Commissioner’s Decision #1406

Décision du commissaire #1406

TOPIC: O00 (Obviousness)

SUJET: O00 (Évidence)

Application No.: 2,470,999

Demande n°.: 2,470,999

IN THE CANADIAN PATENT OFFICE

DECISION OF THE COMMISSIONER OF PATENTS

Patent application number 2,470,999 having been rejected under subsection 30(3) of the *Patent Rules*, has been reviewed in accordance with paragraph 30(6)(*c*) of the *Patent Rules*. The recommendation of the Patent Appeal Board and the decision of the Commissioner is to allow the application.

Agent for the Applicant:

Gowling WLG
2600 – 160 Elgin Street
Ottawa, Ontario
K1P 1C3

INTRODUCTION

[1] Application 2,470,999, entitled "SYN3 compositions and methods", is owned by Merck Sharpe & Dohme Corp. It stands rejected after the issuance of a Final Action because the claimed subject matter was considered by the examiner to be obvious, contrary to section 28.3 of the *Patent Act*.

[2] For the reasons that follow, we recommend that the application be allowed.

CASE HISTORY

[3] The subject application was filed in Canada on December 20, 2002 and published July 3, 2003.

[4] Examination was requested December 11, 2007 and culminated with the issuance of a Final Action on October 17, 2013 at which time the eleven claims on file were rejected under subsection 28.3 of the *Patent Act* for being obvious in view of three prior art references.

[5] The Applicant replied to the Final Action on April 15, 2014 and argued that the claims defined non-obvious subject matter. Three scientific articles and a declaration were provided to support the Applicant's position.

[6] Since the Examiner remained of the view that the application was non-compliant, a Summary of Reasons (SOR) was prepared and the application was referred to the Board for review. The Applicant was informed accordingly on February 18, 2015 and the present panel was constituted to conduct the review.

[7] Upon being informed that the application was pending review by the Board, the Applicant requested a hearing and expressed a desire to provide written submissions in advance of our preliminary review of the application. However, neither are required at this time because, based on a review of the application and the record as it presently stands, our recommendation is to allow the application.

THE ISSUE

[8] The issue is whether the subject matter defined by claims 1-11 would have been obvious to a person skilled in the art as of the application's filing date, and therefore not compliant with subsection 28.3 of the Act.

LEGAL PRINCIPLES

Claim construction

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

Obviousness

[10] The *Patent Act* requires that the subject matter of a claim not be obvious. Section 28.3 of the Act provides as follows:

> 28.3 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.

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

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

CLAIM CONSTRUCTION

Background

[12] The present application relates to pharmaceutical compositions for treating cancer by gene therapy. One method of gene therapy involves delivering a therapeutic gene to target cells using a gene delivery vector, such as a man-made virus.

[13] In the present case, the inventors have developed a gene therapy system that has two principal components:

> 1) a gene delivery vector that carries a therapeutic gene; and,
>
> 2) a lyophilized gene transfer-enhancing composition.

[14] The second component is the focus of the invention.

[15] The gene transfer-enhancing composition in this case is prepared by first mixing a unique enhancement agent known as "SYN3" with chemical carriers, or "excipients". The

resultant mixture is then lyophilized[1] for storage purposes. In practice, the lyophilized gene transfer-enhancing composition is reconstituted with water and then mixed with the other component, the gene delivery vector, just prior to administration to a patient.

[16] SYN3 is a surfactant-like compound previously known to enhance the delivery of genes carried by gene delivery vectors to bladder cells. The challenge the inventors faced in the present case was to formulate SYN3 and suitable excipients to yield a gene transfer-enhancing composition that can be lyophilized, stored, and then used in gene therapy.

The person skilled in the art

[17] The Final Action identifies the person skilled in the art as "an oncologist having knowledge of gene therapy techniques as well as formulations used therein." In our view, since the skilled person is knowledgeable in formulations, it follows that the skilled person can be regarded as a team comprised of an oncologist and a formulations specialist. Such a definition would also be consistent with the nature of the invention and the Background portion of the description.

The common general knowledge

[18] The totality of the common general knowledge is the sum of the common general knowledge possessed by each member of the team mentioned above.

