Commissioner's Decision #1371
Décision du Commissaire #1371

TOPIC: O00
SUJET: O00

Application No. : 2,438,942
Demande n^{o} : 2,438,942

IN THE CANADIAN PATENT OFFICE

DECISION OF THE COMMISSIONER OF PATENTS

Patent application number 2,438,942 having been rejected under subsection 30(3) of the *Patent Rules*, has consequently been reviewed in accordance with paragraph 30(6)(*c*) 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] Patent application number 2,438,942, entitled "Influenza Vaccine Formulation for Intradermal Delivery", filed on February 21, 2002, was rejected by the Examiner because the claimed invention was considered obvious in view of a number of prior art publications.

[2] The application was therefore referred to the Patent Appeal Board for review, and a panel of three Board members was established. This review is based on the prosecution record, including the reports exchanged between the Examiner and the Applicant, the Applicant's written submissions to the panel and those submissions presented during a hearing which took place on March 28, 2014.

[3] For the reasons that follow, we recommend that the application be refused.

BACKGROUND

[4] Influenza A and B are the two types of flu viruses responsible for causing human epidemics. In flu viruses, the antigens—the structures capable of triggering antibody generation—appear as spikes on the outer surface of the virus particle. When someone is exposed to a flu virus, either through vaccination or routine infection, their immune system generates antibodies against the specific antigens on the surface of that particular strain of influenza. The antibodies are then able to neutralize that strain by recognizing and binding to the specific surface antigens, preventing further infection.

[5] Unlike type B, influenza A is broken into subtypes based on the two major surface antigens hemagglutinin (H) and neuraminidase (N). At the time the present application was filed, influenza subtypes A-H1N1, A-H3N2 and type B were in global co-circulation and had been since 1977. Both A and B type flu viruses undergo constant natural mutation referred to as "antigenic drift" which can alter their surface antigens to the point they may no longer be recognized by the immune system, which is one reason why influenza is one of the most pervasive viruses in the world. The specific strain of A-H1N1, for example, used in a seasonal vaccine will typically change from one year to the next because of antigenic drift that has occurred within that subtype. Yearly vaccination is recommended because, in

addition to antigenic drift, immunity generally declines during the year following vaccination.

[6] The present application combines a flu vaccine with a short needle intradermal (ID) device for the intradermal delivery of the vaccine, which was a departure from the standard intramuscular (IM) route of administration. ID injection targets the dermis, which is located only 1-2 mm below the surface of the skin. At the time the application was filed, seasonal flu vaccines typically contained three strains (i.e., the vaccines were "trivalent") and used inactivated virus, meaning the virus was "killed" and therefore non-infectious. The vaccines were either whole virus or split virus, "split" indicating the virus particles are disrupted by a detergent—a process which reduces side effects at the injection site. The vaccine used in the present application is such a trivalent inactivated split vaccine.

[7] According to the Examiner's Final Action, combining the short needle ID device with a trivalent split flu vaccine would not have required any degree of invention at the claim date. To support this argument, the Examiner cited seven documents referred to herein as documents D2[1] to D8 (full references provided at [63]). The Applicant disputed this allegation, arguing there was no evidence that vaccinating against influenza intradermally would work, that the skilled person investigating the ID route would never have employed a trivalent split vaccine, and that the person skilled in the art would not have been motivated to change from the conventional IM route of administration.

THE ISSUE

[8] This review addresses the following question:

(1) Are the claims obvious?

Obviousness of the invention is determined based on the claims in question, therefore we will begin by considering the claims.

[1] the Examiner withdrew document D1 during prosecution after the Applicant challenged its relevance since it did not disclose ID administration

CLAIMS CONSTRUCTION

[9] Purposive construction is done to objectively determine what the person skilled in the art would have understood the scope of the claims to be, based on the particular terms used in the claims: *Free World Trust v Electro Santé Inc*, 2000 SCC 66, [*Free World Trust*], para. 51. During purposive construction, the elements of the claimed invention are identified as essential or non-essential (*Free World Trust*, para. 50). Claims are construed in an informed and purposive manner from the viewpoint of the notional "person skilled in the art" in light of that person's common general knowledge (*Free World Trust*, para. 51). An element is considered non-essential if, based on a purposive construction, the skilled person would appreciate an element of the claim could be omitted or substituted without having a material effect on the working of the invention (*Free World Trust*, para. 55).

[10] Common general knowledge is knowledge generally known by persons skilled in the relevant art at the relevant time (*Apotex Inc v Sanofi-Synthelabo Canada Inc*, 2008 SCC 61 [*Sanofi*], para. 37). The person skilled in the art is reasonably diligent in keeping up with advances in the field to which the patent relates, and their common general knowledge undergoes continuous evolution (*Whirlpool Corp v Camco Inc*, 2000 SCC 67, para. 74). Information contained in reference works such as textbooks of the day which are published at or before the claim date can help to establish whether information was part of the common general knowledge or not (*Eli Lilly and Company v Apotex Inc*, 2009 FC 991 at para. 100, citing a passage from Simon Thorley et al. *Terrell on the Law of Patents*, 16th ed. (London: Sweet & Maxwell, 2006) at 6-39; *Bayer Aktiengesellschaft v Apotex Inc* [(1995), 60 CPR (3d) 58 (On Ct G D)] at page 83).

[11] Before the claims are considered, we must first characterize the person skilled in the art and their common general knowledge.

<u>The Person Skilled in the Art</u>

[12] In the Final Action, the Examiner characterized the skilled person as a "person or group of people working in the fields of immunology and vaccinology, including medical professionals." Since the Applicant did not dispute this characterization, and it is reasonable in view of the teachings of the description, we accept this definition.

Common General Knowledge

[13] In the Final Action, the Examiner characterized the common general knowledge as generally including:

> …adequate knowledge about efficacy and reactogenicity of the existing influenza vaccines and their suitable routes of administration.

