Federal Court Cour fédérale

Date: 20150501

Docket: T-772-13

Citation: 2015 FC 570

Montebello, Quebec, May 1, 2015

PRESENT: The Honourable Mr. Justice O'Reilly

BETWEEN:

TAKEDA CANADA INC.
AND TAKEDA GMBH

Applicants

and

THE MINISTER OF HEALTH
AND APOTEX INC.

Respondents

JUDGMENT AND REASONS

I. Overview

[1] The applicants, Takeda Canada Inc and Takeda GmbH (together, Takeda), seek an order prohibiting Apotex Inc from going to market with a generic version of Takeda's product called OMNARIS®. OMNARIS is a nasal spray used in the treatment of conditions such as allergic rhinitis.

[2] The active ingredient in OMNARIS is ciclesonide (CS). Takeda's first patent on CS expired in 2011 (Canada Patent No 2,050,812).

[3] Takeda has listed three other patents for its product on the register. Canadian Patent No 2,388,322 (the '322 patent) relates to a pharmaceutical composition for CS. Canadian Patent No 2,388,325 (the '325 patent) relates to an aqueous pharmaceutical composition for CS. Canadian Patent No 2,538,419 (the '419 patent) relates to the use of CS in the treatment of respiratory diseases in children.

[4] By way of a notice of allegation (NOA), Apotex alleges that the three Takeda patents are invalid on various grounds, including anticipation, obviousness, double-patenting, lack of utility, sufficiency and overbreadth. Since Apotex has tendered sufficient evidence to put these issues into play, Takeda bears the burden of establishing that Apotex's allegations are unjustified.

[5] I find that Takeda has failed to meet its burden on obviousness in respect of all three patents. Therefore, I must dismiss its application. It is unnecessary to consider Apotex's other allegations.

II. General Description of the Patents in Issue

A. *The '322 Patent*

[6] The '322 patent, published on April 26, 2001, is entitled "Ciclesonide Contained Pharmaceutical Composition for Application to Mucosa". The abstract explains that the

invention provides a pharmaceutical composition with low osmotic pressure that contains CS, a water insoluble and/or water-low soluble substance, and an aqueous medium, for application to the mucosa. It goes on to say that the composition is superior to others due to its CS retentivity and permeability to the submucosa, or to the blood at the mucosa.

[7] A more detailed description of the invention outlines the prior art as teaching that the application of medications directly to the mucosa, such as through the use of nasal sprays, can be useful. Further, the prior art discloses that the absorption of drugs can be enhanced in a number of ways, including by varying osmotic pressure.

[8] The patent describes CS as a "newly generated lipophilic corticoid". However, CS compositions tend to cause liquid dripping, which does not allow the drug to be transported or permeated to the mucosa tissue. Use of an absorption enhancer could help, but it might cause irritation of the nasal mucosa. Accordingly, the patent states, it is "strongly desired" to find a suitable CS composition that would allow transport of an adequate amount of active ingredient through the mucosa to the submucosa, or to the blood.

[9] The invention, then, is stated to be an aqueous pharmaceutical composition with markedly efficient and high CS permeability. This was achieved by using a composition with low osmotic pressure; the corresponding increase in CS absorption is "drastic". Data in the patent, based on a rabbit study, shows that CS retentivity was better at an osmotic pressure of 5 mOsm than at 330 mOsm. The corresponding increase in permeability would mean that good results could be achieved at comparatively low doses, thereby reducing side-effects.

[10] The patent claims compositions of CS with varying osmotic pressures, ranging from 10 mOsm or less, to 290 mOsm or less. Some of the compositions include an osmotic pressure-controlling agent; others include water-insoluble and/or water-low soluble substances, and/or a surfactant such as Polysorbate 80.

B. *The '325 Patent*

[11] The '325 patent, also published on April 26, 2001, is entitled "Ciclesonide-Containing Aqueous Pharmaceutical Composition". The abstract explains that the invention provides an aqueous composition of CS and hydroxypropylmethylcellulose (HPMC). This composition, the patent says, avoids variations in CS concentrations as well as decreases in CS recovery during production.

