference to a Aunit dose@ that can also be *varied* according to the weight of a subject is at odds with the notion of a *fixed* quantity of drug. Indeed, in the Final Action the Examiner objected to this claim language as being indefinite. Although this issue is formally addressed later in the decision, the Board=s findings on indefiniteness have been imported to help facilitate our construction. As indicated below, the Board finds that the reference to a unit dosage form comprising a unit dose that can be varied according to the weight of a subject introduces unnecessary ambiguity that can be avoided by simply referring to the composition as being in a unit dosage form comprising a dose that can be varied according to the weight of a subject. Indeed, this interpretation is supported by the Applicant=s oral submissions wherein they indicated that said pharmaceutical composition is intended to be sold as a liquid suspension which is then further diluted to an appropriate volume for administration (i.e. as a stock solution). It is also consistent with the teachings of the description. Specifically, Example 3 discloses:

> α-Gal A Purified Bulk is diluted to final concentration with α-Gal A Diluent. Based on the volume of

purified bulk to be formulated, the concentration of α-Gal A (mg/mL), and the desired concentration of α-Gal in the final formulation, the volume of α-Gal A diluent required is determined.

[...]
α-Gal A diluent is added to α-Gal A purified bulk in a mixing vessel to give a 1 mg/mL final solution.

[33] Based on the above, representative claim 40 has been construed to define a pharmaceutical composition having the following essential elements:

(i) comprising a pharmaceutically acceptable carrier
(ii) comprising a human α-Gal A preparation having at least 50% complex glycans
(iii) in the form of a stock solution which can be diluted to provide a dose of between about 0.1-0.3 mg/kg of body weight of a subject.

[34] In contrast, claim 53 indicates that the composition must be in a form sufficient to *provide a desired dose when it is administered in a single dose*. Therefore, not only must the composition be in the form of a solution for injection, it must also provide a desired dose for a given subject. This suggests that the claim encompasses an infinite number of pharmaceutical compositions to accommodate every combination covered by the dosage range of 0.1-0.3 mg/kg of body weight of a subject. Indeed, at the hearing the Applicant indicated that the pharmaceutical composition in a form of a solution for injection contemplated comprises an intravenous bag containing the desired amount of drug in a single dose. Although this interpretation seems to be endorsed by the description which discloses supplying the preparation as a liquid for intravenous administration, including sterile bags for direct administration, it is unlikely that the skilled person, being reasonable and practical, would prepare a seemingly vast number of compositions, each comprising a different amount of drug to accommodate both a desired dose and the weight of a subject. Neither would one would expect a pharmaceutical company to market and sell such a vast number of compositions. Moreover, the skilled person would anticipate that prolonged storage of such dilute pharmaceutical compositions would compromise the

stability of the α-Gal A enzyme.

[35] An alternative interpretation, which we prefer, considers the pharmaceutical composition of claim 53 in a manner much like the subject matter of claim 40. Specifically, the pharmaceutical composition of claim 53 is not considered to be limited by the restriction that the composition *per se* is administered in a single dose. Rather, it must be in the form of a solution that can be provided to a clinician in a dose sufficient to provide a desired dose (i.e., as a stock solution). It would then be up to the clinician B working outside the scope of the claim B to vary the dose taken from the composition in accordance with the dosage range as defined in the claim depending on the determined treatment.

[36] Therefore, representative claim 53 has been construed to define a pharmaceutical composition having the following essential elements:

(i) comprising a pharmaceutically acceptable carrier
(ii) comprising a human α-Gal A preparation having at least 50% complex glycans
(iii) in the form of a stock solution comprising an amount of the α-Gal A preparationsufficient to provide a desired dose of 0.1-0.3 mg/kg of body weight of a subject when diluted for administration.

[37] Claims 50 and 63 are dependent on claims 40 and 53, respectively. Necessarily they incorporate the same essential elements as the claims from which they depend. However, these claims also describe the composition of a specific diluent for α-Gal A which comprises polysorbate 20, sodium chloride, sodium hydroxide, sodium phosphate monobasic, and water for injection. As there is no reason to conclude otherwise, the diluent will also be considered an essential element of these claims.

[38] Therefore, in addition to the essential elements identified for claim 40 (para. [30]) and claim 53 (para. [33]), representative claims 50 and 63, respectively have also been construed to contain the following essential element:

(iv) comprising polysorbate 20, sodium chloride, sodium hydroxide, sodium phosphate monobasic, and water for injection.

[39] Claims 68 and 69 are presented as use claims comprising a human α-Gal A preparation. Unlike claim 14, there is no mention of a medical use; rather the claims are directed to the *manufacture of a pharmaceutical composition* (according to any one of claims 40 to 50, or, as the case may be, according to any one of claims 53 to 63). Therefore, they will be considered along with the other pharmaceutical composition claims. The preambles to claims 74 and 75 indicate that the claims are directed to commercial packages that contain an α-Gal A preparation. Like claims 70-73, they also reference Ainstructions@, but in this case the instructions are for use of an α-Gal A preparation for *making a pharmaceutical composition* (according to any one of claims 40 to 50, or, as the case may be, according to any one of claims 53 to 63). Again, there is no mention of a medical use. Therefore, for the purposes of this decision, they will be treated as related to the other pharmaceutical composition claims.

[40] Representative claims 68 and 74 are therefore each construed to have the following essential elements:

(i) human α-Gal A having at least 50% complex glycans

(ii) for use in the manufacture of a pharmaceutical composition according to any one of claims 40 to 50.

[41] In sum, claims 40-50, 53-63, 66-69, 74 and 75 relate to pharmaceutical compositions

without a restriction to a medical use.