[14] There was no agreement between the Applicant and the Examiner on what this knowledge encompassed at the relevant date. In order to establish the scope of knowledge represented by the above statement, the panel has considered a number of publications submitted and/or cited by the Applicant and the Examiner, as well as statements made in the Applicant's own description. Three references which were placed on the record in Applicant's letter of July 2, 2010 are considered particularly relevant to establishing the common general knowledge at the claim date:

- a textbook by Plotkin and Orenstein, "Vaccines", 3rd edition, Philadelphia, W.B. Saunders Company, 1999 [Plotkin];
- a review article by Seiho Nagafuchi et al., "Intradermal Administration of Viral Vaccines", Reviews in Medical Virology, 8, 1998, pages 97-111 [Nagafuchi]; and
- the product insert for the commercial vaccine Fluzone™ [Fluzone insert] used in the 1999-2000 flu season, "Influenza Virus Vaccine USP Trivalent Types A and B, Fluzone", A.H.F.S. Category 80:12, Connaught Laboratories Inc., Swiftwater, Pennsylvania, USA, April 1999.

[15] Having considered the Applicant's submissions, the application and the references of record, in our view the common general knowledge of the skilled person at the claim date would have included the following knowledge:

- the convention was to use trivalent vaccines, typically split virus, delivered by the IM route;
- trivalent vaccines were recommended because, at the claim date, there were three types of flu viruses in worldwide co-circulation: types A-H1N1, A-H3N2 and B;
- split vaccines were recommended across all age groups, whereas whole virus vaccines were

recommended only for those older than 12 years;

- immunogenicity (i.e., the ability to provoke a protective immune response) of whole and split vaccines was similar among adults, but whole virus was more immunogenic in the elderly;

- for the conventional trivalent split vaccines, two doses were recommended for subjects that had not been previously exposed to the virus, either through vaccination or prior infection from routine exposure, and everyone else was given one dose. The recommendations were based on age, and assumed that everyone had been exposed to the viruses by the age of 9;

- immunogenicity decreased with every additional strain used in a vaccine;

- when the influenza strains in circulation were close to those in the vaccine, the vaccine was 70-90% effective in healthy persons younger than 65, and while they were only 30-40% effective in preventing the flu in the elderly living in chronic care facilities or nursing homes, vaccination was specifically recommended for this group because the vaccine was effective in preventing secondary complications related to influenza;

- the "Mantoux" injection technique was the standard manner for ID delivery, even though it was known to require highly skilled operators, making it impractical for yearly mass vaccination campaigns;

- the ID route had the advantage of using less vaccine (only 1/5 of the standard dose of parenteral[2] injection), and was able to target cellular immunity via Langerhans cells enriched in the dermis;

- substituting the IM route with the ID route for a flu vaccine would have been expected to be equally effective in subjects primed by prior infection or vaccination;

- no licensing authority had ever approved a seasonal flu vaccine for intradermal administration; and

- flu vaccines were immunogenic by the ID route, but the IM route was recommended by health authorities, and there was a general lack of interest in the scientific community in

[2] "parenteral" refers to intramuscular (IM) or subcutaneous (SC) administration

evaluating vaccine performance when administered by alternative routes.

Existing Influenza Vaccines

[16] There is a great deal of variability between flu vaccines. The Applicant and the Examiner agreed they were known in the prior art to: (i) employ live or inactivated strains, (ii) be whole or split virus, (iii) contain between one and three strains (i.e., mono, bi or trivalent), and (iv) to be delivered by IM, subcutaneous (SC) or ID injection. However, the Applicant submitted in the letter of May 23, 2012, that the convention at the time before the application was filed was to use "intramuscular injection of a trivalent inactivated vaccine, typically a split virus vaccine."

[17] For ease of reference, and to provide context throughout this section, the table containing the US national committee recommendations for the 1997-1998 flu season, taken from page 537 of the Plotkin textbook, is reproduced below. These recommendations are identical to those in the Fluzone insert for the 1999-2000 flu season. The panel notes that both Plotkin and the Fluzone insert were added to the record by the Applicant and were cited during prosecution by the Applicant and the Examiner.

Influenza Vaccine Dosage By Patient's Age in the United States (1997-1998)

Age Group	**Product**	**Dosage**	**Number of Doses**	**Route**
6-35 months	Split virus only	0.25 mL	1 or 2	IM
3-8 years	Split virus only	0.50 mL	1 or 2	IM
9-12 years	Split virus only	0.50 mL	1	IM
>12 years	Whole or split virus	0.50 mL	1	IM

[18] These recommendations confirm the Applicant's submissions. The skilled person would have known at the claim date that the convention was IM injection of trivalent flu vaccines, typically using a split virus.

[19] It is explained in Plotkin that trivalent vaccines were recommended because, at the claim date, there were three (sub)types of flu viruses in co-circulation: A-H1N1 strains, A-H3N2 strains and B strains (page 535). The Fluzone insert also explains the specific strains of each (sub)type to be contained in the seasonal vaccine are those deemed by the World Health Organization [WHO] to be most likely to circulate in the upcoming winter.

[20] Also, both Plotkin and the Fluzone insert state the known vaccines are propagated in chicken embryos, they are split using a Triton™ surfactant, and they contain 15µg of

hemagglutinin of each flu strain (i.e., 45µg total) in each 0.5 mL dose.

Efficacy (Immunogenicity) and Reactogenicity (Side Effects)

[21] According to the Fluzone insert, when the flu strains in circulation were close to those in the vaccine, the vaccine was 70-90% effective in preventing the flu in healthy persons younger than 65, but only 30-40% in preventing the flu in the elderly living in chronic care facilities or nursing homes. However, vaccination is specifically recommended for this group since the vaccine was very effective in preventing secondary complications related to influenza (Fluzone insert).