[19] Illustrative of the common general knowledge of an oncologist is the Background portion of the description. It indicates that the following information was commonly known to oncologists:

- The skilled person, being an oncologist, would have knowledge of bladder cancer and know that the disease is typically treated using established chemotherapy protocols or surgical methods (para. [0003])
- A variety of gene therapy strategies were under development as alternative therapeutic approaches for treating bladder cancer (para. [0004])

1 The process of lyophilization is also known as freeze-drying.

- Gene delivery vectors genetically engineered to carry a therapeutic gene are able to transfer the gene to cancer cells, including to bladder cells *in vitro* (para. [0007])

[20] A standard textbook (*Remington: The Science and Practice of Pharmacy*, 20th Ed., A. R. Gennaro ed., Mack Publishing. Co., Easton, Pa. 1995; "*Remington*") and portions of the description can be taken as representative of the common general knowledge carried by a formulations specialist:

- Chemical compositions can be lyophilized for improved stability during storage and then reconstituted with water before use (*Remington*, page 802)

- There are a number of types of excipients that can be added to chemical compositions for different purposes, including solubilizers, detergents, complexing agents, buffering agents, and bulking agents (*Remington*; paras. [0061] – [0068])

- Hydroxypropyl-beta-cyclodextrin ("HPβCD") is a large complexing/solubilizing agent that has an intramolecular cavity that can carry small "guest" molecules, or parts thereof, and thereby stabilize them in solution (*Remington*, pages 190-191; para. [0061])

- Polysorbates are non-ionic surfactants that can solubilize hydrophobic molecules; they exist as oily viscous liquids (*Remington*, page 1037; para. [0061])

The problem

[21] In general terms, the skilled person understands that there is a need to provide safe and effective therapies for cancer. Considering the specific context of the present specification, and the common general knowledge, the skilled person would understand that there is a particular need to address the problem of enhancing the transfer of therapeutic genes using a gene delivery vector to bladder cancer cells inside a patient, i.e., *in vivo*. This is reflected in para. [0008] of the specification: "[t]here exists a need for formulations for therapeutic use that improve the efficiency of the transgene delivery."

The solution

[22] In general, the description teaches a gene therapy system made up of two principal components:

1) a gene delivery vector that carries a therapeutic gene; and

2) a lyophilized gene transfer-enhancing composition.

[23] The description focusses on the second component as the inventor's solution and teaches that, in practice, the gene transfer-enhancing composition can be lyophilized, stored, reconstituted with water, and then mixed with the first component of the system, the gene delivery vector, just prior to administration to a patient (para. [0058]; Examples 1 and 17).

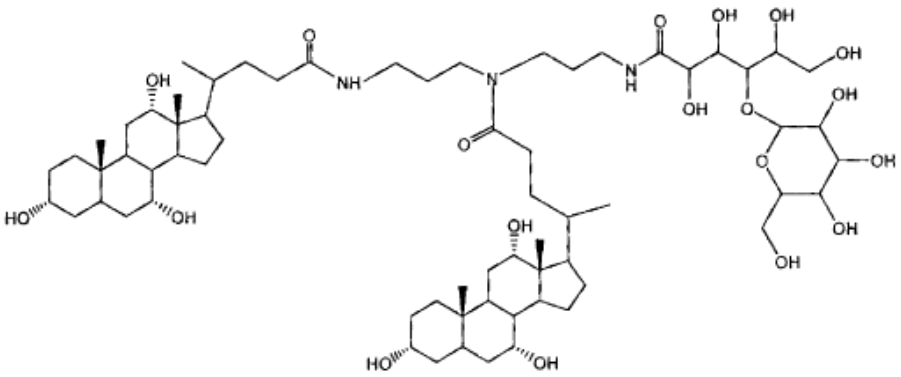
[24] The description indicates that the solution involves, in part, the use of a surfactant-like chemical known as "SYN3" in the gene transfer-enhancing composition. SYN3 has the property of enhancing the transfer of a therapeutic gene to bladder cells *in vivo* via a gene delivery vector (para. [0035]). It is also non-toxic to tissues, and does not impart instability to gene delivery vectors (paras. [0032] – [0033]).

[25] Therefore, the solution the inventors propose, in general terms, is to formulate SYN3 in a lyophilized gene transfer-enhancing composition in such a manner that its properties are not compromised: "[o]ne aspect of the invention is that a unique surfactant-like molecule SYN3 is formulated with excipients to maintain solubility and stability as well as compatibility with the [gene delivery vector]" (para. [0031]).

[26] Although the description covers a wide range of possible excipients that the skilled person could select for combination with SYN3 in the hopes of solubilizing and stabilizing SYN3 in lyophilized form, the skilled person would understand that the solution to the problem faced by the inventors is more limited, and is especially reflected in the examples which recite the use of the same particular excipients mentioned in the claims at issue. Example 17 is noteworthy in that regard since it is the sole teaching of a lyophilized composition that can be reconstituted with water and remain compatible with an adenoviral vector. It bears mentioning that the excipients used in Example 17 are those recited in claim 11.