PRIOR ART

[42] The following prior art was cited in the Final Action and is relevant to the issues of anticipation and obviousness:

PCT Application

WO 9811206	19 March 1998	Selden et al.

[43] Selden et al. disclose the expression and purification of human α-Gal A in cultured human fibroblast cells. The human α-Gal A is enzymatically active and efficiently internalized by cells making it suitable for the treatment of Fabry disease. With respect to the therapeutic use of the α-Gal A enzyme, page 44 of the description states: AFurthermore, skilled artisans are aware that the route of administration and dosage of a therapeutic protein may be varied for a given patient until a therapeutic dosage level is obtained. Typically, doses of α-Gal A of 0.01-100 mg/kg of body weight will be administered.@ It is noted that this application represents work done previously by some of the same inventors as the present application.

ISSUE 1: ANTICIPATION

Legal Framework

[44] The statutory provision relevant for assessing anticipation is subsection 28.2(1) of the *Patent Act*. That subsection provides, in part:

> The subject-matter defined by a claim in an application for a patent in Canada (the Apending application@) must not have been disclosed
>
> (*a*) 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 subject-matter became available to the public in Canada or elsewhere;
> (*b*) before the claim date by a person not mentioned in paragraph (*a*) in such a manner that the subject-matter became available to the public in Canada or elsewhere.

[45] In *Free World Trust* (at para. 25) the Supreme Court made clear that if a single prior art publication discloses all of the essential elements of the claimed invention in an enabling manner, there is anticipation.

[46] In *Apotex Inc. v. Sanofi-Synthelabo Canada Inc.*, 2008 SCC 61 [*Sanofi*], the Supreme Court further clarified the test for anticipation by explicitly endorsing a two-step approach in which the requirements of Aprior disclosure@ and Aenablement@ should be considered separately and proven. In *Sanofi*, the Supreme Court based this approach on the decision of the House of Lords, per Hoffman L.J., in *Synthon BV v. Smithkline Beecham plc*, 2005 UKHL 59, 2006 1 All ER 685 [*Synthon*].

[47] Concerning the disclosure aspect, the Supreme Court indicated that a prior disclosure Amust disclose subject matter that, if performed, would necessarily result in something within the claims@ (*Sanofi* at para. 25). That is, it must contain clear and unambiguous directions which would inevitably lead the skilled person to something that, if performed, would infringe the claims. This aspect of the disclosure requirement was emphasized by both Hughes J. (in *Eli Lilly Canada Inc. v. Apotex Inc.*, 2008 FC 142, aff=d 2009 FCA 97) and Snider J. (in *Merck & Co. v. Apotex Inc.*, 2010 FC 1265 at para. 607).

[48] If the disclosure requirement is met, the second requirement of enablement must also be satisfied; this means:

> [t]hat the person skilled in the art would have been able to perform the invention [para. 26]

and that:

> [t]he person skilled in the art is assumed to be willing to make trial and error experiments to get it to work.

[para. 27]

Analysis under the *Sanofi* Two-Step Approach

Claims Related to Medical Uses (claims 1-39, 51, 52, 64, 65 and 70-73)

[49] The claims related to medical uses call for the use of an α-Gal A preparation within a particular dosage range in order to treat subjects with an α-Gal A deficiency.

[50] In the Final Action, the Examiner explained that Selden et al. disclosed genetic expression constructs identical to those in the present application. Further, incorporation of these constructs into human cells, as taught by Selden et al., would inevitably produce an α-Gal A preparation that would fall within the scope of the claims. As indicated above, the Applicant acknowledged in their response to the Final Action that the α-Gal A preparation disclosed in Selden et al. inherently has the same pharmacokinetic properties as that of the α-Gal A preparation that is the subject of the present claims. Selden et al. also disclose the use of such preparations for the same purposes (i.e., for the treatment of an α-Gal A deficiency). Therefore, it is common ground that the prior art discloses two of the three essential elements found in each of the medical use claims. What is less clear, and in dispute, is whether the dosage range of 0.1 to 0.3 mg/kg confers novelty on these claims over the disclosure of Selden et al.

[51] The Applicant has argued that Selden et al. does not in any way teach or disclose the

very specific dosage ranges presently claimed. Specifically, the Applicant submitted that nothing in Selden et al. marks the end points of the range presently claimed so clearly that an ordinary person skilled in the art would Ain every case, and without possibility of error@ be led to the specific dosage range presently claimed, as required for a finding of anticipation. Further, in view of *Sanofi*, the Applicant maintained that it is irrelevant that the claimed range of about 0.1 to about 0.3 mg/kg falls within the previously disclosed range of Selden et al., as Selden et al. does not disclose this narrower, more specific range it is not specifically disclosed.

[52] In a case such as the present one, where a narrower dosage range is claimed subsequent to a prior disclosure of a broader dosage range, one might conclude that, since the later claimed range falls within the broad range, there is anticipation. The Final Action makes this point. Selden et al. disclose the range of 0.01-100 mg of a human α-Gal A preparation per kilogram of body weight of a subject; i.e., a broad range that encompasses the narrower dosage range now claimed. On that basis it is arguable that Selden et al. *may* lead a person skilled in the art to use a dosage that falls within the narrow range now claimed.

[53] However, as indicated above, the prior art must disclose subject matter which, if performed, would necessarily result in something within the claims. In this context, what must be considered is whether the skilled person would inevitably work within the specific dosage range of 0.1 to 0.3 mg/kg based on the disclosure of Selden et al.

[54] The Board observes that the dosage range of 0.1 to 0.3 mg/kg was not specifically disclosed in Selden et al. We also find that the range described by Selden et al. starts at 0.01 mg/kg and extends to 100 mg/kg. As opined by Dr. Kinoshita in her affidavit, the broad therapeutic range disclosed by Selden et al. is not specific to a-Gal A and appears to cover almost every conceivable dose at which a protein therapeutic (or almost any therapeutic) could be used. Moreover, Selden et al. fails to disclose specific examples which could establish definite end points of any range or any operative dosages within a range.