[22] At the hearing, the Applicant submitted that the common general knowledge would have included the knowledge that whole virus vaccines are more immunogenic than split vaccines. While this statement may be true in general, it is not entirely consistent with what was generally known and accepted for trivalent flu vaccines at the claim date. According to the Fluzone insert, in reference to the national committee recommendations, immunogenicity and side effects were similar among adults for trivalent split and whole virus vaccines. These statements are consistent with Plotkin, which adds there was a study in the elderly that showed whole virus was more immunogenic than split in that age group (page 540). Accordingly, the skilled person would have known whole virus may be more immunogenic in the elderly, but would likely be equivalent in adults.

[23] As mentioned above, the side effects of split and whole virus flu vaccines were similar among adults but, as can be seen from the table above, whole virus vaccines were contraindicated in subjects younger than 12 years because they had prohibitive side effects in children (Plotkin, page 536, Fluzone insert).

[24] The Applicant also submitted at the hearing that the skilled person would have known that multiple doses are more efficient and more immunogenic than a single dose. Again, this is not entirely consistent with what was known for flu vaccines at the time the application was filed. It was known that the number of doses depended on whether or not the subject has been exposed to the flu viruses contained in the vaccine. As it is shown in the table above, children younger than 9 years that had never been vaccinated for the flu were given two doses, everyone else was assumed to have been "primed" (i.e., previously exposed to the viruses) either by prior vaccination or infection, thus requiring only one dose (Fluzone insert, Plotkin page 536). Since influenza subtypes A-H1N1 and A-H3N2 and B-type influenza were in global co-circulation at the claim date, those were the strains included in the vaccine. Moreover, since those (sub)types of the flu had been in global co-circulation

since 1977, everyone was presumed to be primed by infection caused by routine exposure by the age of 9 years. In this vein, the Fluzone insert teaches that in adults, studies had indicated little or no improvement in antibody response when a second dose of the trivalent split vaccine was administered during the same season. Moreover, Plotkin teaches that repeated administration of flu vaccine in primed subjects at 6-month intervals did not increase the number of subjects with protective levels of antibody (page 537).

[25] Another submission made at the hearing was that the common general knowledge of the skilled person would have included knowledge that with every additional strain contained in the vaccine, antigen interference increases, causing immunogenicity to decrease. This means a monovalent vaccine would be more immunogenic than a bivalent vaccine, etc. This fact was not disputed by the Examiner, nor was it contradicted by any of the references under consideration. We accept this submission.

Suitable Routes of Administration

[26] Before we proceed with a discussion of ID delivery, it is apparent in reviewing the record that a brief explanation of ID delivery using a standard needle and syringe is warranted. During the course of our review, the panel asked the Applicant to clarify whether the skilled person would understand a reference to ID injection which is "performed manually by an operator using a standard needle and syringe" as necessarily referring to the "Mantoux technique" (a special technique explained below). Our question was directed to document D4 (Di Pietro et al., full reference provided at [63]) specifically, which is discussed further in the following section, but this clarification is equally important in establishing the common general knowledge and in how the skilled person would understand a number of references on file.

[27] At the hearing, the Applicant responded by saying there was no indication in D4 that the authors were talking about the Mantoux technique. Neither the gauge of the needle nor the angle of administration were identified, and so based on the limited information provided one could not extrapolate that the author was referring to the Mantoux technique. When asked, the Applicant was unable to suggest what this passage might alternatively be referring to, if not the Mantoux technique.

[28] Based on the evidence before us, we are not persuaded that the skilled person would understand a reference to ID injection performed manually using a standard needle and syringe to be different from a reference to the "Mantoux technique." The general process

for administering ID injections using a standard needle and syringe is explained in Plotkin: the entire bevel of a 3/8 to 3/4 inch, 25-27 gauge needle is inserted into the epidermis at an angle parallel to the long axis of the forearm, and care is taken to ensure the injected solution raises a small bleb (i.e., a fluid-filled blister) "thus demonstrating intradermal rather than subcutaneous injection of the vaccine" (page 52). While it is not explicitly identified as such, Plotkin is describing the Mantoux technique. At the hearing, the Applicant described the technique as using a shallow angle of "5-10° parallel to the skin", as opposed to "an angle parallel" used in Plotkin, but we do not consider this to be a difference. Moreover, on page 5 of the Applicant's written submissions presented at the hearing, it is said in reference to document D6 (Halperin et al., full reference provided at [63]) that the vaccine was "provided in a standard syringe and needle (Mantoux technique) for intradermal delivery." Notably, the phrase "Mantoux technique" is not used in D6, yet that extrapolation was made by the Applicant. Likewise, the Applicant uses the "Mantoux technique" on page 4 of those same submissions in reference to D2, which refers to ID injection, but never to the Mantoux technique. In our view, the skilled person at the claim date would have understood 'ID injection carried out using a standard needle and syringe' as being synonymous with the "Mantoux technique."

[29] It is clear from the references that follow that it was common general knowledge of the skilled person at the claim date that ID injection using a needle and syringe requires the operator to have a specialized skill set. According to the Nagafuchi article (reference at [14]), the requirement for specialized skills in administering ID injections is a disadvantage of this route. In the description, the Applicant states on page 5 there was a widely held view that there was difficulty associated with administration by this route, and page 19 states that ID administration using conventional syringes "in the classical mantoux [*sic*] method requires highly skilled operators." Also, the authors of document D6 warn the reader that the results of their study may not have been as good "in the hands of those less proficient with ID injection", pointing out the significant experience of their operators. Moreover, in reference to the rabies vaccine, Plotkin teaches that in the event of a vaccine shortage, the ID route would only be indicated if staff experienced in the ID injection technique were available (page 751).