The claims

[27] Consistent with the description, claims 1-10 refer a gene therapy system made up of two principal components: 1) a gene delivery vector that carries a therapeutic gene; and 2) a lyophilized gene transfer-enhancing composition. Claim 11 refers only to the latter component and is representative of the solution that the inventors propose:

> A lyophilized composition comprising a compound (SYN3) having the formula:
>
> 
>
> wherein the compound is present in a delivery enhancing amount, Polysorbate 80 in a concentration of 1 to 36 mg/ml prior to lyophilization, hydroxypropyl-beta-cyclodextrin in a concentration of 50 to 500 mg/ml prior to lyophilization, and a citrate buffering system providing a pH ranging from 5 to 6 prior to lyophilization.

[28] The claim includes the following elements:

1) A lyophilized composition;

2) SYN3 in a delivery enhancing amount;

3) Polysorbate 80 in a concentration of 1 to 36 mg/ml prior to lyophilization;

4) Hydroxylpropyl-beta-cyclodextrin [HPβCD] in a concentration of 50 to 500 mg/ml prior to lyophilization; and,

5) Citrate buffering system providing a pH ranging from 5 to 6 prior to lyophilization.

[29] In our view, the skilled person would understand that all five elements are essential as they provide a combination that solubilizes SYN3, is stable under storage as a lyophilized mixture, can be readily reconstituted with water and is compatible with the other component of the gene therapy system, the gene delivery vector. The skilled person would not appreciate, based either on their common general knowledge or the teachings of the description, that any of the elements could be omitted or substituted without materially affecting the working of the invention; they are representative of the combination of excipients indicated in Example 17 to work.

OBVIOUSNESS

[30] The Final Action separates the obviousness analysis along the lines of two claim groupings:

A. claims 1-10 relating to the gene delivery vector that carries a therapeutic gene, plus a lyophilized gene transfer-enhancing composition; and,

B. claim 11 which concerns only a lyophilized gene-transfer-enhancing composition.

[31] However, the issue of obviousness in respect of all claims can be resolved by considering only claim 11 belonging to the second grouping because its subject matter is within the scope of claims 1-10 and would lend patentability to these claims if found to be non-obvious.

[32] We therefore start by considering claim 11.

Claim 11

[33] Claim 11 is indicated in the Final Action and SOR to be obvious in view of one reference, D1, and the common general knowledge.

The person skilled in the art and the common general knowledge

[34] The first step of the *Sanofi* four-step approach to obviousness has been dealt with above as a matter of claim construction.

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

[35] The Final Action states that the inventive concept is "a lyophilized composition comprising 'Syn3', polysorbate 80, [HPβCD] and a citrate buffering system."

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

[36] Reference D1 is United States patent application 2001/0006946 A1, published July 5, 2001. It describes the isolation and properties of a novel compound termed "SYN3". SYN3 is a surfactant-like compound discovered as an impurity in commercial preparations of another surfactant. It is disclosed to have the ability to significantly enhance transfer of genes to bladder cells *in vivo* when certain gene delivery vectors are used.

[37] Notably, SYN3 is said to be poorly soluble in water, requiring the presence of a solubilizer to maintain its solubility (para. [0159]).

[38] D1 is described in the Final Action as follows:

> D1 discloses pharmaceutical compositions comprising a compound identical to that described in the instant application as 'Syn3' for use in enhancing gene transfer *in vivo* for the treatment of various diseases including bladder cancer. Said pharmaceutical compositions further comprise pharmaceutically acceptable solubilizers, detergents, carriers, stabilizers, buffers and bulking agents. D1 discloses the particular use of Tween®/polysorbate 80 in said compositions as well as the use of said composition with a gene encoding interferon α which may be present in a recombinant adenoviral vector system.

[39] The Final Action states the following in relation to D1: "[D1] does not explicitly teach lyophilized compositions comprising 'Syn3', [HPβCD] and a citrate buffering system having a pH ranging from 5 to 6."

[40] D1 therefore differs from the inventive concept in at least three respects:

1) a lyophilized composition comprising SYN3;

2) HPβCD; and,

3) a citrate buffering system having a pH ranging from 5 to 6.

[41] Not mentioned in the Final Action is something that provides context to the inventive concept: that the lyophilized gene transfer-enhancing composition of claim 11 is one component of a two-part gene therapy system, the other component being a gene delivery vector that carries a therapeutic gene. As such, the skilled person would understand that the composition of claim 11 is not a stand-alone product; it has been specifically formulated such that it can be reconstituted with water, and then mixed with the gene delivery vector just prior to administration to a patient. In that regard, we note that D1 does not discuss a two-part gene therapy system comprising two components. D1 discloses only compositions in which a gene delivery vector is already mixed with excipients.