[55] In view of the foregoing, the Board finds the 10, 000 fold range disclosed by Selden et al. is not a credible operating range, but rather it represents a starting point for experimentation to determine a useful range at which a human α-Gal A preparation can be used for the treatment of an α-Gal A deficiency. Remembering also that there is no room for trial and error experimentation when considering the disclosure requirement, the Board finds that based on the disclosure of Selden et al. the skilled person would not necessarily, or inevitably, be led to dose a patient with a dosage that falls within the claims.

[56] A single prior publication must disclose all of the essential elements of the claims in order to anticipate. The Board considers that the presently claimed operating range is not disclosed by Selden et al. It follows that Selden et al. does not anticipate the claimed subject matter.

[57] Since the broad medical use claims have been found to define novel subject matter, it follows that their narrower dependent claims also define novel subject matter.

Claims Related to Pharmaceutical Compositions (claims 40-50, 53-63, 66-69, 74 and 75)

[58] Like the medical use claims, the pharmaceutical composition claims have been construed to include the dosage range as an essential element.

[59] Here the dosage element is essential because the claimed compositions must *comprise*, or be capable of *providing*, certain amounts of the human α-Gal A preparation based on the weight of a subject. This simply means that the composition must be in a form that allows for its partitioning by a clinician B in accordance with the specified dosage range. For example, where the pharmaceutical composition is in the form of a solution for injection (as specified in claim 53), the solution must be of sufficient volume and concentration so as to provide a dosage that can be calculated by a clinician during the course of treatment. This does not mean that the solution itself is necessarily new. A dosage that is calculated and then administered during treatment need not alter the nature of its originating stock solution B such calculating and dosing activities are outside the scope of the claim.

[60] In this case, Selden et al. disclose a human α-Gal A preparation that undeniably fits within the scope of the broad composition claims. An enzyme preparation produced in accordance with the teachings of Selden et al. has at least 50% complex glycans. They are disclosed in forms that are suitable and *capable of providing* dosages within the

ranges called for in the claims. The simple mention in the present claims of a target dosage range does not change the nature of the pharmaceutical compositions that were previously disclosed by Selden et al.

[61] Accordingly, claims 40-49, 53-62, 66-69, 74 and 75 are anticipated since all of the essential features are disclosed in Selden et al. and because that reference provides a disclosure that would enable the skilled person to formulate compositions that fall within the scope of the claims.

[62] With respect to dependent claims 50 and 63, as indicated above, these claims feature a specific diluent for α-Gal A as an essential element. The pharmaceutical compositions taught by Selden et al. do not include the specific combination of buffers and excipients defined by said diluent. Therefore, these claims are not anticipated by what is disclosed in Selden et al.

[63] In summary, the claims related to medical uses (claims 1-39, 51, 52, 64, 65 and 70-73) and pharmaceutical composition claims 50 and 63 are not anticipated by Selden et al. In contrast, claims 40-49, 53-62, 66-69, 74 and 75 are anticipated by Selden et al.

ISSUE 2: OBVIOUSNESS

Legal Framework

[64] The statutory provision relevant to obviousness is found in section 28.3 of the *Patent Act* which states:

> 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.

[65] In *Sanofi*, Rothstein J. adopted the approach to assessing obviousness updated by Jacob L.J. in *Pozzoli SPA v. BDMO SA*, [2007] EWCA Civ 588, 2007 FSR 37. Accordingly, an obviousness assessment should include the following four-step approach:

> (1) (a) Identify the notional Aperson 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 Astate 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?

[66] At the fourth step the Court further indicated that an Aobvious to try@ inquiry might be appropriate in areas of endeavour where advances are often won by experimentation, such as the pharmaceutical industry. A non-exhaustive list of factors to be taken into consideration is proposed at paragraph 69 of *Sanofi*.

(1) Is it more or less self-evident that what is being tried ought to work?

Are there a finite number of identified 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 under the *Sanofi* Four-Step Approach

[67] Although many of the claims related to pharmaceutical compositions have been found to be anticipated, for the sake of completeness, we will also consider whether the cited prior art renders obvious the subject matter of all the claims.

Step 1: Identify the notional Aperson skilled in the art@ and the relevant common general knowledge of that person

[68] These have been discussed above at paras. [20-23].

Step 2: Identify the inventive concept of the claim in question or if that cannot readily be done, construe it

[69] In the SSOR, the Examiner did not provide an identification of the inventive concept of the claims even though all of the claims were objected for being obvious.

[70] In its submissions to the Board, the Applicant asserted that the claimed invention is as set forth in the independent claims.

[71] In order to determine the inventive concept of the claims it is useful to consider the specification as a whole, from the perspective of the person skilled in the art. In this context, the ABackground of the Invention@ mentions three relevant publications: United States patent 5,356,804 (Desnick et al.); Ioannou et al., J. Cell Biol. 119:1137 (1992); and WO 90/11353 (Calhoun et al.). These publications discuss the cloning and expression of the gene encoding human _-Gal A in different cell systems. Desnick et al. and Ioannou et al. are from the same research group and both reference work done in Chinese Hamster Ovary (CHO) cells as the recombinant expression system. Calhoun et al. uses insect cells to express human _-Gal A. Each proposes that the expressed enzyme can be used for treating Fabry disease. The ABackground of the Invention@ then states that Acurrent preparations have limited efficacy.@ Along the same lines is the statement that A_-Gal A produced by the methods in the prior art is rapidly eliminated by the liver@ and that Aa need remains in the art for _-Gal A preparations with an increased circulating half-life and increased uptake in specific tissues other than liver.@ These statements imply that preparations then available had been proven effective, but only in a limited manner. Therefore, the skilled person would not understand the description to say that an enzyme replacement therapy for Fabry disease had been well established as of the relevant date. Against this backdrop the ASummary of the Invention@ states that the present invention Aprovides methods and dosages for administering an α-Gal A preparation to a subject.@ The claimed invention would not, therefore, be understood by the skilled person as an improvement or optimization of an existing therapy. The inventive concept(s) should therefore be understood keeping

these facts in mind.