[12] A more detailed description of the invention explains that CS is resistant to wetting and tends to aggregate in an aqueous solution. The prior art discloses use of a wetting agent, including the surfactant Polysorbate 80, or vigorous stirring to address this problem. The prior art also shows the use of a cellulose-based polymer like HPMC was in the context of redispersion, that is, to address concentration variations caused by settling during storage, not dispersion of the drug during production. The latter involves the migration of CS towards bubbles created by stirring, and the adsorption of CS to the walls of instruments used in production.

[13] Therefore, the invention of the '325 patent is stated to be the use of HPMC to effect a more uniform concentration of CS throughout the manufactured solution, and in order to lose less CS to adsorption during production.

[14] The patent includes comparative data showing the concentrations of CS achieved with different amounts of HPMC, as well as the recovery rates for the various compositions. These were compared with compositions not containing HPMC. In most cases (3 out of 5), the compositions containing HPMC achieved uniform concentrations of CS. All of them yielded recovery rates of CS at about 100%. The compositions not containing HPMC showed variations in CS concentration, as well as lower recovery rates (43% and 78%).

[15] The inventors deduced from these data that use of HPMC avoided variations in CS concentration and decreases in CS recovery during production.

[16] The patent claims compositions of CS and HPMC in various concentrations, as well as those compositions in combination with water soluble, water insoluble, and water-low soluble substances, such as crystalline cellulose carmellose sodium (a mixture of carboxymethylcellulose sodium and crystalline cellulose).

C. *The '419 Patent*

[17] The '419 patent, published on March 24, 2005, is entitled "Use of Ciclesonide for the Treatment of Respiratory Diseases". The abstract explains that the invention relates to a new method of treating respiratory diseases, particularly asthma in children.

[18] A more detailed description of the invention explains that children with respiratory diseases can be treated effectively with CS, and that common side-effects associated with use of

other corticosteroids, including growth-suppression, can be reduced or avoided. The patent addresses a variety of delivery mechanisms for CS.

[19] The patent describes a clinical study of children with asthma in which 24 patients, aged 6 to 12, received varying doses of CS. The clinicians concluded that there was no evidence of side-effects commonly associated with similar compounds.

[20] The patent claims numerous CS compositions for a variety of uses, mostly for children.

III. Has Takeda shown that Apotex's allegations of obviousness are unjustified?

[21] The test for obviousness is well-settled (*Apotex v Sanofi-Synthelabo Canada*, 2008 SCC 61, [2008] 3 SCR 265 at para 67). It involves a comparison between the state of the art and common general knowledge of the skilled person, on the one hand, and the inventive concept of the patent's claims, on the other. If there is no difference between the two comparators, the claims are obvious. If there is a difference, the claims are obvious if the skilled person would not need to take any inventive steps to bridge the gap. In pharmaceutical cases, it will often be useful also to consider whether the steps taken by the inventors were "obvious to try". Relevant factors to take into account would include: whether there was a motive to find the solution that the patent teaches; whether it was more or less self-evident that the steps taken would work; and whether routine trials were carried out, as opposed to prolonged and arduous experimentation.

A. *The '322 Patent*

(1) The Skilled Person

[22] According to the experts, the '322 patent is addressed to a person with a Bachelor's or Master's degree in pharmacy or chemistry, with experience in the pharmaceutical industry, particularly in formulating drugs (Dr Russell Mumper; Dr Roland Bodmeier. See Annex A for description of experts' qualifications). I agree with these opinions and would add, as Dr Bodmeier did, that the skilled person would also have experience in formulating drugs to be applied to the mucosa.

(2) The Inventive Concept

[23] The inventive concept of the claims of the '322 patent is not seriously in dispute. It is clear from the patent's description of the invention: an aqueous pharmaceutical composition for application to the mucosa, which contains CS, and a water-insoluble and/or water-low soluble substance, and which has an osmotic pressure of less than 290 mOsm. The inventive concept includes superior CS retentivity and permeability compared to conventional compositions.

