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Case Number: T 0906/10 - 3.3.04

Application Number: 00992122.2

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Title of invention:
Compositions and methods for stimulating an immune response against infectious agents

Applicant:
Novartis Vaccines and Diagnostics, Inc.

Headword:
Vaccination per os/NOVARTIS

Relevant legal provisions:
EPC Art. 54, 56, 83, 84, 123(2)

Keyword:
"Main request - compliance with the requirements of Articles 54, 56, 83, 84 and 123(2) EPC (yes)"

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T 1020/03

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Case Number: T 0906/10 - 3.3.04

D E C I S I O N
of the Technical Board of Appeal 3.3.04
of 9 April 2013

Appellant: (Applicant)
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Decision under appeal:
Decision of the Examining Division of the European Patent Office posted 25 November 2009 refusing European patent application No. 00992122.2 pursuant to Article 97(2) EPC.

Composition of the Board:

Chairman: C. Rennie-Smith
Members: G. Alt
M. Montrone

Summary of facts and submissions

I. This is an appeal against the decision of the examining division to refuse the European patent application No. 00 992 122.2 on the basis of Article 97(2) EPC. The application has the title "Compositions and methods for stimulating an immune response against infectious agents". It claims the priority date of 18 October 1999 and was published under the Patent Corporation Treaty as International application No. WO 01/35993.

II. The following documents are referred to in the present decision:

D1 Infection and Immunity, vol. 67, no. 8, Aug. 1999, pages 4276-4279, Barackman, J.D. et al.

D2 WO 99/26654

D3 Options for the control of influenza III; Brown, L.E., Hampson, A.W., Webster, R.G., editors; 1996, pages 292-297, Katz, J.M. et al.

D6 WO 98/42375

D7 Vaccine, vol. 17, 1999, pages 695-704, Barchfeld, G.L. et al.

D8 Methods, vol. 19, pages 148-155, 1999, Del Giudice, G. et al.

D9 Infection and immunity, vol. 71, no. 12, 2003, pages 6850-6856, Bagley, K.C. et al.

D10 PNAS, vol. 105, February 5, 2008, pages 1644-1649, Song J.-H. et al.

D11 Infection and immunity, vol. 64, no. 3, 1996, pages 974-979, Di Tommaso, A. et al.

III. The independent claims 1 and 4 dealt with by the examining division in the decision under appeal read as follows:

"1. A composition comprising
(i) an immunogenic amount of a hemagglutinin antigen of an influenza virus, and
(ii) at least one heat-labile, mutant E. coli enterotoxin selected from the group consisting of LT-K63 and LT-R72, characterised in that the composition is for oral administration to a human and is in the form of ingestible tablets, buccal tablets, troches capsules, elixirs, suspensions, syrups or wafers.

4. Use of
(i) a hemagglutinin antigen of an influenza virus and
(ii) a heat-labile, mutant E. coli enterotoxin selected from the group consisting of LT-K63 and LT-R72, in the manufacture of a medicament for oral administration to a human to elicit an immune response."

IV. The examining division decided that the subject-matter of claim 1 was novel over the disclosure in documents D6 and D7. Although these documents disclosed compositions falling structurally under the terms of claim 1, the compositions so disclosed were for **intranasal** or **parenteral** administration. It was not appropriate to conclude on the basis of this disclosure

that they were also suitable for the claimed **oral** administration.

V. The examining division considered that the subject-matter of claims 1 and 4 lacked support in the description (Article 84 EPC) because if - like the examining division - one accepted the applicant's argument in relation to novelty that no inference to an **oral** application in humans could be drawn from data concerning the administration by a different mucosal route, i.e. **intranasal** administration, then, by the same token, no extrapolation to **oral** administration in humans could be made from data disclosed in the application concerning **intragastric** administration to mice.

VI. Moreover, the examining division held that the disclosure of the invention was insufficient with regard to claim 1 (Article 83 EPC), the main reason being that novelty of the composition of claim 1 had been acknowledged on the assumption that the preparations disclosed in documents D6 and D7 did not fulfil the feature of the claimed composition "for oral administration to a human", i.e. they were considered not to be suitable for such administration. It followed that in order to be suitable a composition had to have special properties, for example the antigen must be protected from degradation in the stomach. However, the description did not provide a single example of such a composition. It was certainly not sufficient simply to recite all possible vehicles known to be available for oral administration to humans such as tablets, troches, elixirs, etc.