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?

[42] According to the Final Action, the subject matter of claim 11 would have been obvious to the skilled person. However, we are not convinced that the skilled person, relying on D1 and their common general knowledge, would see that the differences mentioned above constitute steps which would have been obvious to the person skilled in the art.

[43] Firstly, there was a degree of unpredictability in formulating SYN3 as it was not a surfactant commonly known to the skilled person. It was disclosed in D1 as a novel compound but its properties had not been fully elucidated. The skilled person would not, therefore, have carried an expectation that a lyophilized form of any kind could have been routinely prepared, let alone one that could be readily reconstituted with water and yet remain compatible with gene delivery vectors.

[44] Regarding difference (1) noted above – a lyophilized composition comprising SYN3 – the Final Action asserts that D1 discloses SYN3 "in the form of a powder (which is the end result of lyophilization)" and that the skilled person "would lyophilize the liquid compositions of 'Syn3' for better storage."

[45] In our view, the skilled person would not equate the disclosure of a white powder in D1 as one that necessarily results from lyophilization. We note that para. [0174] of D1 discusses a "white powder" of SYN3 as the result of its chemical synthesis, not as a result of its lyophilization so as to form "a white to off-white cake" as disclosed in Example 17 of the present case.

[46] Although the skilled person understands from their common general knowledge that lyophilization is generally known as a useful technique to stabilize compositions for better storage, there is no clear direction or suggestion in D1 to adopt it in the specific case of SYN3. We note also that there is no suggestion in D1 to lyophilize only one part, the lyophilized gene transfer-enhancing composition, of a two-part gene therapy system.

[47] Stabilization of SYN3 is discussed in D1 only as a matter of solubility. In that regard, the Final Action is accurate where it observes that "D1 explicitly teaches the use of polysorbate 80 in aiding solubilisation of 'Syn3' so said skilled person would routinely include said additive in a lyophilized composition of 'Syn3'". However, D1 does not discuss the use of polysorbate 80 in a lyophilized composition, and further does not disclose successful reconstitution of such compositions and maintenance of gene delivery vector compatibility in a manner similar to that disclosed in the present case. In our view, it would not be clear to the skilled person that a viscous oily substance such as polysorbate 80, when used in the amounts suggested in D1, could be formulated to yield a white to off-white cake upon lyophilisation, as was successfully done for the first time in the present case.

[48] Regarding differences (2) and (3) noted above – the use of HPβCD and a citrate buffering system – the Final Action asserts that they can be accounted for simply on the basis of routine behaviour expected of the skilled person. Although these two excipients would have individually been known to the skilled person as part of their common general knowledge, we are not convinced that the skilled person would have been specifically guided to success only by D1 and their common general knowledge. D1 is silent on the individual use of either of these two excipients, let alone their combined use.

[49] Further, in response to the Final Action, the Applicant argued that the skilled person would have been led away from the use of HPβCD as a SYN3 complexing/solubilizing agent because the skilled person would appreciate that SYN3 is too large to be accommodated within HPβCD's cavity, and because the skilled person would view its combined use with polysorbate 80 as potentially confounding SYN3's stability. In support of these arguments the Applicant relied on the teachings of three scientific articles[2] on cyclodextrins as well as a declaration by one of the inventors[3].

[50] Having reviewed the articles and the declaration, we are of the view that there is merit in the Applicant's arguments. We are satisfied that the scientific articles are consistent with the common general knowledge of cylodextrins and that the skilled person would be left with some doubt as to whether the selection of HPβCD would lead to success in the case of a molecule such as SYN3, more so if a second, potentially confounding molecule, is also used.

[51] The Final Action and the SOR express a concern that the description does not disclose any unexpected or surprising result obtained by the use of HPβCD and a citrate buffer system, supporting the view that the claimed compositions do not result from an inventive step being taken. The SOR for instance indicates that there is "no indication whether [gene delivery vector stability] is better or worse than the composition without the cyclodextrin compound."

[52] In our view, this line of reasoning presumes that useful lyophilized compositions of the type claimed could have been routinely made, and that the skilled person would thereby realize the storage benefits generally expected of such compositions. As explained above, we are of the view that the skilled person would have had neither an expectation of success nor have had sufficient guidance from D1 to prepare the specific lyophilized compositions claimed. For there to be an expected and unsurprising result in the properties of the

2 Albers *et al*., *Crit Rev Ther Drug Carrier Syst*, 12:311-337 (1995); Muller et al., *J Pharm Sci*, 80: 599-604 (1991); Albers *et al*., *J Pharm*, 81: 756-761 (1992)

3 Declaration of Dr. Peter Ihnat dated July 29, 2013; also sworn before the United States Patent Office

claimed compositions, the skilled person would first have to be equipped to make them using only routine skill – a premise which, in our view, the record does not support.