(3) The State of the Art and Common General Knowledge

[24] The relevant date for considering the state of the art and the skilled person's general knowledge is the claim date of the '322 patent – October 20, 1999.

[25] Dr Bodmeier stated that the skilled person would have had difficulty applying knowledge of other pharmaceutical compositions to the task of creating a CS formulation with high retentivity and permeability. In his view, the prior art, as described in the patent, taught only that a composition containing a hormone-releasing agent and having an osmotic pressure of 290 mOsm or lower would be effective. Similarly, the prior art would inform the skilled person that a secretin solution with an osmotic pressure of 290-1450 mOsm was quickly absorbed through the mucosa. Further, the prior art taught that absorption enhancers could improve absorption through the mucosa.

[26] I note that Dr Bodmeier relied only on three of the prior art references contained in Apotex's NOA and cited by Dr Mumper. Dr Bodmeier did not address all of the relevant prior art, and never referred to the standard text sources mentioned in the NOA and cited by Dr Mumper. I find, therefore, that on the subject of the state of the art and the common general knowledge, Dr Mumper's opinion is more helpful.

[27] Dr Mumper did not confine his opinion to the prior art cited in the patent. Rather, after confirming that a skilled person tasked with formulating an effective CS composition would have readily found it, he reviewed the prior art cited in Apotex's NOA. Before knowing what the invention was, Dr Mumper concluded that the skilled person, based solely on the prior art and his or her common general knowledge, would have prepared an aqueous CS composition containing a viscosity increasing agent, such as a cellulose-based polymer, and having a low osmotic pressure, just as claimed in the '322 patent.

[28] Dr Mumper stated that a skilled formulator would begin by conducting a literature search on CS formulations in various databases, standard texts, scientific journals, and patents. The skilled person would obviously look for information specifically about CS, but also for related subjects, such as, "corticosteroid", "nasal", "delivery", "allergic rhinitis", and compounds similar to CS.

[29] In my view, Dr Mumper's methodology provided a helpful tableau that depicted the state of the art and the common general knowledge available to the skilled person at the relevant time. His opinion was given before knowing what was claimed in the patent in dispute. This approach has gained favour in other cases: *Astrazeneca Canada Inc v Apotex Inc*, 2014 FC 638 at para 321; *Teva Canada Innovation v Apotex Inc*, 2014 FC 1070 at para 94.

[30] According to Dr Mumper, the information obtained from a reasonably diligent search would have revealed the following:

- CS is an anti-inflammatory glucocorticoid that is poorly water-soluble;
- CS has been used in formulations for treating allergic rhinitis;
- Glucocorticoids tend to cause side-effects when administered systemically, as compared to application at local sites, so the preferred method of delivering CS would be by way of topical administration to the mucosa;
- Intranasal delivery would be appropriate;
- An aqueous suspension would be most desirable;
- A means of enhancing retentivity would be sought in order to maximize the amount of time the drug remained in the nasal cavity;

- Formulations that either have low osmotic pressure or high osmotic pressure have high absorption rates;
- Retentivity can also be enhanced by increasing the viscosity of the formulation, and cellulose-based polymers act as suspending and/or viscosity increasing agents;
- Various tonicity adjusting agents were known, including dextrose and sodium chloride; and
- Aqueous suspensions of CS (and similar compounds) were already known, including ones that employed tonicity adjusting agents (*e.g.*, sodium chloride) and viscosity enhancers.

[31] The parties dispute whether a paper referred to as the "Dua study" would form part of the state of the art or the skilled person's common general knowledge (*Dua et al.*, "The influence of tonicity and viscosity on the intranasal absorption of salmon calcitonin in rabbits" (1997) 147:2 *International Journal of Pharmaceutics* 233-242). Dr Bodmeier notes that the Dua study examines viscosity and tonicity, but it does not mention CS. The study concluded that both low tonicity and high tonicity compounds achieved greater bioavailability of the active ingredient, than an isotonic compound.

[32] While the Dua study does not mention CS specifically, I agree with Dr Mumper that it discloses the benefits of both low and high tonicity compounds. Other prior art, including a patent cited in the '322 patent, pointed to the benefits of using a compound with low osmotic pressure. In my view, the skilled person, based on the state of the art and common general knowledge, would have been led toward a formulation with low tonicity.