VII. Finally, the examining division considered that the subject-matter of claims 1 and 4 lacked an inventive step (Article 56 EPC). The closest prior art was a document disclosing the immunization of mice with the composition of the application by the **parenteral** or **intranasal** route as disclosed in document D6 or D7. The difference between the subject-matter of claims 1 and 4 and this disclosure lay in the route of administration. The application disclosed **intragastric** administration of the composition to **mice**. There was however no data about **oral** administration, let alone about oral administration to **humans**. Hence, if the technical effect to be achieved by the oral administration was the immunisation of humans against influenza virus infection, then there was no evidence of such an effect. Therefore, this effect could not be used in the formulation of the problem which therefore had to be formulated simply as finding an alternative way to administer the prior art compositions to humans. The composition disclosed for example in document D6 was a non-toxic solution suitable for injection. It was obvious to give this solution to a human, i.e. to let the human drink this solution.

VIII. With the statement of the grounds of appeal the applicant (hereinafter "appellant") filed a new main request and two auxiliary requests. The main request differed from that dealt with in the decision under appeal in that (i) the word "human" had been replaced by the word "mammal" in claims 1 and 5 (the latter claim being the former claim 4), (ii) claims 4 and 10 had been added to specify that that the "mammal" was a "human", and in that (iii) claim 11 - reading: "The

composition of any of claims 1 to 4, for use in medicine." - had been added.

IX. In a communication the board indicated *inter alia* its preliminary view that the subject-matter of claim 1 was not novel. The board observed that it considered that the feature "for oral administration to a mammal" in the context of a claim to a product meant only that the product had to be "suitable" for administration via the oral route in a mammal. According to claim 1 a product suitable for oral administration to a mammal was the composition referred to in claim 1 in the form of a "suspension". In the board's view, suspensions with the claimed features were disclosed in documents D1, D6 and D7.

X. In response the appellant filed a new main request and a new auxiliary request I. Their claims were identical to those of the previous main request and auxiliary request I except that the reference to "suspensions" had been deleted from claim 1 of both requests. Auxiliary request II was maintained unamended.

XI. The written submissions made by the appellant, insofar as they are relevant for the present decision, may be summarised as follows:

Article 84 EPC - Support by the description

The experimental data about intragastric administration in the application supported the view that the compositions elicited an immune response when administered orally.

Article 83 EPC

The examples in the application described the administration of an influenza vaccine adjuvanted with LT-K63 or LT-R72 to the stomach of mice and good immune responses achieved after that intragastric administration. The tested composition was exposed to the gastric environment without protection. Thus, the examining division's assertion that the composition would need protection from degradation in order to be effective was wrong.

Other evidence had not been provided by the examining division. Therefore its objection did not meet the established standard, namely that any objection of insufficiency of disclosure needed to be supported by serious doubts substantiated by verifiable facts.

Article 56 EPC

Either of documents D6 or D7 could be the closest prior art document, although document D7 seemed to be closer because it disclosed a mucosal - intranasal - delivery route.

The problem to be solved was more ambitious than proposed by the examining division. It had to be formulated as: providing a more convenient way to administer the composition of document D6 or D7 while retaining the ability to elicit an anti-influenza immune response.

A skilled person at the priority date would have known that it was not possible to predict success for oral

administration based on results obtained after the intranasal administration of the same composition: compare the teaching in document D11 that LT-K63 was a good intranasal adjuvant for ovalbumin with the teaching in document D9 disclosing that this was not so when the combination was administered orally; see also the teaching in document D12 that the combination of LT-K63 and Herpes simplex Virus (HSV)2-protein gD2 elicited a good immune response when given intranasally, but not when given orally (see the data included in the appellant's submission of 6 December 2004).

A skilled person at the priority date would have also known that success with the administration of LT-K63 or LT-R72 as adjuvant in combination with a particular antigen via a particular mucosal route did not mean that these adjuvants would also work when administered with a different antigen via the same mucosal route: see document D4 suggesting that mutant LT adjuvants worked well in combination with keyhole limpet hemocyanin and intragastric administration, while they did not do so when administered in combination with influenza antigen after intragastric administration (see page 4401, first column).

The skilled person would have also been aware that the potency as an adjuvant differs between different LT mutants, see document D13. Thus, successful administration with one mutant, for example the oral administration of whole virus in combination with the mutant LT-G192, did not make it possible to predict success if another mutant was used.