[72] Bearing in mind our previous construction of medical use related claims 1-39, 51, 52, 64, 65 and 70-73, the Board finds that the inventive concept of these claims is the use of a human α-Gal A preparation wherein more than 50% of the total glycans of the preparation are complex glycans, for the treatment of an α-Gal A deficiency, in the specified dosage range of 0.1 to 0.3 mg/kg of body weight.

[73] Similarly, in considering our construction of pharmaceutical composition related claims 40-49, 53-62, 66-69, 74 and 75, the Board finds that the inventive concept of these claims is a pharmaceutical composition comprising human α-Gal A having at least 50% complex glycans and a pharmaceutical carrier *that can provide* a dose in the range of 0.1 to 0.3 mg/kg of body weight of a subject.

[74] With respect to claims 50 and 63, the inventive concept of these pharmaceutical composition related claims additionally includes the presence of the specified diluent.

Step 3: Identify what, if any, differences exist between the matter cited as forming part of the Astate of the art@ and the inventive concept of the claim or the claim as construed

[75] In the SSOR, the Examiner did not address what, if any, differences exist between Selden et al. and the inventive concept of the claims.

[76] In its submissions to the Board, the Applicant continued to emphasize that the present application identifies the types of glycans found on human α-Gal A when produced in human cells as being quite different from the types found on the enzyme when produced in non-human cells, however, the Board does not consider this finding relevant.

[77] As indicated above, it is common ground that Selden et al. disclose an α-Gal preparation produced in human cells and it necessarily falls within the scope of the claims. Therefore, there is no difference, in that respect, between the claims and Selden et al. The reference discloses a preparation that inherently has the glycosylation pattern called for in the claims. Further, Selden et al. teaches that human α-Gal A prepared in human cells is useful for the treatment of α-Gal A deficiency.

[78] Therefore, the Board finds that the difference between the inventive concept of medical use related claims (claims 1-39, 51, 52, 64, 65 and 70-73) and the disclosure of Selden et al. is the use of a human α-Gal A preparation in the specific dosage range of 0.1 to 0.3 mg/kg.

[79] With respect to pharmaceutical composition related claims (claims 40-49, 53-62, 66-69, 74 and 75), the Board finds no difference between the inventive concept of these claims and the disclosure of Selden et al. The human α-Gal A pharmaceutical compositions disclosed in Selden et al. have the desired glycosylation pattern and can provide a dose in the range of 0.1 to 0.3 mg/kg of body weight of a subject.

[80] Concerning composition claims 50 and 63, the Applicant asserted that ASelden et al. clearly does not teach or suggest the specific combination of polysorbate 20, sodium chloride, sodium hydroxide, sodium phosphate monobasic and water for injection as recited in new claims 50 and 63.@ Therefore, in respect of these claims, the Board finds that the difference between the inventive concept and the disclosure of Selden et al. is the specific nature of the diluent.

Step 4: 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?

[81] As discussed above, it is at this step of the obviousness inquiry that the Supreme Court in *Sanofi* has set forth several Aobvious to try@ considerations. Their application in this case is helpful and warranted because the invention is of the general type contemplated by the Supreme Court in *Sanofi* when it spoke of Aareas of endeavour where advances are often won by experimentation@ (*Sanofi* at para. 68); i.e., the medical and pharmaceutical arts. The considerations are addressed in turn, below.

Is it more or less self-evident that what is being tried ought to work?
Are there a finite number of identified predictable solutions known to persons skilled in the art?

[82] We answer these questions in the affirmative for the following reasons.

[83] In the Final Action, the Examiner found that given the broad range disclosed in Selden et al., it would have been obvious to the skilled person to select a narrower range within the broad range in order to increase the cost-effectiveness of the therapeutic use and to minimize the amount of active ingredient required, thereby mitigating any possible side effects to the subject.

[84] In its submissions to the Board, the Applicant argued that nothing in Selden et al. would lead the skilled person directly and without difficulty to the dosage range of about 0.1 to about 0.3 mg/kg presently claimed. As indicated above, the Applicant provided an affidavit by Dr. Kinoshita in which she opined that the broad therapeutic range disclosed by Selden et al. is not specific to α-Gal A, and appears to cover almost every conceivable dose at which a protein therapeutic (or almost any therapeutic) could be used.

[85] It is common ground that the prior art teaches that human α-Gal A prepared in human cells is useful for the treatment of α-Gal A deficiency, therefore, it is expected that a dosage of some amount ought to work. Although the range disclosed by Selden et al. is broad,

the Board finds that the skilled person would understand that the 10,000 fold range disclosed is unrealistic and that the therapeutic index for α-Gal A is actually much narrower. Further, the Board finds that the skilled person, having experience in conducting clinical trials, would be well versed in the assessment of the safety and efficacy of therapeutic proteins.