(4) Conclusion on Obviousness

[33] In my view, in light of this evidence, Takeda has failed to discharge its burden of establishing that Apotex's allegation of obviousness is unjustified.

[34] For Takeda, Dr Bodmeier concluded that the prior art would not have helped a skilled person arrive at the invention contained in the '322 patent. However, as discussed above, Dr Bodmeier did not canvass the entire state of the art and the common general knowledge of the skilled person at the relevant time.

[35] Dr Mumper concluded that, based on the state of the art and the common general knowledge at the time, the "skilled formulator would therefore prepare an aqueous suspension of micronized [CS] with increased viscosity, by including viscosity increasing agents such as cellulose-based polymers, … and with a low osmotic pressure." Again, he arrived at that opinion before being provided the '322 patent. Unsurprisingly, Dr Mumper went on to conclude that the only difference between the inventive concept of the '322 patent, as compared to the prior art and common general knowledge, is that there was no explicit disclosure of a CS formulation with low osmotic pressure in the prior art.

[36] Dr Mumper was reinforced in his conclusion by the absence of evidence of any prolonged study or experiments on the part of the inventors. The patent simply mentions a routine test comparing two formulations that differed in osmotic pressure. It could have been completed in a matter of hours. The formulation with low osmotic pressure performed better, as

would be expected, than a formulation that was only slightly hypertonic. Therefore, the difference between the inventive concept of the ‘322 patent and the state of the art and common general knowledge did not, according to Dr Mumper, involve any inventive steps.

[37] The preponderance of the evidence shows that a skilled person would have arrived at the formulation set out in the ‘322 patent simply by reviewing readily-available relevant publications and applying his or her general knowledge. The inventive concept of the ‘322 patent and the relevant art, taken as a whole, are coextensive. There was no gap to bridge; no inventive step was taken.

B. *The ‘325 Patent*

(1) The Skilled Person

[38] The experts agree that the ‘325 patent is directed to a person with a degree in pharmacy or chemistry, with experience in pharmaceutical formulations, especially pharmaceutical suspensions (Dr Bodmeier; Dr Pardeep Gupta).

(2) The Inventive Concept

[39] The inventive concept of the claims of the ‘325 patent is clear from the patent itself, and is not in dispute. It involves a pharmaceutical composition containing CS and HPMC in an aqueous medium. The composition avoids variations in CS concentration and decreases in CS recovery during production.

(3) The State of the Art and Common General Knowledge

[40] The relevant date for considering the state of the art and the skilled person's common general knowledge is the claim date of the '325 patent – October 20, 1999.

[41] Dr Bodmeier explained that the skilled person would have had difficulty using knowledge about other unrelated compounds to produce a CS composition that would avoid variations in CS concentration and decreases in CS recovery during production. While CS was known as an active pharmaceutical compound, little was known about how to avoid variations in CS concentration or decreases in recovery during production. However, HPMC was a known excipient, and the surfactant Polysorbate 80 was known to help increase dispersivity. Use of Polysorbate 80 is mentioned in the prior art references set out in the '325 patent. Another prior art reference related to redispersion of a composition after storage (not dispersion during production) and, therefore, according to Dr Bodmeier, it would not help the skilled formulator in addressing the problems solved in the '325 patent.

[42] Again, on this point, I am persuaded by the contrary opinion of Dr Gupta. His approach was similar to Dr Mumper's. He agreed that the skilled formulator asked to prepare a CS formulation in 1999 would begin by conducting a literature search. In doing so, he or she would have located all the prior art mentioned in Apotex's NOA. In addition, the skilled formulator would have had access to general knowledge relating to CS, excipients, preservatives, stabilizers, tonicity-adjusting agents, wetting agents, viscosity modifiers, and dispersing agents.

[43] In my view, Dr Gupta's approach provided a helpful overview of the state of the art and the common general knowledge available to the skilled person. His opinion was given before knowing what was claimed in the patent in dispute.