[30] In the written submissions presented at the hearing, the Applicant submitted that it was common general knowledge that the "gold standard" or convention in ID delivery at the claim date was to use the Mantoux technique, adding that ID delivery by jet injector[3] had been "discarded for cause of cross-contamination." This statement is consistent with the

[3] jet injectors deliver liquid doses intradermally as a high-pressure stream without using a needle

teachings of Plotkin that, in 1999, the WHO discouraged the use of jet injectors because of the potential for patient-to-patient transmission of blood-borne pathogens (page 52-53), even though they can be helpful in mass vaccination campaigns where the use of needles and syringes is not practical.

[31] Whether or not "suitable routes of administration" as in the definition of the common general knowledge provided at [13] includes the intradermal route was in dispute. One point of dispute was whether or not the following advantages associated with the ID delivery of vaccines were part of the common general knowledge:

> i) the ability to target dendritic (Langerhans) cells, which are enriched in the dermis layer, to induce cellular immunity; and
>
> ii) the ability to stretch vaccine supplies in times of shortage since smaller amounts of vaccine are needed.

[32] In response to the Final Action, the Applicant disputed the Examiner's assertion that these advantages were part of the common general knowledge, emphasizing that no references were provided to support this. The Applicant conceded the skilled person knew of the ID route, but disputed that "a decisive benefit had been shown for intradermal administration" (page 5).

[33] Even though the Examiner's statements are consistent with statements made in the Applicant's description, the panel requested a Supplemental Analysis from the Examiner to address this issue in order to facilitate our analysis.

[34] The Supplemental Analysis presented a number of references in an effort to establish that these advantages were part of the common general knowledge, two of which were found to be particularly relevant, and were already part of the record: Nagafuchi and Plotkin. In support of the first point the review article by Nagafuchi provides a comprehensive explanation of the mechanism of cell mediated immunologic reactions that occur in response to ID vaccination, including a description of the role played by dendritic Langerhans cells. Given the advanced level of detail known for this reaction in 1998, we accept that this was part of the common general knowledge of the skilled person.

[35] In support of the second point, the Examiner cited an excerpt from page 537 of the Plotkin textbook. This reference confirms it was common general knowledge that the ID route had indeed been used to administer flu vaccines with the rationale of "conserving vaccine

during times of shortage" (page 537).

[36] Another point of dispute was whether or not the skilled person would have expected immunogenicity of the known trivalent split vaccine to diminish if the route were changed from IM to ID. According to page 537 of Plotkin, while it was recommended that flu vaccines were to be given by IM injection, they were known to be immunogenic by other routes, including the ID route. Moreover, Plotkin goes on to say:

> A consensus suggests that the limited amount of vaccine that can be given by intradermal administration is equal in efficacy to larger amounts given by parenteral routes only when it is administered to elicit a secondary response in immunologically primed subjects (emphasis added).

[37] As mentioned previously, "immunologically primed" means the subjects have had previous exposure to the virus, either through prior infection or vaccination, which is why it is said to elicit a "secondary response." As we have already established at [24], since the (sub)types of flu contained in the conventional vaccine had been in global co-circulation since 1977, it was part of the common general knowledge that the population was presumed to be primed against the conventional trivalent split vaccine by the age of 9 years, or earlier if they had been vaccinated previously. That is why the dosing recommendations shown in the table are set up as they are, by age or vaccination history (Plotkin, page 536). In this view, the skilled person would logically have expected the trivalent split vaccine to be as effective by the ID route as they were by the IM route for all subjects over 9 years of age and younger children that had been previously vaccinated against the flu.

[38] Nagafuchi also supports the position that changing the route from IM or subcutaneous (SC) injection to ID may be as effective, citing three articles: Brown et al.[4], Herbert et al.[5] and Halperin et al. (document D6, full reference at [63]). At the hearing, the Applicant asked that the panel set aside the Nagafuchi document, as it pertains to this issue, and consider the primary sources directly since they were each previously addressed by the Applicant on the record. In particular, the Applicant submitted that the conclusions drawn in Nagafuchi were not credible in respect of influenza because these cited studies show contradictory results.

[4] Brown et al., "The Immunizing Effect of Influenza A/New Jersey/76 (Hsw1N1) Virus Vaccine Administered Intradermally and Intramuscularly to Adults", J. Infect. Dis., vol. 136, Supplement, December 1977, pages S466-S471.

[5] Herbert et al., "Comparison of Responses to Influenza A/New Jersey/76-A/Victoria/75 Virus Vaccine Administered Intradermally or Subcutaneously to Adults with Chronic Respiratory Disease", J. Infect. Dis., vol. 140, no. 2, August 1979, pages 234-238.

We agree to consider the three articles, and Applicant's arguments of record, directly.

[39] The Applicant maintained throughout prosecution that the teachings of Brown et al. and Herbert et al. were at odds, which they submitted was evidence the skilled person would not have known whether or not an ID flu vaccine would be effective. Specifically, the Applicant submitted Herbert et al. finds ID vaccination performed better in subjects previously exposed to the strains (i.e., in primed subjects), whereas Brown et al. showed ID vaccination performed worse in primed subjects. Moreover, at the hearing, the Applicant submitted the results were so poor in D6 after the first dose of what was supposed to be a two-dose protocol, that the protocol had to be stopped because it did not work.

[40] The panel notes that the Brown et al., Herbert et al. and D6 studies were carried out circa 1976-1977, at which point the A-H1N1 subtype was beginning to circulate for the first time in twenty years—the subtype had abruptly disappeared from circulation in 1957. This is why so many subjects were unprimed against A-H1N1 in these studies.