[86] The Applicant has also submitted that Selden et al. does not teach the specific combination of polysorbate 20, sodium chloride, sodium hydroxide, sodium phosphate monobasic and water for injection as recited in claims 50 and 63. However, the Board finds that the skilled person, as a pharmachemist, would be knowledgeable in the preparation of protein pharmaceutical formulations. With respect to a pharmaceutical formulation intended for intravenous administration, the skilled person would appreciate the need for a diluent which can ensure protein stability, patient acceptability and prevent unwanted interactions between the preparation and the container it is stored in. Further, it would be common general knowledge to the skilled person that a suitable diluent will necessarily include a combination of pharmaceutically acceptable excipients and physiologically compatible carriers.

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?

[87] In the SSOR, the Examiner found that, since variations of the dose are disclosed in the application as routine practice, there would have been no undue burden or experimentation involved in testing different dose ranges within the fixed endpoints of the previously defined range to deliver the desired result.

[88] The Applicant contends that the elucidation of a therapeutic range for human α-Gal A is based on experimentation done to identify the glycans present on human α-Gal A produced in human cells. This detailed elucidation of glycans present on human α-Gal A produced in human cells, and the advantages they offer, is said to be absent from

Selden. It is this detailed knowledge of the glycan structure that the Applicant asserts helped determine that α-Gal A with increased amounts of complex glycan are useful for the treatment of α-Gal deficiency, and can be used at a dose range of between about 0.1-0.3 mg/kg of body weight.

[89] After having considered both arguments, we agree with the Examiner=s view.

[90] Although the present application does indeed disclose the identification of the glycans present on human α-Gal A produced in human cells, the Board finds that it fails to clearly establish the significance of the levels of complex glycans and the disclosed therapeutic dosing regimen.

[91] It should also be remembered that the skilled person would have been focussed on developing a therapeutic dose suitable for treating α-Gal A deficiencies, not on further characterizing a product already known to be suitably equivalent, both in structure and function, to native α-Gal A isolated from human plasma. Thus, the skilled person would not necessarily be led to undertake detailed glycan analysis before moving to the clinical setting. In our view, the critical experimentation to be done would be determining an appropriate dosage range and acceptable pharmaceutical formulation and it is this work that we consider to be non-inventive.

[92] As indicated above, the skilled person has experience in conducting clinical trials and would have been directed to well-known and well-established guidelines for determining therapeutic dosing regimens and good clinical research practices. Necessarily, the research process includes preclinical pharmacokinetic and toxicological studies in animal models to determine a suitable dose and route of administration. General principles for

identifying the most appropriate dose, dosing interval and route of administration include the use of single, escalating dose and multiple dose pharmacokinetics, toxicokinetics and tissue distribution studies. Subsequently, evaluation of preclinical data for safety and scientific validity is performed by regulatory bodies, such as the U.S. Food and Drug Administration and Health Canada, as a mandatory requirement for authorization to begin clinical trials in humans.

[93] Further, the skilled person is knowledgeable in the preparation of pharmaceutical formulations for protein therapeutics and would have been directed to the preparation of useful formulations for a given mode of administration as defined in, for example, *Remington=s Pharmaceutical Sciences* (Gennaro, A., ed., Mack Pub., 1990) B a reference described on page 37, line 11 of the description as disclosing Amethods well known in the pharmaceutical art.@

[94] In the absence of any evidence to the contrary, on these bases, the Board finds that the determination of the specific dosage range of 0.1 to 0.3 mg/kg defined in the instant medical use claims would have been a consequence of routine testing carried out by a person skilled in the art. Similarly, as there is no indication to the contrary, the Board also finds that the determination of the specific formulation as recited in pharmaceutical composition claims 50 and 63 required nothing more than routine experimentation to achieve.

[95] Lastly, although the Board considers that the 10, 000 fold range disclosed by Selden et al. is an unrealistic operating range, for the sake of completeness we will consider the possibility that the present case, being one related to a narrower dosage range, might be thought of as akin to a so-called Aselection@ and therefore may be analyzed in that context. Narrower subject matter which is selected from a previously disclosed broader class of related subject matter can be considered inventive if the narrower subject matter is disclosed to have unexpected advantages. However, the present application is totally silent with respect to unexpected advantages provided by the selection of the narrow dose range of 0.1-0.3 mg/kg over the broad range disclosed by Selden et al. In the absence of any comparative information demonstrating any unexpected or surprising advantage,

the selection of the presently claimed dosage range is considered to be non-inventive in view of Selden et al.

[96] To conclude on the second consideration, we would say that the extent, nature and amount of effort required to achieve the invention are neither prolonged nor arduous.

Is there a motive provided in the prior art to find the solution the patent addresses?

[97] At the time of filing there was no effective treatment for patients with α-Gal A deficiency, such as Fabry disease. In the early 1970's attempts at enzyme replacement therapy were shown to be promising; however, further progress was limited by the lack of sufficient quantities of purified protein. The production of large amounts of recombinant human α-Gal A provided the means to further explore the efficacy of enzyme replacement therapy. Further, Selden et al. disclose that treatment of Fabry fibroblasts with recombinant human α-Gal A was efficient to restore intracellular enzyme levels similar to those of normal cells. For these reasons, we find that the person skilled in the art would have been motivated to use said recombinant human α-Gal A to determine a therapeutic dosing regimen for the treatment of patients with α-Gal A deficiency.

[98] The development of a dosage formulated using suitable excipients and carriers would be the next logical step and we therefore conclude that there was sufficient motivation in the prior art to find the solution that the patent addresses.

Conclusion on Obviousness

[99] Having addressed the obvious to try considerations, we find that claims 1-75 define obvious subject matter.

ISSUE 3: METHOD OF MEDICAL TREATMENT

Legal Framework

[100] Section 2 of the *Patent Act* defines Ainvention@ as:

> 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.

[101] A method claim that encompasses a medical treatment is not considered to be directed to patentable subject matter: *Tennessee Eastman Company et al. v. Commissioner of Patents* (1972), 8 CPR (2d) 202 SCC [*Tennessee Eastman*]; *Imperial Chemical Industries Ltd. v. Commissioner of Patents* (1986), 9 CPR (3d) 289 FCA.