[44] Dr Gupta concluded that the skilled formulator would know that:

- CS is an anti-inflammatory steroid administered in a variety of ways, including nasal inhalation, for the treatment of conditions of the nose or lungs;
- CS is poorly soluble in an aqueous solution, so it would most likely be used in an aqueous suspension, as the prior art already disclosed;
- Viscosity agents are often used to improve uniformity in the concentration of an active ingredient contained in a formulation;
- One of the most common viscosity agents used in drug formulations, including formulations of glucocorticosteroids, is HPMC;
- Other formulations of corticosteroids use suspending agents, such as Avicel, a combination of microcrystalline cellulose and sodium carboxymethylcellulose;
- Formulations that involve suspended particles may also use a dispersing agent which helps reduce particle agglomeration and adsorption of particles to the surface of containers; and
- HPMC was known to act as a dispersing agent.

[45] Dr Bodmeier refuted the relevance of some the prior art references contained in Apotex's NOA and cited by Dr Gupta, particularly a number of prior patents or patent applications. However, Dr Bodmeier did not address all of them and never referred to the standard text

sources mentioned in the NOA and cited by Dr Gupta. I find, therefore, that on the subject of the state of the art and common general knowledge, Dr Gupta's opinion is more helpful.

(4) Conclusion on Obviousness

[46] Based on the prior art and common general knowledge, Dr Gupta concluded that a skilled formulator would have prepared a composition of CS in a stable, aqueous suspension and, to optimize the manufacturing process, would have selected appropriate excipients, particularly HPMC, which acts both as a suspending and a dispersing agent. In other words, the skilled formulator, using only the prior art and his or her general knowledge, would have arrived at the putative invention set out in the '325 patent.

[47] Therefore, the preponderance of the evidence relating to the state of the art and common general knowledge shows that a skilled person would have arrived at the formulation set out in the '325 patent simply by reviewing the relevant literature and applying his or her general knowledge. There is no difference between the relevant art and the inventive concept of the '325 patent.

C. *The '419 Patent*

(1) The Skilled Person

[48] According to Dr David Skoner, the '419 patent is addressed to a physician, someone experienced in treating allergies and respiratory illnesses using corticosteroids, with a particular focus on children. This skilled person would have at least five years' experience in the area.

However, Dr Skoner conceded that some aspects of the ‘419 patent are addressed to issues of formulation and medicinal chemistry, particularly as they relate to CS.

[49] In contrast, Dr Gary Rachelefsky believed that the skilled person should be viewed as a notional team, including a physician experienced in developing and treating respiratory diseases in adults and children, and a pharmacologist involved in studying the properties of drugs, including corticosteroids like CS.

[50] Dr Leslie Hendeles, a clinical pharmacist, stated that the ‘419 patent is directed to persons involved in the development of treatments for pediatric allergic diseases. This would include physicians, formulators, and clinical pharmacists working in the area.

[51] I agree that the ‘419 patent is addressed both to physicians experienced in treating respiratory diseases, particularly in children, and to persons knowledgeable about CS and related compounds, whether formulators, chemists or clinical pharmacists.

(2) The Inventive Concept

[52] Even though the patent claims a broad range of CS compositions, means of administration, and dosages, Dr Skoner interpreted the inventive concept of the claims of the ‘419 patent as being simply the daily use of an aqueous CS formulation in an intranasal spray for the safe treatment of rhinitis in children. Dr Rachelefsky’s opinion is similar, but he would add that the inventive concept includes the reduction or avoidance of side-effects long associated

with corticosteroids, particularly growth suppression in children with long-term exposure to the drug. Dr Hendeles, in effect, agreed with Dr Rachelefsky.

[53] I, too, agree with Dr Rachelefsky– the inventive concept of the ‘419 patent, according to the description set out in it, involves the use of CS in the treatment of children with chronic respiratory diseases with reduction or avoidance of common side-effects associated with use of other corticosteroids, including growth-suppression.

(3) The State of the Art and Common General Knowledge

[54] The relevant date for the obviousness analysis of the ‘419 patent is September 15, 2003.