Thus, the skilled person starting from the teaching in documents D6 or D7 would have had no reasonable expectation that the adjuvanted influenza compositions taught in these documents would be effective when administered orally. Therefore the claimed subject-matter involved an inventive step.

Requests

XII. The appellant requested that the decision under appeal be set aside and that the case be remitted to the department of first instance with an order to grant a patent based on the main request or on one of the auxiliary requests 1 or 2 all filed with its letter of 14 February 2013. Oral proceedings were requested in case of a decision which was adverse to the appellant.

Reasons for the decision

Decision under appeal

Support of the claims in the description - Article 84 EPC

1. The examining division was of the opinion that the claims lacked support because an extrapolation to the claimed oral administration could not be made on the basis of the data in the application disclosing only the intragastric administration (see section V above).

2. The requirement that the claims have support in the description means that the subject-matter of the claim must be taken from the description, or in other words, that it is not admissible to claim something which is

not described (Case Law of the Boards of Appeal, 6th edition 2010, II.B.4.1, first paragraph).

The boards have taken different views on the question of the quantity and quality of disclosure in the application that is necessary for claims to be considered as supported by the description. Some boards were of the view that purely formal support could not meet the requirement (Case Law of the Boards of Appeal, 6th edition 2010, II.B.4.1, third paragraph). On the other hand the board in decision T 1020/03 of 20 October 2004 stated that "[a] review of the discussions in the various drafts to be found in the preparatory material of the various meetings and conferences which ultimately led to the European Patent Convention 1973, suggests however that the requirement for support of the claims was viewed rather as a formal matter to ensure that the description and claims had the same extent" (see point 10 of the Reasons).

3. The board considers that claims 1 and 4 are both formally and substantively supported by the description (see points 6 to 8 and point 18 below). Hence, the board does not concur with the examining division's view.

Sufficiency of disclosure - Article 83 EPC

4. The examining division's objection of lack of sufficiency of disclosure with regard to claim 1 is essentially based on the consideration that the claimed composition had to have special properties in order to be suitable for oral administration, i.e. it had to be suitable in the sense that it is capable of eliciting

an influenza-virus specific antibody response. To that end the antigen had for example to be protected from degradation in the stomach. The application however did not disclose what these special properties were that ensured successful oral administration and how they could be achieved. In the examining division's view it was certainly not sufficient to refer to possible vehicles known to be available for oral administration such as tablets, capsules, elixirs, etc. (see section VI above).

5. Example 1.1.1 discloses that the vaccine compositions were composed of monovalent A/Beijing8-9/93 (H3N2) or A/Johannesburg/97 (H1N1) split virus influenza antigens as antigens and LT-K63, LT-R72 or wild-type LT as adjuvants, that they were formulated in phosphate-buffered saline and that the compositions prepared for intragastric administration included additionally 1.5% w/v sodium bicarbonate.

6. Accordingly, Examples 1.2.2, 1.2.3, 1.2.4 of the application describe the administration of vaccine compositions with different combinations of these antigens and adjuvants to the stomach of mice, i.e. intragastric adminstration. The appellant submits that the compositions were "exposed to the gastric environment without protection".

7. The results of these immunisations in terms of the level of serum IgG or mucosal IgA antibodies are shown in Figures 1, 3, 5 and 2, 4 and 7, respectively and the results in terms of the titer of the hemagglutinin inhibition activity in the serum are shown in Figure 6. The results demonstrate that by the intragastric

administration of the compositions IgG and IgA immune responses are achieved.

8. Hence, in view of the disclosure in the application itself the board is not persuaded by the examining division's argument that protection from degradation was needed in order that the vaccine compositions be effectively immunogenic.

Inventive step - Article 56 EPC

Closest prior art

9. The examining division considered either of documents D6 or D7 as the closest prior art (see section VII above).

10. It is established case law that the primary criterion that the closest prior art document has to fulfil is that it discloses subject-matter conceived for the same purpose or aiming at the same objective as the claimed subject-matter. A secondary criterion is the commonality of features (Case Law of the Board's of Appeal, 6th edition 2010, I.D.3.1).

11. The purpose of the composition according to claim 1 is that it is used for **oral**, i.e. **oral mucosal** and **gastrointestinal** immunisation against an **influenza virus infection** in a mammal (see point 20 below).