[102] However, medical Ause@ claims have been considered to be directed to patentable subject matter: see *Merck & Co. Inc. et al. v. Apotex Inc.*(1994), 59 CPR (3d) 133 at pp. 175-177 (FCTD), aff=d on this point 60 CPR (3d) 357 (FCA); *Apotex Inc. v. Wellcome Foundation Ltd.,* 2002 SCC 77, 21 CPR (4th) 499 [*AZT*].

[103] In the *AZT* case the Supreme Court suggested that a complication may arise in a case where a claim, although drafted as a medical use, nonetheless attempts to Afence in@ an area of medical treatment by indicating Ahow and when@ (e.g., by indicating a dosage range or treatment regime) a pharmaceutical composition is to be used. In that decision the Supreme Court considered a claim directed to a pharmaceutical composition comprising an old compound (AAZT@) for a new use in treating AIDS and found that the patentee had not attempted to fence in a method of medical treatment:

> The AZT patent does not seek to Afence in@ an area of medical treatment. It seeks the exclusive right to provide AZT as a commercial offering. How and when, if at all, AZT is employed is left to the professional skill and judgment of the medical profession. [para. 50]

[104] Lower courts and the Patent Appeal Board have also dealt with the validity of claims that concern a dosage range or regime. These decisions include: *Merck and Co., Inc. et al. v. Apotex Inc. et al.,* 2005 FC 755 [*Merck*[1]]; *Merck and Co., Inc. et al. v. Pharmascience Inc. et al.,* 2010 FC 510 [*Merck*[2]]; *Pfizer Canada Inc. v. Apotex Inc.*, 2005 FC 1421 [*Pfizer*]; *Axcan Pharma Inc. v. Pharmascience Inc.,* 2006 FC 527 [*Axcan*]; *Janssen Inc. et al. v. Mylan Pharmaceuticals et al.,* 2010 FC 1123 [*Janssen*]; *Re: Application No. 003,772 of Ijzerman*, Commissioner=s Decision No. 254 (1975); *Re: Application No. 2,300,723 of Allergan,* Commissioner=s Decision No. 1292 (2009) [*Allergan*]. The claims considered in these decisions can generally be divided along two lines: valid claims that relate to commercial offerings or vendible products wherein dosage forms, pharmaceutical packages or kits embody a dosage regime or prescribed dosage amount; and, invalid claims related to the use of pharmaceutical products in which physicians are prevented from exercising their professional skill and judgment through the existence of a patent monopoly.

[105] For instance, in *Merck*[1], the claims in question were directed to the use of alendronate for treating osteoporosis where a once weekly dose of 70 mg was specified. Each of the claims in question covered a unit oral dosage form comprising 70 mg of alendronate. Because the dose was defined in a unit dosage form, Mosley J. accepted Merck=s submission that the claims were directed to a vendible product, distinguishable from the work of a physician:

> The how and when of administration is not part of the patent. The inventors provide a new product which physicians may choose to use in treating patients, based on their own skill and judgment. [para. 136]

> I find that the patent is for a vendible product having real economic value, as demonstrated by its immediate success in the market, and is, therefore, not for an unpatentable method of treatment. [para. 137]

[106] This view was recently endorsed by Hughes J. in *Merck*[2], where he found that a claim which was restricted to a particular fixed dosage was also directed to a vendible product:

> In the present case, we have a 1.0 mg tablet taken as a daily dose. No skill or judgment is brought to bear. It is a vendible product and not a method of medical treatment. [para. 114]

[107] Subsequent to his decision in *Merck*[1], Mosley J. maintained that as long as the claims are distinguishable from the work of a physician, which requires the exercise of professional skill, they will not fall under the method of medical treatment prohibition established by *Tennessee Eastman*; see *Pfizer*.

[108] In *Axcan,* the contentious claim related to a pharmaceutical composition comprising ursodeoxycholic acid for the treatment of primary biliary cirrhosis based on a dose of 13 to 15 mg/kg/day. In that case, Harrington J. noted that, in contrast to *AZT* and *Merck*[1], where the how and when of administration was left to the professional skill and judgment of the physician, by including a dosage range the claim sought to monopolize an area of medical treatment by limiting the range within which physicians must exercise their professional skill and judgment for a given patient:

> It is up to the physician based on his or her knowledge of the patient=s rate of metabolism and other factors to determine the appropriate daily dosage. I cannot, for a moment, contemplate that *Axcan* could claim exclusive property in the dosage and sue a physician for prescribing Ursodiol for the treatment of PBC at a dosage less than 13 mg/kg/day or greater than 15 mg/kg/day. [para. 46]

[109] In distinguishing over *Merck*[1], Harrington J. stated:

> There is a distinction between the dosage in a capsule and a dosage range based on the patient's weight. As I read the claim, the emphasis is on the dosage range, and a dosage range is not a vendible product. [para. 51]

[110] In *Allergan*, at para. 95, the claims were directed to the use of botulinum toxin (Botox) for treating pain associated with either a muscle disorder or spasticity and specified a dosage range. The Commissioner and the Patent Appeal Board followed *Axcan* and found that the claims sought to fence in a range within which physicians must exercise their professional skill and judgement.