[55] Dr Skoner stated that the skilled person would be familiar with the use of steroidal and non-steroidal treatments for respiratory diseases. CS would be included among the former. The skilled person would also be aware of the variety of delivery mechanisms available, including nasal sprays. He or she would also be familiar with techniques for monitoring and adjusting dosages, including titration, and the array of potential systemic side-effects from use of corticosteroids, including adrenal suppression and growth suppression. The skilled person would also be familiar with the available tests for detecting growth suppression, including stadiometry and knemometry, but would only be capable of conducting less than adequate stadiometry tests. Knemometry can only be conducted by a few leading researchers across the world, and not the skilled person. Further, the skilled person would not have been able to interpret the results of growth suppression tests.

[56] Dr Skoner explained that the skilled person would have been familiar with CS and its properties as a pro-drug that acts locally, rather than systemically. The skilled person would also have been aware of the safety concerns around the use of corticosteroids in children, particularly the risk of growth suppression. However, literature also described the safe use of some corticosteroids, including budesonide, at comparatively low doses. However, as a class, corticosteroids were regarded as having the potential to cause growth suppression. Accordingly, the US FDA required a warning in respect of all corticosteroids.

[57] Dr Skoner himself conducted studies in the late 1990s in which he found that corticosteroids caused growth suppression in certain doses over time, even where adrenal suppression was absent. Other studies yielded similar results.

[58] Dr Rachelefsky provided a contrary opinion. In his view, in 2003, the skilled person would have known that certain leading corticosteroids could be safely administered to children at doses of up to 200 μg or higher. Further, the skilled person would have been familiar with CS and its high therapeutic index, and would have developed a CS formulation that could be safely administered to children.

[59] Both Dr Rachelefsky and Dr Hendeles were of the view that the skilled person tasked with developing or prescribing corticosteroids for the treatment of respiratory diseases, including in children, would begin by conducting a literature search for information about CS, corticosteroids, systemic side-effects, intranasal administration, and so on. They both confirmed that the art cited in Apotex's NOA would have been located on a reasonably diligent search.

[60] In my view, this approach provides a helpful overview of the state of the art and the common general knowledge available to the skilled person. Both of these experts provided their opinions on this issue before knowing what was claimed in the patent in dispute.

[61] Based on those documents and the common general knowledge at the time, Dr Rachelefsky concluded that the skilled person would have known that:

- Poorly controlled asthma can affect growth;
- Allergic rhinitis causes inflammation of the nasal mucosa;
- Corticosteroids have anti-inflammatory properties and have long been recognized as being suitable for the treatment of asthma and allergic rhinitis;
- Corticosteroids, when administered orally, were known to cause systemic side-effects, so researchers explored means of administering them locally by way of nasal inhalers;
- By 2003, inhaled corticosteroids were considered the most effective treatment available for asthma and allergic rhinitis. Several were on the market;
- Concern about growth suppression caused by corticosteroids led the US FDA to require drug companies to give warnings to users;
- Physicians used stadiometry to measure growth rates in patients. In 2003, no one, other than Dr Skoner, was using knemometry;
- Growth suppression was considered to be linked to adrenal suppression, so drugs with little adrenal effect were considered unlikely to cause growth suppression;
- CS was known to be a pro-drug, whose method of action reduced its potential to cause side-effects;

- A long-term study of an inhaled corticosteroid (budesonide) in 1993 showed no effect on growth suppression in pediatric patients. A similar study in 1995 came to the same conclusion;
- By 2003, it was widely accepted that inhaled corticosteroids at doses of 400 µg or less were safe for children. Any effects on growth were considered to be minimal and transient;
- CS was recognized as early as 1992 as having high anti-inflammatory effects with low systemic effects;
- By 2002, CS was in Phase III clinical trials, and CS nasal inhalers were in development; and
- CS was regarded as being superior to budesonide at lower doses, with fewer risks of side-effects.