11.1 Document D6 discloses the **parenteral** and document D7 the **intranasal** immunisation of mice against an influenza virus infection. In contrast, document D3 discloses the **gastrointestinal** immunization of mice

with a combination of inactivated influenza virus and the Escherichia coli heat-labile enterotoxin mutant LT-G192 as adjuvant. The co-administration of the two compounds increased levels of antiviral serum IgG and mucosal IgA antibodies when compared to the administration of the antigen alone (see Figures 1 and 2). It is disclosed that mice receiving the inactivated virus in the presence of adjuvant were completely protected from infection in the upper (nose) and lower (lung) respiratory tract (see page 295, passage after "[9]").

11.2 Therefore, with regard to claims 1 to 4, the subject-matter of which is a product, the board considers document D3 and neither document D6 nor D7 as the closest prior art.

Problem and solution

12. The claimed composition and the one disclosed in document D3 differ in that

(i) a hemagglutinin antigen of an influenza virus and not whole virus is used as antigen;

(ii) the adjuvant compounds are the LT-K63 or LT-R72 mutants of the Escherichia coli heat-labile enterotoxin and not the LT-G192 mutant;

(iii) the composition is not in any of the forms mentioned in claim 1, but is a simple liquid.

13. In the absence of comparative data demonstrating an improvement over the properties of the composition

disclosed in document D3, the problem to be solved in the light of this document is the provision of an alternative composition for the oral immunisation against influenza virus infection.

14. The question of whether or not the claimed solution, i.e. the subject-matter of claims 1 to 4, can be regarded as a solution to the problem formulated above does not arise in view of the language of claim 1. The composition is explicitly defined in the claim as comprising an "immunogenic amount" of the antigen and as being "for", i.e. suitable for, "oral administration". Therefore, all compositions falling within claim 1 have to be considered as solving the problem.

15. Thus, the board disagrees with the examining division not only that in the absence of data in the application the technical effect "oral administration" could not be used in the formulation of the problem and also that, consequently, the problem had to be formulated as an alternative way to administer the prior art compositions to humans (see section VII above).

16. It follows from the observations in points 2 to 15 above that the reasons given in the decision under appeal are not persuasive.

Hence the appellant's request to set aside the decision under appeal is granted (see section XII above).

The appellant further requests that the case be remitted to the department of first instance with the order to grant a patent on the basis of either the main

claim request or of one of the auxiliary requests. Oral proceedings are requested in case of a decision which was adverse to the appellant (see section XII above).

17. Since the amendments introduced into the claims of the main and the two auxiliary requests clearly do not overcome the objections raised in the decision under appeal and in view of the board's reasons for finding that the objections in the decision under appeal are not justified, further examination of the patentability of the subject-matter of these requests is necessary. Therefore, before a decision on the appellant's request that the case be remitted to the department of first instance with the order to grant a patent can be taken, the board has to decide how to exercise the discretionary power given to it by Article 111(1) EPC, i.e. whether or not the case should be remitted to the first instance for further prosecution in accordance with Article 111(1) EPC, last half sentence. In view of the appellant's request which does not ask for remittal for further prosecution, but for grant and also for reasons of procedural efficiency the board has decided to deal with the case itself in accordance with Article 111(1) EPC, first half sentence of its second sentence.

Main request

Amendments - Article 123(2) EPC

18. The amended claims have the following basis in the application as originally filed:

– claims 1, 3, 8, 9, 11 in claim 11 and on page 12, lines 9 and 10;

– claims 2 and 7 on page 12, lines 10 and 11;

– claims 4 and 10 in claim 12; and

– claims 5 and 6 on page 13, lines 6 to 14.

19. The requirements of Article 123(2) EPC are fulfilled.

Requirements of Article 84 EPC

20. The present claims are both formally and substantively (see point 3 above) supported by the description for the reasons given in points 6 to 8 and 18 above. The claims also fulfil the other requirements of Article 84 EPC. In particular in relation to the clarity of claims 1, 5 and 11 and insofar as the expression "oral administration" is concerned, the board observes that - in the light of the reference to "buccal tablets" in claims 1 and 8 - the skilled person would understand that the expression "oral administration" encompasses two meanings, i.e. (i) the administration to the mouth and subsequent absorption of the therapeutic composition by the oral mucosa; and (ii) the administration via the mouth to the stomach with subsequent absorption of the composition by the mucosa of the gastrointestinal tract.