[111] More recently, in *Janssen*, Barnes J. summarized the law in this area by saying that Aa patent claim over a method of medical treatment that, by its nature, covers an area for which a physician's skill or judgment is expected to be exercised is not patentable in Canada.@ This includes Athe administration of a drug whereby the physician, while relying upon the dosage advice of the patentee, would still be expected to be alert and responsive to a patient's profile and to the patient's reaction to the compound.@

[112] Further, Barnes J. held that claims which included a dosage regimen attempted to impose a monopoly over the prescribing practices of medical professionals:

> In conclusion, I have no doubt whatsoever that the >950 Patent relevant claims cover a method of medical treatment. By attempting to monopolize an effective titration regimen for galantamine, the >950 Patent interferes with the ability of physicians to exercise their judgment in the administration of generic versions of the drug . This is because, absent a license from Janssen, any physician attempting to administer a generic version of galantamine to treat Alzheimer=s disease by the method claimed by the =950 Patent would infringe. [para. 52]

[113] In that case, the fact that the claim recited a regime comprising a specific dosage did not save it from the method of medical treatment exclusion.

[114] In reaching this conclusion Barnes J. reviewed expert testimony that discussed a number of factors, including: the availability of clinical data, dosing information provided in a product monograph, the patient=s profile (e.g., their medical history, weight, drug tolerability, etc.), the dosage to be given, the need for patient monitoring, and the need to adjust the dosage. More generally the court considered the need for a physician to adopt an Aindividualized@ approach to treatment that Adoes not begin and end with the manufacturer=s dosing advice@ (para. 50).

[115] According to *Janssen*, the concern in this area of patent law arises because the Aphysician may be prevented from exercising skill and judgment in using a known compound for an established purpose absent a license from the patentee. (para. 51)@ Applied more practically, within this framework, in order for a claim to constitute a method of medical treatment, the dosage of a known compound for an established purpose must be an essential element of the claim and the effect of the dosage would be to bring the professional skills of a clinician within its scope.

[116] In its submissions to the Board, the Applicant pointed out that dosage regimes are patentable in the United Kingdom and the European Patent Office despite the statutory prohibition on patents for methods of medical treatment. In that regard, the Applicant referred to the decision in *Actavis UK Ltd. v. Merck & Co. Inc.*, [2008] EWCA Civ 444, [2008] R.P.C. 26 and the decision of the Enlarged Board of Appeal in *Kos Life Sciences*, *supra*. We note that these decisions have been considered by Canadian courts, albeit in the context of *Patented Medicines (Notice of Compliance)* proceedings, but do not appear to have altered the law; see *Merck*[2] *and Janssen*, for example.

Analysis

[117] Thus far each claim has been found to define either old or obvious subject matter. Nonetheless, for the sake of completeness, the claims will also be analyzed for compliance with section 2 of the *Patent Act*.

Claims Related to Medical Uses (claims 1-39, 51, 52, 64, 65 and 70-73)

[118] In the Final Action, the Examiner maintained that the use of human α-Gal A preparations to treat α-Gal A deficiencies was known, therefore, drawing attention to the dosage range mentioned in the claims. The Examiner asserted that the dosage was an essential element and concluded, in view of *Axcan*, that the claims were directed to a method of medical treatment, which is non-statutory subject matter and does not comply with section 2 of the *Patent Act*.

[119] In its submissions to the Board, the Applicant argued that the Federal Court has in multiple recent decisions endorsed the validity of use claims that recite dosage regimes. Only the cited decisions which deal with the issue of methods of medical treatment in the context of use claims are considered pertinent, namely, *Merck*[1] and *Pfizer*.

[120] Further, the Applicant submits that *Axcan*, is not applicable because the present claims do not impinge on a physician=s professional skills or judgment. There is no evidence that determining a suitable dose within the narrow prescribed range of about 0.1 to 0.3 mg of the α-Gal A preparation per kilogram of body weight would involve a physician=s professional skills or judgment. Moreover, claims 2-4, 15-17, 28-30, 41-43 and 54-56 recite discrete dosages of an α-Gal A preparation per kilogram of body weight. Indeed, in these claims, nothing is left to the professional judgment of the physician.

[121] As indicated by the Applicant, recent Federal Court decisions have found that some use

claims which feature dosage regimes are not considered to be methods of medical treatment. However, in such cases, notably *Merck'* and *Pfizer,* the claims were held to be distinguishable from the work of a physician which requires the exercise of specialized skill. In *Merck'*, it was held that because the use claims featured a unit dosage form they were directed to a vendible product. Similarly, in *Pfizer*, the use claim did not instruct physicians and pharmacists on how to treat the patient.

[122] The present description discloses the need for a patient to undergo clinical monitoring to continuously evaluate the status of his or her disease and measure the effects of α-Gal A enzyme replacement therapy (pages 40-41). Further, changes to dose and/or dosing frequency may be made to ensure that certain pharmacokinetic parameters are maintained to allow for relatively constant levels of receptor-mediated uptake of α-Gal A into tissues. Therefore, the determination of an effective dosage regimen is patient specific and requires the skill and judgment of a physician.

[123] Further, the medical use claims are directed to a specific dosage range or dose per kg of body weight of a patient. Therefore, analogous to *Axcan* and *Janssen*, the Board finds that these claims are attempting to monopolize an effective dosage regime for a human α-Gal A preparation. By seeking to place restrictions on the Ahow and when@ α-Gal A is to be administered, the claims are interfering with the ability of physicians to appropriately treat their patients. Indeed, the present description makes clear that determining the dosage for administration is expected to remain within the purview of a physician:

> The route of administration and the amount of protein delivered can be determined by factors that are

> well within the ability of skilled artisans to assess. Furthermore, skilled artisans are aware that the route of administration of a therapeutic protein may be varied for a given patient until a therapetuic dosage level is obtained. [para. bridging pages 36-37]

[124] In other words, as was the case in *Janssen*, an Aindividualized@ approach is also required, especially in view of the fact that an enzyme replacement therapy for Fabry disease had not been well-established in the first place.