[41] Herbert et al. compare the SC and ID administration of a bivalent whole virus vaccine containing A/H1N1/New Jersey/76 (swine flu) and A/H3N2/Victoria/75. Pre-vaccination levels of antibody indicated widespread exposure of the patients to the Victoria strain, but not the swine strain. The results were different for the two strains: antibody response for the SC route was superior to the ID route for the swine strain, but the two routes were equivalent for the Victoria strain. Consistent with the Applicant's argument, it was concluded that efficacy of the vaccine by the ID route depended on whether or not the subject was primed against the particular strain. This finding is also consistent with the teachings of Plotkin above.

[42] Brown et al. compares IM and ID administration of a monovalent whole virus vaccine containing A/H1N1/New Jersey/76 (swine). The unprimed subjects showed different results depending on their age: the antibody response was worse by the ID route compared to the IM route for those aged 18-24, yet for those older than 24 the response was the same by ID and IM. A booster (second dose) increased antibody levels somewhat in the 18-24 year old ID group, but no such increase was observed for those older than 24 or for those vaccinated by IM injection. No explanation was given for this disparity at the time, but Plotkin appears to address this at the bottom on page 536. In relation to a discussion of nonimmune (unprimed) populations, Plotkin refers to a study of H1N1 (swine) where an adequate antibody response to a single ID dose was achieved but only in subjects older than 24 years "who were presumably primed by prior exposure to other H1N1 viruses."

[43] Contrary to the Applicant's conclusion that Brown et al. shows ID vaccination performed worse in primed subjects, it is stated that whether by IM or ID, greater increases in antibody titres were achieved in primed subjects than in those that were not primed. However, the vaccine was significantly more immunogenic by the IM route as compared to the ID route in those primed subjects: the seroconversion rate was 100% for the IM group, and only 73% for the ID group. Notably, these values are still well above the 40% seroconversion rate required according to the European standards for influenza vaccines referenced on page 7 of the Applicant's description.

[44] Throughout prosecution, the Applicant repeatedly cited the following from Brown:

> Although the lower incidences and severity of systemic reactions after intradermal than after im vaccinations are desirable features, the differences in serologic response are disturbing. The antibody responses were lower after the intradermal vaccination for those with preexisting antibody and for those in the younger age group.

[45] To place this quote in its proper context, it is clear the disturbing "differences in serologic response" refers at least in part to the difference in response among the two different age groups of the unprimed subjects. Moreover, the lower antibody responses obtained is referring to a comparison of the ID vs. IM route in primed subjects, it is not a comparison of antibody response in primed vs. unprimed subjects.

[46] We do agree with the Applicant that the significantly better result in primed subjects vaccinated by the IM route compared to the ID route goes directly against the teachings from Plotkin that the two routes should be equal in primed subjects. However, in our view, it appears the Brown study was considered to be an outlier. Both Nagafuchi and Plotkin refer to this study and draw their conclusions in spite of the teachings of Brown et al. For this reason, it is our conclusion that the skilled person at the claim date would have expected the conventional trivalent split vaccine to be equally effective by the ID route, since the population was known to be primed against the types of flu viruses contained in the vaccine at the claim date.

[47] With regard to D6, we disagree with Applicant's statement that the performance was so poor after the first dose the protocol was stopped. The protocol was stopped because of the well-publicized cancellation of the National Influenza Immunization Program on December 16, 1976 (page 1249), after the vaccine was linked to Guillain-Barré Syndrome. In fact, after one dose of a bivalent split vaccine administered by ID injection, the results were poor

for the A/H1N1/New Jersey/76 (swine) strain, but a seroconversion rate of 54.7% was achieved for the A/H3N2/Victoria/75 strain. Since this value is above the 40% required by the European standards for flu vaccines referred to on page 7 of the Applicant's description, we do not agree with the Applicant that vaccination by this route did not work. Pre-vaccination antibody titres showed that, unlike the Victoria strain, none of the subjects tested were primed against the New Jersey strain. At the claim date, the skilled person would immediately recognize this would explain the poor results obtained for the swine flu. The skilled person would therefore not consider D6 to teach away from using ID vaccination.

[48] Nevertheless, according to Nagafuchi, as of 1998 an intradermal vaccine had never before been approved by a licensing authority (page 97). Moreover, the skilled person would be aware that IM injection was the recommended route of administration (Fluzone insert, Plotkin page 537). According to the Fluzone insert since "recent influenza vaccines have not been adequately evaluated when administered by other routes, the intramuscular route is recommended." In reference to this excerpt, the Applicant argued in the letter of January 23, 2013, that this indicated a strong preference towards the IM route and a lack of interest in evaluating vaccine performance when administered by alternative routes (page 4). We agree with the Applicant, the common general knowledge includes knowledge that there was a preference towards the IM route and a general lack of interest in evaluating vaccine performance when administered by alternative routes.

The Claims

[49] There are four independent claims on file. Claims 1 and 20 are independent use claims, and claims 12 and 15 are independent product claims defining pharmaceutical kits. We will first consider independent claim 15, which is representative of the kit claims:

> 15. A pharmaceutical kit comprising:
>
> (i) a short needle intradermal delivery device adapted to a location between 1.0 mm and 2.0 mm below the surface of the skin; and
> (ii) a trivalent split influenza vaccine.

[50] In the Final Action, the Examiner construed "a location between 1.0 and 2.0 mm below the surface of the skin" from the independent claims as being synonymous with ID delivery for two reasons: "1) the recited location is anatomically within the dermis layer of the skin, and 2) the entire description has clearly stated the alleged invention is for intradermal delivery

of influenza vaccine formulations." The Applicant did not dispute this construction. We agree that this is how the skilled person would construe this statement, based on the teachings of the description. We can therefore construe claim 15 as:

> 15. A pharmaceutical kit comprising:
>
> (i) a short needle intradermal delivery device; and
> (ii) a trivalent split influenza virus vaccine.