[62] Based on those same documents and the common general knowledge at the time, Dr Hendeles concluded that the skilled person would have known that:

- The typical treatment for asthma was by way of inhaled corticosteroids;
- The typical treatment for allergic rhinitis was oral anti-histamines, although severe cases were treated with intranasal steroids;
- Inhaled corticosteroids reduced or avoided the systemic side-effects associated with oral treatments and were the most effective treatment available for allergic rhinitis. Several products were on the market at that time;
- Growth suppression and adrenal suppression were rare for children receiving effective, but low, doses of inhaled corticosteroids;

- With one exception, nasal steroids had no systemic side-effects, including growth suppression, on children;
- Some corticosteroids, when administered on a long-term basis to pre-pubertal children, caused growth suppression and adrenal suppression. Low doses of inhaled corticosteroids did not have that effect. Still, the FDA requires a warning label on corticosteroids;
- CS was known to have a high therapeutic index and would be expected to cause fewer systemic side-effects;
- Prolonged administration of another corticosteroid, budesonide, was found to be beneficial and safe for children – it had no long-term effect on growth;
- Inhaled corticosteroids in doses of 800 µg over 1 to 5 years did not affect bone growth in children;
- Low doses of budesonide (less than 400 µg) had a marked anti-asthmatic effect without systemic side-effects;
- The consensus view was that inhaled corticosteroids at relatively low, but effective, doses did not cause systemic side-effects;
- CS was known to have a superior pharmacological profile to other corticosteroids;
- Inhaled corticosteroids were the first-choice anti-inflammatory treatment for asthma. Doses at 100 to 200 µg were highly effective and safe for children;
- Clinical trials of CS showed anti-asthmatic activity with no clinically relevant side-effects at doses from 100 to 1600 µg; and
- Phase II and III clinical trials of CS showed good efficacy without systemic side-effects. It appeared that doses below 400 µg would be safe for children;

[63] Dr Hendeles also considered the ‘322 and ‘325 patents and the disclosures contained in them as part of the state of the art and common general knowledge for purposes of the ‘419 patent.

(4) Conclusion on Obviousness

[64] Based on the prior art and the common general knowledge, Dr Rachelefsky concluded that the invention described in the ‘419 patent simply conformed to what the skilled person would have expected – that inhaled intranasal CS compositions would be effective and would not affect children’s growth in the prescribed dosages of 20 to 200 µg. Certainly, according to Dr Rachelefsky, the CS compositions in the ‘419 patent would have been obvious to try. A routine clinical trial, such as that described in the patent itself, is all that would have been required to confirm what the skilled person would already have expected. Appropriate doses of CS for children could readily be determined by the skilled physician, based on studies in corticosteroids in adults.

[65] Dr Rachelefsky specifically addressed Dr Skoner’s contrary opinion. In Dr Rachelefsky’s view, Dr Skoner overlooked the evidence showing how favourable CS was viewed in the relevant time period. Dr Rachelefsky actually co-authored a study in 2000 with Dr Skoner, which Dr Skoner cited as providing evidence of growth suppression by a corticosteroid (beclomethasone dipropionate). Dr Rachelefsky points out that that study involved a fairly high dosage (336 µg) compared to the dosages claimed in the ‘419 patent. In addition, a skilled person would have known that CS had a superior pharmacological profile than the studied drug. Dr Rachelefsky expressed the same opinion in respect of a 2000 study of budesonide.

[66] Dr Hendeles also concluded that there was no difference between the inventive concept of the claims of the ‘419 patent and the state of the art. Further, no inventive ingenuity would have been required to arrive at the ‘419 patent’s inventive concept.

[67] Therefore, the preponderance of the evidence relating to the state of the art and common general knowledge shows that a skilled person would have known that administering CS in the dosage range set out in the ‘419 patent would not cause systemic side-effects. Therefore, there is no difference between the relevant art and the inventive concept of the ‘419 patent.

IV. Conclusion and Disposition

[68] All three patents in issue reflect the state of the art and the common general knowledge of the respective skilled persons at the relevant time. Even if there had been gaps between the prior art and the patents’ inventive concepts, no inventive steps would have been required to bridge them. Accordingly, Takeda has not persuaded me that Apotex’s allegations of obviousness are unjustified. I must, therefore, dismiss Takeda’s application, with costs.