21. The requirements of Article 84 EPC are fulfilled.

Sufficiency of disclosure - Article 83 EPC

22. In view of the observations in point 6 above the board has no reason not to accept that the application (see in addition the disclosure on page 11, last paragraph to page 12, line 3 of the application) teaches the skilled person how to make the compositions referred to in the claims.

23. Claims 5 to 10 and 11 are drafted as claims to second and first medical uses, respectively. It is established case law that achieving the claimed therapeutic effect or, as far as claims to a first medical use are concerned, the therapeutic effect underlying the invention, is considered to be a functional technical feature of the claim. As a consequence, in order to fulfil the requirements of Article 83 EPC, unless this is already known to the skilled person at the priority date, the application must disclose the potential suitability of the product for the therapeutic application (see for example decision T 219/01, point 4 of the Reasons for the first and decision T 609/02, point 9 of the Reasons for the second medical use).

23.1 In view of the observations in points 7 and 8 above the board accepts that the application provides evidence for the suitability of the composition to induce an immune response after **oral intragastric** delivery (see also point 4 above).

23.2 There are no examples in the application disclosing the **oral mucosal** delivery of the formulations referred to in the claim, let alone results about an immune response, i.e. a therapeutic effect following this

route of administration. Moreover, there is no evidence before the board, in general or relating specifically to influenza vaccination, that at the priority date of the application the skilled person knew that an immune response is generated after oral mucosal administration.

23.3 However, in view of the mucosal delivery by other routes it is not completely unlikely that such a response is generated. Therefore the absence of positive evidence is not sufficient in the present case to come to the conclusion that an immune response is not generated. Under these circumstances there may be at best serious doubts that an immune response is induced.

23.4 It is established by the case law that in examination proceedings an objection of lack of sufficiency of disclosure can only be successful if the examining division or - as the case may be - the board substantiates its serious doubts by verifiable facts (Case Law of the Boards of Appeal, II.A.7, first paragraph).

In the present case the board has no such facts. It appears rather to have facts to the contrary. The post-published document D10 discloses that sublingual vaccination with influenza virus induced both systemic and mucosal antibody response that conferred protection against a challenge with a lethal dose of influenza virus. In summary, the board cannot come to the

conclusion that the compositions are not suitable to achieve a therapeutic effect after administration by the **oral mucosal** route.

24. The requirements of Article 83 EPC are fulfilled.

Novelty - Article 54 EPC

25. The subject-matter of independent claim 1 and its dependent claims 2 to 4 and also that of independent claim 11 is novel since none of the documents available in these proceedings discloses the combination referred to in claim 1 **in the form of either an ingestible tablet, a buccal tablet, a troche, a capsule, an elixir, a syrup or a wafer**.

26. The subject-matter of claim 5 and its dependent claims 6 to 10 is novel because none of the documents available in these proceedings discloses the combination referred to in claim 5 for the manufacture of a medicament **for oral administration** to a mammal.

27. The requirements of Article 54 EPC are fulfilled.

Inventive step - Article 56 EPC

Claims 1 to 4

28. The board's conclusions regarding the closest prior art document, formulation of the problem to be solved and its solution (see points 10 to 15 above) apply to present claims 1 to 4. It remains to be assessed whether or not the subject-matter of these claims is obvious.

Obviousness

29. Given the differences between the claimed subject-matter and that disclosed in document D3 (see point 13 above) a first question to be answered in relation to the assessment of the obviousness or non-obviousness of the subject-matter of claim 1 is whether or not the skilled person - starting from the disclosure in document D3 of a composition for the oral immunisation against influenza virus infection consisting of inactivated whole influenza virus as an antigen and the Escherichia coli enterotoxin mutant LT-G192 as an adjuvant and searching for an alternative composition for oral immunisation against influenza virus infection - would have chosen the compositions according to claim 1, i.e. compositions comprising a hemagglutinin antigen of an influenza virus and at least one Escherichia coli enterotoxin mutant, the mutant being either LT-K63 or LT-R72.

30. At the priority date it was known that mutant LT-G192 retains the toxicity of the wild-type enterotoxin to a large degree (see document D8, page 149, second column, first paragraph). In comparison, the mutant LT-R72 was known to be "several orders of magnitude less toxic than the LT-G192 mutant" and LT-K63 was considered as "fully nontoxic". Therefore both were considered as "very safe mucosal adjuvants after both intranasal and oral delivery (see document D8, last sentence).