[51] Using the same shorthand, independent clam 1, which is representative of the use claims, is:

> 1. Use of a trivalent, split influenza virus antigen preparation in the manufacture of a one-dose intradermal influenza vaccine, said vaccine provided in a short needle intradermal delivery device.

[52] In the letter of July 2, 2010, the Applicant said it is important to appreciate the distinction between a unit dosage form presented as a pre-filled syringe and a one dose vaccine wherein protection is afforded by the provision of a single dose rather than a series of doses (page 5). The panel notes, in relation to this statement and based on the application as a whole, the skilled person would recognize that claim 1 defines a unit dosage form, and indicates this is a one-dose vaccine that would provide protection after a single dose. The independent kit claims do not contain the unit dosage form: the syringe and vaccine can be contained separately or, according to dependent claim 19, the device can be supplied pre-filled with the vaccine. Moreover, these claims do not indicate it is a one-dose vaccine.

[53] The panel notes that claim 1 uses the "Swiss" format, in that the use is directed to "the manufacture" of the intradermal vaccine, rather than defining a medical use. In a recent decision the Federal Court observed that the "artificial nature" of Swiss claims should be disregarded, stating the "real subject matter of the claim" should be considered instead, which they concluded in their case related to a medical use: *Novartis Pharmaceuticals Canada Inc v Cobalt Pharmaceuticals Company*, 2013 FC 985, para. 101. This was in line other decisions where "Swiss claims" have been judicially interpreted as medical use claims: see see *GD Searle & Co v Canada (Minister of Health)*, 2008 FC 437, aff'd 2009 FCA 35; *Eli Lilly Canada Inc v Apotex Inc*, 2008 FC 142; and *Pfizer Canada Inc v Apotex Inc*, 2007 FC 971, aff'd 2009 FCA 8. In our view, the real subject matter of the use claims before us relates to the medical use of an ID vaccine to prevent the flu, and so this is how we construe claim 1:

> 1. Use of a trivalent, split one-dose influenza vaccine provided in a short needle intradermal delivery device for the prevention of influenza.

[54] Dependent claim 2 specifies the antigen is egg-derived. Claims 5-7 specify the presence of surfactants/bile acids. Claim 8 and 18 define the dose volumes. Claim 9 specifies the amount of haemagglutinin, and claims 10 and 11 further include an adjuvant. Claim 19 specifies the device is supplied already filled with the vaccine[6].

[55] Dependent claims 3, 4, 13, 14, 16, 17, 21 and 22 define a specific minimum protection rate, seroconversion rate or conversion factor which the vaccine is capable of inducing in one of two age groups: 18-60 years, and older than 60 years. Notably, claims 4, 14, 17 and 22 are more restrictive in that all three of the defined protection rate, seroconversion rate and conversion factor are met by the vaccine for either age group, whereas only one of the three must be met for one of the age groups in claims 3, 13, 16 and 21.

[56] Claim construction is carried out to distinguish those elements of the claimed invention which are "essential" from those which are "non-essential." The essentiality of the claim elements was never in dispute. As will be seen in the following section, the Applicant and Examiner agreed to an inventive concept based on the language of claim 1 which includes all of the claim elements: namely i) a short needle intradermal delivery device, and ii) an influenza vaccine, which is a trivalent, split one-dose vaccine. We agree that these are all essential elements, and that the nature of the specific vaccine components have a material effect on the working of the invention, in that they impact who can be treated and the scope of protection provided by intradermal vaccination.

ISSUE (1) ARE THE CLAIMS OBVIOUS?

[57] Section 28.3 of the *Patent Act* sets out the information considered when assessing the obviousness of a claim:

> 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

[6] since the individual elements of the kit are assembled in claim 19, it is questionable whether the subject matter of the claim can still appropriately be termed a "kit"—although nothing turns on this point

> (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.

[58] Our obviousness assessment follows the four-step approach set out in *Sanofi*:

> (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?

Analysis

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

[59] These are common to our claim construction. The person skilled in the art is defined at [12], and their common general knowledge is summarized at [13] and [15].

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

[60] In the Final Action, the Examiner characterized the inventive concept for the independent claims as being equivalent to—and including all of the elements of—claim 1. The Applicant did not dispute this characterization of the inventive concept for the independent claims. Since we have construed claim 1 at [53] as being a direct use, disregarding the

Swiss format, we will re-write the inventive concept in a manner consistent with claim 1, as construed:

> Use of a trivalent, split one-dose influenza vaccine provided in a short needle intradermal delivery device for the prevention of influenza.

[61] For the reasons discussed at [52], we do not agree that this inventive concept should apply equally to the independent use claims and kit claims. Unlike the use claims, the kit does not define (i) a unit dosage form, or (ii) a one dose vaccine. In our view, the inventive concept for the independent kit claims is more appropriately characterized as:

> A pharmaceutical kit comprising (i) a short needle intradermal device, and (ii) a trivalent split flu vaccine.

[62] Our analysis will begin by focusing on the two inventive concepts of the independent claims, and thereafter the further features of the dependent claims will be considered.

Step 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

[63] The Final Action cites the following prior art documents:

Patent Documents

D3: WO 98/15287, 16 April 1998, Garcon N. et al.
D4: WO 99/34850, 15 July 1999, Di Pietro A.
D5: WO 94/19013, 1 September 1994, Dillon S. et al.

Journal Articles

D2: Lawee D. et al., "Efficacy of Influenza Innoculation: Intradermal versus Subcutaneous Route", Can. Fam. Physician, vol. 27, March 1981, pages 411-414.
D6: Halperin W. et al., "A Comparison of the Intradermal and Subcutaneous Routes of Influenza Vaccination with A/New Jersey/76 (Swine Flu) and A/Victoria/75: Report of a Study and Review of the Literature", AJPH, vol. 69, no. 12, December 1979, pages 1247-1251.
D7: Vasil'eva R. I. et al., "Summing Up the Results of the Study of New Inactivated Whole-Virion Influenza Vaccines in the USSR", Zh. Mikrobiol. Epidemiol. Immunobiol., vol. 3,

1987, page 42.