JUDGMENT

THIS COURT'S JUDGMENT is that the application is denied, with costs.

"James W. O'Reilly"
Judge

Annex "A"

List of Experts

Dr Roland Bodmeier

Dr Roland Bodmeier is a drug formulator and professor. He has published extensively in the area of drug delivery and formulation, and acts in various capacities with numerous academic journals. In addition to supervising a plethora of students and other researches, Dr Bodmeir's research includes, among other drug delivery systems, nasal and bioadhesive drug delivery formulations, as well as coating technologies and drug solubilisation. He also has acted as a pharmaceutical industry consultant.

Dr Pardeep Gupta

Dr Pardeep Gupta is a formulator and professor. He has authored and co-authored publications, book chapters and research abstracts on drug solutions, emulsions and inorganic pharmaceutical chemistry. In addition to his academic and industry teaching responsibilities involving controlled drug delivery, drug solubility and pharmaceutical formulations, Dr Gupta's research focuses on the formulation of various drugs, such as aqueous pharmaceutical compositions, and more particularly, on the formulation and evaluation of nasal mucoadhesive gels.

Dr Leslie Hendeles

Dr Leslie Hendeles is a clinical pharmacist, professor and a founding member of the American College of Clinical Pharmacy. Throughout his career, Dr Hendeles has been involved in the care of children with asthma, and his current research includes the improvement of adherence to asthma medications and the delivery of inhaled drugs to children. He has been the principal investigator of several studies of inhaled drugs for asthma, and has 175 publications with a focus on asthma therapy. He is a Certified Asthma Educator, and has been appointed to a number of advisory committees relating to pulmonary and allergic diseases.

Dr Russell Mumper

Dr Russell Mumper is a drug formulator, professor and founder of the Center for Nanotechnology in Drug Delivery. He has authored or co-authored over 300 publications, many relating to drug delivery to mucosal tissues. He has experience developing numerous drugs, including those involving nasal mucosa administration. Dr Mumper's research focuses on drug

delivery systems, such as transmucosal and oral, as well as nasal dosage forms and other aspects of drug development.

Dr Gary Rachelefsky

Dr Gary Rachelefsky is a pediatric allergist and professor. For numerous years, his focus has been pediatric and adult allergy and immunology, and he has published over one hundred articles, book chapters and guidances in these fields. He has also served as the principal investigator in a similar number of clinical trials of allergic and non-allergic diseases. Dr Rachelefsky has held membership in a number of professional societies relating to allergies, respiratory conditions, immunology and pediatrics, and has helped develop guidelines for the diagnosis and management of asthma. Further, he is a founding member of two non-profit research foundations for the education of health care professionals about respiratory diseases and treatments.

Dr David Skoner

Dr David Skoner is a pediatric allergist, professor, and director of the Division of Allergy, Asthma, and Immunology at the Allegheny Health Network. He has extensive clinical experience in the field of pediatric respiratory diseases, and has supervised many students, fellows and residents-in-training in this field. In addition to publishing over fifty papers specifically on pharmaceutical treatments for pediatric respiratory diseases, he has published countless other papers, books, book chapters and abstracts in his field. Dr Skoner's research includes the efficacy and safety of inhaled steroids, as well as growth measurements by stadiometry and knemometry in children. Further, he has received prestigious awards for his contributions, and founded a non-profit corporation with the aim of assisting asthma patients.

FEDERAL COURT

SOLICITORS OF RECORD

DOCKET:	T-772-13
STYLE OF CAUSE:	TAKEDA CANADA INC. AND TAKEDA GMBH v THE MINISTER OF HEALTH AND APOTEX INC.
PLACE OF HEARING:	OTTAWA, ONTARIO
DATE OF HEARING:	FEBRUARY 16-20, 2015
JUDGMENT AND REASONS:	O'REILLY J.
DATED:	MAY 1, 2015

APPEARANCES:

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Unrepresented	FOR THE RESPONDENT- THE MINISTER OF HEALTH

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