30.1 Moreover, at the priority date LT-K63 and LT-R72 were known as good mucosal adjuvants in mice. In particular, after **intranasal** administration in mice, compositions

comprising influenza virus subunit antigens and LT-K63 or LT-R72 induced serum and mucosal antibodies (see documents D1 and D7). A combination of LT-K63 with keyhole limpet hemocyanin (see document D4, for example the title, the abstract and Figure 3) and a combination of LT-K63 with recombinant antigens from Helicobacter pylori (see document D5, page 355, first column, last 6 lines) induced immune responses after **oral** administration in mice.

30.2 Thus, although LT-G192 was perceived as a very stable and potent adjuvant and was therefore considered to be particularly suitable for immunisation via the oral route (see document D4, page 4401, first column, first paragraph), its toxicity would have motivated the skilled person to replace LT-G192 in the vaccine composition disclosed in document D3 with the functional but less toxic mutants LT-K63 or LT-R72.

31. At the priority date of the application the skilled person was aware that a disadvantage of vaccination with preparations containing inactivated whole pathogens is that, even though they are usually highly immunogenic, they may cause undesirable side effects (see document D2, page 1, paragraph 3) or even disease in immunosuppressed individuals through reversion to a more virulent phenotype (see document D5, last paragraph on page 349). This known disadvantage may have generally prompted the skilled person to avoid using whole pathogen-containing vaccines.

31.1 Some of the commercial influenza vaccines available at the priority date of the application, 18 October 1999, in fact already included "split virus or subunit

formulations"(see document D7, page 695, second column, second sentence).

However, these vaccines were for **parenteral**, and **not oral** administration (see document D7, page 695, second column, second sentence). The skilled person might have had doubts that these vaccines would be effective when used via the intragastric route because he or she would have perceived that the environment in the stomach is particularly hostile to them (see document D4, page 4405, first column lines 10 to 14).

31.2 Moreover, the following is disclosed in document D4 on page 4401, first column, second paragraph and on page 4404, second column, end of first paragraph, respectively:

"KLH was chosen in this comparative study as we have shown previously that several other antigens (including ovalbumin, tetanus toxoid, and purified surface antigen from influenza virus) induce very poor and variable immune responses when coadministered to the gastrointestinal tract with LT."

"The reasons for lack of response to ovalbumin observed in these experiments are not known. Although we do not know whether E112 and ovalbumin are able to resist degradation in the intestine, **we have found that ovalbumin in particular is a poor p.o.** [note by the board: "per os"] **bystander antigen** (7). More recently, E112 has been described as having adjuvant activity when immunized i.n. [note by the board: intranasal] with hemagglutinin from influenza virus (20) suggesting that the lack of response resulted from the route of

immunization rather than the mutation in the toxin." (emphasis added).

Additionally, document D11 discloses that a combination of ovalbumin and LT-K63 when administered **intranasally** induced an immune response.

31.3 In the board's view, the skilled person taking together these disclosures in document D4 and D11 would firstly have considered that an antigen which works well after nasal administration (document D11) would not necessarily do so after gastrointestinal administration (document D4).

In this respect the board notes that the appellant's argumentation as to why the skilled person would not have extrapolated the results from the intranasal administration to the oral administration in view of a combination of documents D11 and D9 and document D12 with the appellant's own data submitted in the year 2004 during the examination proceedings of the present application are not persuasive since document D9 and the appellant's data were available only after the priority date and could thus not have influenced the skilled person's motivation at the relevant point in time, i.e. the priority date.

31.4 Moreover and secondly, the skilled person would have understood from the first cited statement from document D4 above, and in particular when this statement is read in the light of the second statement that ovalbumin is a poor oral bystander antigen, that the authors of document D4 consider that also purified surface antigen

from influenza virus has poor antigenic properties when administered intragastrically.

31.5 The board concludes therefore that in the light of these observations the skilled person would not be motivated to use a hemagglutinin antigen of an influenza virus in a vaccine formulation meant for **oral intragastric** administration and therefore that it was not obvious to provide the now claimed composition for **oral intragastric** administration.

32. As to the question of whether or not the skilled person would be motivated to provide the claimed composition for **oral mucosal** administration the board notes the following.