D8: Niculescu E. Z. et al., "Efficacy of an Adsorbed Trivalent Split Influenza Vaccine Administered by Intradermal Route", Arch. Roum. Path. Exp. Microbiol., vol. 40, no. 1, January-March 1981, pages 67-70.

[64] In our view, after reviewing all of the references, the skilled person would read documents D2, D6, D7 and D8 as reflecting the common general knowledge, and not the state of the art. Since we have already addressed the common general knowledge at step 2, there is no need to consider these documents further. In our view, the state of the art is represented by D4, as well as documents D3 and D5 which disclose elements of the formulation relevant to some of the dependent claims.

[65] Even though D2 will not be part of our analysis, the panel will address the Applicant's argument pertaining to this reference for the sake of completeness before we proceed with our analysis. At the hearing, the Applicant submitted that D2 and D6—which it understood from the Examiner to be the primary references—both teach away from the claimed subject matter. The teachings of document D6 have already been addressed at [47].

Document D2

[66] Document D2 discloses a one-dose trivalent whole virus flu vaccine administered intradermally using a needle and syringe to a geriatric population living in a nursing home. According to the Applicant, it would be clear to the skilled person the vaccine was not found to be efficacious, citing from the conclusions "[i]n at least 60% of the participants, Fluviral inoculation by either route did not produce clear serological evidence of protection against influenza." Moreover, the authors question "whether annual vaccination is justified", which the Applicant submits is a clear indication an effective immune response was not obtained.

[67] To place these quotes in their proper context, the panel notes that the 60% of participants that did not achieve protective levels of antibody referred to a group of unprimed subjects. Based on their common general knowledge, the skilled person at the claim date would not have expected unprimed subjects to achieve protective levels of antibody after only one dose of vaccine. Notably, there was clear evidence of protection in the group that included primed subjects. Regarding the second point, the authors were questioning whether annual vaccination is justified for those who reach an antibody plateau, meaning the initial levels of antibody in primed subject are already high prior to vaccination. This is a consideration

in D2 because the subjects are geriatric and are hence prone to having high antibody levels prior to vaccination. The skilled person would know that high pre-vaccination antibody levels relate directly to the subjects and are independent of the vaccine or route of administration. Notably, the Applicant's own example 6 (description, page 42) which vaccinated an elderly population also had very high pre-vaccination levels of antibody. Knowing that the conventional vaccines of the day were specifically recommended for this group to prevent secondary complications, the skilled person would not have questioned whether vaccination is justified for this group at the claim date. For these reasons, we do not agree that the skilled person would consider D2 to teach away from ID delivery of flu vaccines.

Document D4

[68] Document D4 is a patent application to Di Pietro which published about 19 months before the earliest priority date of the present application. It is for a device which is fitted to a syringe to control the penetration depth of the needle when carrying out intradermal injections. As explained in D4, it is difficult to obtain proper penetration depth when carrying out ID injections as it is dependent on the manual skills of the operator (page 1). The device can be used with existing syringes, thus eliminating the need for a skilled operator to perform controlling operations manually (page 3). The device, which can be easily constructed using commercially available elements and materials, is specifically designed for application to an intradermal injection syringe (pages 1-2). Notably, there is no mention in D4 of using the device for the delivery of vaccines of any kind.

[69] The difference between D4 and the inventive concept of the independent use claims is that D4 makes no mention of combining the short needle device with a flu vaccine that is protective after a single dose.

[70] The difference between D4 and the inventive concept of the independent kit claims is that D4 makes no mention of combining the short needle device with a flu vaccine.

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?

[71] As we established at [18], the trivalent split flu vaccine was part of the common general knowledge at the time the application was filed. It was known for IM administration, but as was established at [37], the skilled person would have expected the vaccine to be just as

effective by the ID route in primed subjects: i.e., everyone older than 9 years, or in younger children previously vaccinated against the flu. Moreover, with respect to the inventive concept of the use claims, the skilled person would have known the vaccine would be protective in those primed subjects after only one dose.

[72] Paraphrasing the Final Action, the Examiner reasoned that since the specific vaccine was known, and had been used previously by the ID route in a single dose, the principal difference between the inventive concepts and the prior art was that a short-needle ID device had never before been used with a flu vaccine. The Examiner reasoned that since the advantages of ID delivery were known to the skilled person—including the ability to induce cellular immunity by targeting dendritic cells enriched in the dermis, and dose sparing—and the disadvantage associated with the skill required to administer ID injection by the Mantoux technique was known, then:

> …using a short needle intradermal delivery device available in the state of the art for intradermal delivery of a known trivalent split influenza vaccine as defined in independent claims 1, 11, 12 and 15 does not require any degree of invention. (page 4)

[73] We agree with the Examiner. In first considering the inventive concept of the independent use claims, not only would the skilled person have expected the known trivalent split vaccine to be immunogenic by the ID route after only one dose in primed subjects, they would also know that changing the nature of the delivery device (short needle vs. jet injector, or Mantoux) would change neither the manner and location of vaccine delivery, nor the vaccine itself. It is these factors that impact immunogenicity, not the nature of the delivery device.

[74] Since the inventive concept of the independent kit claims is even less restrictive than the use claims, in that there is no limitation on the number of doses, the independent kit claims are also not considered to have required any degree of invention.

Applicant's Arguments

[75] Throughout prosecution, the Applicant argued that there was no incentive or motivation to change from IM delivery to the ID route. In this regard, the Applicant argued in response to the Final Action that if there had in fact existed any desire to use a short-needle device for the delivery of a flu vaccine, it would have been undertaken long before the device of D4, since "suitable devices for the mass intradermal delivery of vaccines existed", pointing to the jet injector of D8 and the short needle device of US patent 4,886,499 which had

published in December 1989.