Claims Related to Pharmaceutical Compositions (claims 40-50, 53-63, 66-69, 74 and 75)

[125] Bearing in mind our previous construction of claims related to pharmaceutical compositions, the dosage element was considered essential because the claimed compositions must *comprise*, or be capable of *providing*, certain amounts of the human α-Gal A preparation based on the weight of a subject. The professional skills of a clinician is not within their scope because there is nothing that prevents a clinician from using the compositions as they see fit. The reference to a dosage range in the claims related to pharmaceutical compositions does not render them non-patentable because, although essential, the dosage range is a descriptor of the composition itself and does not operate to bring the professional skills of a clinician within their scope.

[126] As such, these claims are not considered to place restrictions on how and when α-Gal A is to be administered. It follows that these claims do not violate the method of medical treatment prohibition.

[127] Accordingly, the Board finds that medical use claims 1-39, 51, 52, 64, 65 and 70-73 are directed to an unpatentable method of medical treatment. In contrast, pharmaceutical composition related claims 40-50, 53-63, 66-69, 74 and 75 are directed to a vendible product compliant with section 2 of the *Patent Act*.

ISSUE 4: INDEFINITENESS

Legal Framework

[128] The relevant statutory provision for this defect is found in subsection 27(4) of the *Patent Act* which states:

> The specification must end with a claim or claims defining distinctly and in explicit terms the subject-matter of the invention for which an exclusive privilege or property is claimed.

[129] In *Minerals Separation North American Corp. v. Noranda Mines Ltd.*, (1947) 12 CPR, the Exchequer Court emphasized the obligation an applicant has to make clear in his claims the ambit of the monopoly sought and the requirement for terms used in the claims to be clear and precise:

> By his claims the inventor puts fences around the fields of his monopoly and warns the public against trespassing on his property. His fences must be clearly placed in order to give the necessary warning and he must not fence in any property that is not his own. The terms of a claim must be free from avoidable ambiguity or obscurity and must not be flexible; they must be clear and precise so that the public will be able to know not only where it must not trespass but also where it may safely go. [page 146]

Analysis

[130] As indicated above at para. [29], the following findings in respect of the Examiner=s objection to claims 40-47 as indefinite were used to facilitate our analysis under claim construction.

[131] In the Final Action, the Examiner argued that, because the unit dose amount of α-Gal A for administration is defined on a per kg of body weight of a subject, the total amount of α-Gal A administered to the subject is unclear. This was established to be in view of dependent claims reciting that the unit dose is adapted for weekly or biweekly administration.

[132] In the claim set provided in response to the Final Action, claim 40 was amended to recite a pharmaceutical composition in a unit dosage form comprising a unit dose of between 0.1-0.3 mg/kg. None of dependent claims 41-53 recite that the composition is for weekly or biweekly administration.

[133] In the Summary of Reasons, the Examiner indicated that claims 40-47 were still objectionable for reciting a unit dose range of α-Gal A preparation per kilogram of body weight. However, no further explanation was given as to why the claims were still considered deficient even though the dependent claims no longer referenced a dosing schedule.

[134] In its submission to the Board, the Applicant argued that the objection no longer applied to pending claims 40-47 as none of the dependent claims recite that the composition is for weekly or biweekly administration.

[135] Although claims 40-47 no longer recite a unit dose comprising a specified range of α-Gal A preparation per kilogram of body weight in combination with a dosing schedule, the claims are still considered to lack clarity. By definition a unit dose is considered a standard of measurement which contains a fixed quantity of drug. Therefore, it cannot be defined in terms of an amount per kilogram of body weight of a subject as the value of the unit dose would necessarily vary depending on the body weight of the subject.

[136] A unit dose that can be varied according to the weight of a subject introduces unnecessary ambiguity that can be avoided by simply referring to a dose that can be varied according to the weight of a subject. However, in view of our findings that the claims are also anticipated and obvious, there would be no point in requiring any amendments.

[137] Accordingly, the Board finds that claims 40-47 are indefinite and non-compliant with subsection 27(4) of the *Patent Act*.

RECOMMENDATION

[138] In view of the above findings, we recommend that the rejection of the application be upheld on the basis of the following:

(1) Claims 40-49, 53-62, 66-69, 74 and 75 are anticipated by Selden et al. and therefore non-compliant with subsection 28.2(1) of the *Patent Act*;

(2) Claims 1-75 are obvious in view of Selden et al. and common general knowledge and therefore non-compliant with section 28.3 of the *Patent Act*;

(3) Claims 1-39, 51, 52, 64, 65 and 70-73 are directed to an unpatentable method of medical treatment and therefore non-compliant with section 2 of the *Patent Act*; and

(4) Claims 40-47 are indefinite and therefore non-compliant with subsection 27(4) of the *Patent Act*.

Ed MacLaurin	Serge Meunier	Mark Couture
Member	Member	Member

DECISION OF THE COMMISSIONER

[139] I concur with the Patent Appeal Board=s findings and their recommendation that the rejection of the application be upheld on the basis of the following:

(1) Claims 40-49, 53-62, 66-69, 74 and 75 are anticipated by Selden et al. and therefore non-compliant with subsection 28.2(1) of the *Patent Act*;

(2) Claims 1-75 are obvious in view of Selden et al. and common general knowledge and therefore non-compliant with section 28.3 of the *Patent Act*;

(3) Claims 1-39, 51, 52, 64, 65 and 70-73 are directed to an unpatentable method of medical treatment and therefore non-compliant with section 2 of the *Patent Act*; and

(4) Claims 40-47 are indefinite and therefore non-compliant with subsection 27(4) of the *Patent Act*.

[140] 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.

Sylvain Laporte
Commissioner of Patents

Dated at Gatineau, Quebec,
this 14th day of May, 2013