33. Of the documents available in these proceedings and which are published before the priority date none appears to disclose vaccine delivery via the **oral mucosal** route. This seems to be particularly surprising when looking at document D8, a review article published in 1999 with the title "Mucosal delivery of vaccines". The article mentions nasal and intragastric immunisation and under the heading "Other Routes of Mucosal Immunisation" only intravaginal administration.

Moreover, there is no explicit disclosure, nor is it derivable from any of the present documents that the skilled person would consider that results from **intranasal** immunisation could be extrapolated to **oral mucosal** vaccination.

Under these evidential circumstances there is no basis on which it could be argued that the skilled person

would be motivated to provide the claimed composition for **oral mucosal** administration.

34. In view of the conclusion that the skilled person would not have provided the composition according to claims 1 to 4 in an obvious manner, the question of whether or not it was obvious to give that composition any of the forms mentioned in claim 1 is not decisive.

35. The subject-matter of claim 1 to 4 thus involves an inventive step.

Claims 5 to 11

36. Claim 11 relates to the first medical use of the composition defined in claims 1 to 4. Claim 5 is drafted as a second medical use claim and relates to the use of the compositions of claim 1 - except that they are not characterized by their form - for the manufacture of a medicament for oral administration to a mammal to elicit an immune response.

Closest prior art

37. Since the medical use is the essential aspect of claims to a first and second medical use, in the board's view one of the commercial influenza vaccine formulations available at the priority date (see document D7, page 695, second column, second sentence) is a more appropriate starting point for the assessment of obviousness than the disclosure in document D3 which rather relates to the investigation of the properties of heat-labile Escherichia coli enterotoxin as adjuvant.

38. It is derivable from document D7 that these commercial vaccines were parenterally (intramuscularly) administered as inactivated whole virus, split virus or subunit formulations (see document D7, page 695, second column, first and second sentence) and that a drawback of these formulations was *inter alia* that they induced only a poor mucosal IgA antibody response (see document D7, page 695, second column, third sentence). The parenteral route of administration was generally perceived as a disadvantage *inter alia* due to the absence of the possibility of self-administration, see document D5, page 354, second column, last paragraph highlighting the advantages of mucosal immunisation over "the traditional approach to vaccine delivery, involving im. injection".

Problem and solution

39. Hence, the problem to be solved in the light of the traditional way of influenza vaccination was the provision of an improved way of influenza vaccination, both in terms of IgA antibody response and ease of administration.

40. The question of whether or not it is plausible that the claimed solution indeed solves the problem does not arise because the therapeutic effect is a feature of the claim: "for use in medicine" (claim 11); "to elicit an immune response" (claim 5).

Obviousness

41. At the priority date the mucosal delivery of vaccines, in particular their oral delivery, was generally

considered to be advantageous, see the abstract of document D8: "Oral delivery represents one of the most pursued approaches for large-scale human vaccination."

Thus, in the present case the evaluation of the obviousness of the claimed subject-matter turns on the question of whether or not the skilled person would have been motivated to provide the compositions referred to in claims 5 and 11 for oral administration.

42. The board's finding of the non-obviousness of the compositions according to claims 1 to 4 is exclusively based on the lack of motivation of the skilled person to provide the claimed composition for oral administration (see point 31.5 above). Therefore the considerations in points 29 to 34 also apply in the present context. They lead to the conclusion that the skilled person would not have provided the claimed composition for oral administration , i.e. neither via the mucosae of the mouth nor via the gastrointestinal tract, if he or she was aiming at providing an alternative way of vaccination, let alone an improved way. Thus, the subject-matter of claims 5, its dependent claims 6 to 10 and claim 11 involves an inventive step.

43. The requirements of Article 56 EPC are fulfilled.

Right to be heard - Article 113 EPC

44. In the board's judgement it follows from the above observations that claims 1 to 11 of the main request fulfil the requirements for patentability under the EPC. Hence, the appellant's request that the case be

remitted to the department of first instance with the order to grant a patent on the basis of the main claim request is allowed. The appellant is not adversely affected by this decision. Consequently, the board could take it without hearing the appellant at oral proceedings.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the department of first instance with the order to grant a patent on the basis of claims 1 to 11 of the main request filed with the letter of 14 February 2013.

The Registrar: The Chairman:

P. Cremona C. Rennie-Smith