[76] We do not agree that there was no motivation to use the ID route for flu vaccination. The motivation always existed, on the basis of the need to conserve valuable vaccine in certain circumstances. But it was oftentimes impractical to do so because of the skill required to execute the Mantoux technique on a mass scale and/or undesirable in view of the risks associated with using a jet injector. With the advent of the short needle device of D4, these obstacles were removed and the skilled person would have realized that there was a practical means to deliver split trivalent vaccines intradermally.

[77] We also do not agree with the Applicant's argument that suitable devices for mass vaccination existed long before D4. We have already established at [30] that the skilled person would know jet injectors were not recommended by the WHO for mass vaccination campaigns because of the transmission of blood-borne pathogens between vaccinees. With regard to the US patent, this is a personal portable device worn by the patient which employs a needle-driving means and a pump which allows for the gradual release of a drug over long periods of time. We do not agree the skilled person would have considered this device to be practical for the mass administration of a flu vaccine. These arguments do not change our conclusion that the skilled person would find a practical alternative in D4 to injection by the Mantoux technique or jet-injector.

[78] The other main line of argumentation presented by the Applicant was that if the skilled person had wanted to change from the conventional and recommended IM route to the ID route, they would not have employed the known trivalent split one dose vaccine because: (i) whole virus is known to be more immunogenic than split, (ii) trivalent vaccines are less immunogenic than bi- or monovalent vaccines, and (iii) the efficacy of using only one dose without a booster by the ID route was not known. According to the Applicant, the skilled person would have expected each of these modifications to reduce vaccine efficacy. Based on these statements, the Applicant is suggesting the skilled person would more likely opt for a mono- or bivalent, whole cell vaccine that would be delivered in two doses.

[79] We do not agree. The skilled person at the claim date knew the WHO mandated seasonal flu vaccines to contain three strains; one each of (sub)type A-H1N1, A-H3N2 and B. For this reason, the skilled person at the claim date would not have prepared a seasonal flu vaccine for mass immunization containing anything but these three strains. Moreover, knowing that whole virus vaccines were as immunogenic in adults as split vaccines, but that whole virus vaccines were contraindicated in subjects under 12, the skilled person would not have elected to use a whole virus over a split virus vaccine. Finally, the skilled

person would have expected protection would be achieved in subjects older than 9 years (and younger children previously vaccinated against the flu) after a single dose. Notably, this last point does not apply to the kit claims since they do not contain a limitation on how many doses are required to achieve protection. For these reasons, we conclude that on the balance of probabilities the skilled person would have used the conventional trivalent split vaccine with the device of D4.

[80] For the reasons stated above, we find that none of independent claims 1, 12, 15 and 20 require any degree of invention.

The Dependent Claims

[81] For the reasons that follow, we also find that none of the dependent claims 2-11, 13, 14, 16-19, 21 or 22 require any degree of invention.

[82] As mentioned above, documents D3 and D5 disclose features of some of the dependent claims. Document D3 teaches using a combination of cholesterol, a saponin and the adjuvant 3D-MPL in the formulation of flu vaccines. These formulating agents are defined in claims 10 and 11. Document D5 teaches using sodium deoxycholoate and Tween™ 80 in preparing split antigen preparations for one-dose trivalent, split-virus flu vaccines that can be administered intradermally. These splitting agents are defined in claims 5, 6 and 7.

[83] The panel notes that the additional features of claims 2, 8, 9, 18 and 19, which include the antigens being egg-derived, standard ID dosing volumes and loading the device with the flu vaccine were within the common general knowledge.

[84] Having found the independent claims to be obvious, we also find dependent claims 2, 5-11, 18 and 19 would have been obvious. These claims merely provide standard details relating to splitting, formulating and intradermal dosing of flu vaccines which were disclosed in the prior art and/or were part of the common general knowledge. Moreover, the Applicant never contended the features of these claims lead to a further inventive step.

[85] At the hearing, the Applicant did distinguish the dependent claims which further specify the protection rates, seroconversion rate and conversion factors for two distinct age groups (18-60, and 60 years and older) which the vaccine was allegedly capable of achieving (claims 3, 4, 13, 14, 16, 17, 21 and 22). In particular, the Applicant submitted the present application demonstrates for the first time that intradermal vaccination is capable of meeting the high immunogenicity thresholds recited in the dependent claims 3 and 16, noting there is no

teaching in the prior art which would direct the skilled person seeking a vaccine to meet these thresholds towards an intradermal approach.

[86] As we have already established, the skilled person would not have expected the efficacy of the known vaccine to change if it was administered intradermally instead of by IM injection. In our view, the efficacy would be inherent to the specific vaccine formulation used, not the delivery method. Moreover, the efficacy would be unrelated to its inclusion in a kit.

[87] We therefore find that none of claims 3, 4, 13, 14, 16, 17, 21 and 22 involves an inventive step.

Conclusions

[88] Having found there is no inventive step over the prior art, it follows that claims 1-22 are obvious and do not comply with section 28.3 of the *Patent Act*.

RECOMMENDATION OF THE BOARD

[89] We recommend that the application be refused for lack of compliance with section 28.3 of the *Patent Act*, since the subject matter defined by the claims is obvious.

Cara Weir	Ed MacLaurin	Andrew Strong
Member	Member	Member

DECISION OF THE COMMISSIONER

[90] I concur with the findings and the recommendation of the Board that the application be refused for non-compliance with section 28.3 of the *Patent Act*. Therefore, in accordance with section 40 of the *Patent Act*, I hereby refuse the application.

[91] 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 18 day of September, 2014