[53] We also note that the skilled person may appreciate a relative advantage to using HPβCD in combination with polysorbate 80 based on a review of the description, considered in light of D1. The use of less polysorbate 80 as taught in the present description, relative to the amounts used in D1, could be viewed by the skilled person as an advantage. D1teaches that high concentrations of polysorbate 80 might interfere with the gene delivery to bladder cancer cells (para. [0191]) whereas examples 17 and 15 of the present application indicate that less polysorbate 80 can be used, provided HPβCD is also used.

Conclusion on claim 11

[54] In our view, the person skilled in the art would regard the subject matter of claim 11 as requiring a degree of invention.

Claims 1-10

[55] In the Final Action, claims 1-10 and claim 11 have been separately argued as obvious. As mentioned above, the subject matter of claim 11 is within the scope of claims 1-10 and would lend patentability to these claims if found to be non-obvious. We note also that the reasons for rejection of claims 1-10, insofar as the gene transfer-enhancing composition is concerned, echo those for expressed for claim 11. Our analysis in respect of claim 11 therefore applies to claim 1-10 and leads to the conclusion that they too are non-obvious.

[56] Nonetheless, we will consider whether the disclosures of D2 and D3, which were identified in the Final Action as relevant only to claims 1-10, are also relevant to claim 11 and whether they would render any of the claimed subject matter obvious if considered alone or in any combination.

[57] D2 is a scientific article identified as follows: Ahmed *et al*., *Cancer Gene Therapy*, 8: 788-795 (October 2001). According to the Final Action, D2 discloses an "adenoviral vector delivery system comprising interferon α2b and its use in the inhibition of tumor growth in a patient in gene therapy." It was cited in the Final Action to account for the presence of the same gene delivery vector carrying the same therapeutic gene recited in claims 1-10.

On that basis, D2 is relevant to an obviousness assessment in respect of one of the components mentioned in the claims 1-10: the gene delivery vector carrying a therapeutic gene. However, D2 is not relevant to the second component of claims 1-10 or the subject matter of claim 11, both of which concern a lyophilized gene transfer-enhancing composition. D2 cannot, therefore, disturb the analysis set out above in with respect to claim 11. By extension, it cannot render claims 1-10 obvious.

[58] D3 is a scientific article identified as follows: Croyle *et al.*, *Gene Therapy*, 8: 1281-1290 (September 2001). According to the Final Action:

> D3 discloses the use of beta cyclodextrins in improving formulations of viral vectors in gene therapy. D3 also discloses that lyophilization is a common practice in the formulation of said viral vectors.

[59] D3 would be relevant to an obviousness assessment based on its disclosures of cyclodextrins and lyophilization if the problem addressed concerned stabilizing gene delivery vectors. However, in our view, the skilled person would not regard it as relevant to the problem faced by the present inventors, which is stabilizing and formulating a lyophilized gene transfer-enhancing composition. Although the Final Action suggests that "a person skilled in the art would routinely include [HPβCD] in a composition for gene therapy" it does not follow that the skilled person would be led to do the same when faced with the specific problem of the present application. D3 does not teach anything noteworthy in terms of solubilizing or stabilizing gene transfer-enhancing compositions. D3 taken in combination with D1 and/or D2 would not, therefore, render the subject matter of claim 11 obvious to the skilled person and, by extension, would not render the subject matter of claims 1-10 obvious to the skilled person.

CONCLUSION

[60] Claims 1-11 are compliant with subsection 28.3 of the *Patent Act*.

RECOMMENDATION

[61] For the reasons set out above, we are of the view that the rejection is not justified on the basis of the defect indicated in the Final Action notice and have reasonable grounds to

believe that the application complies with the *Patent Act* and the *Patent Rules*. We recommend that you notify the applicant in accordance with subsection 30(6.2) of the *Patent Rules* that the rejection of the application is withdrawn and that the application has been found allowable.

Ed MacLaurin	Andrew Strong	Dana Eisler
Member	Member	Member

DECISION OF THE COMMISSIONER

[62] I concur with the findings and the recommendation of the Board. In accordance with subsection 30(6.2) of the *Patent Rules*, I hereby notify the Applicant that the rejection of the application is withdrawn, the application has been found allowable and I will direct my officials to issue a Notice of Allowance in due course.

Johanne Bélisle,
Commissioner of Patents
Dated at Gatineau, Quebec,
this 26th day of July, 2016