BESCHWERDEKAMMERN DES EUROPÄISCHEN PATENTAMTS

BOARDS OF APPEAL OF THE EUROPEAN PATENT OFFICE

CHAMBRES DE RECOURS DE L'OFFICE EUROPEEN DES BREVETS

Internal distribution code:
(A) [ ] Publication in OJ
(B) [ ] To Chairmen and Members
(C) [ ] To Chairmen
(D) [X] No distribution

Datasheet for the decision of 4 April 2013

Case Number: T 0291/09 - 3.3.04

Application Number: 00966084.6

Publication Number: 1216053

IPC: A61K 39/145, A61P 31/12

Language of the proceedings: EN

Title of invention:
Influenza vaccine

Patent Proprietor:
GlaxoSmithKline Biologicals S.A.
GlaxoSmithKline Biologicals, Niederlassung der SmithKline Beecham Pharma GmbH & Co. KG

Opponent:
Sanofi Pasteur, Inc.

Headword:
Influenza vaccine/GLAXOSMITHKLINE BIOLOGICALS

Relevant legal provisions:
EPC Art. 56
RPBA Art. 13

Keyword:
"Main request, auxiliary requests 1 and 4: admissibility (no)"
"Auxiliary requests 2 and 3: inventive step (no)"

Decisions cited:
T 0037/82

Catchword:
-

Europäisches Patentamt | European Patent Office | Office européen des brevets

Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0291/09 - 3.3.04

D E C I S I O N
of the Technical Board of Appeal 3.3.04
of 4 April 2013

Appellants: (Patent Proprietor 1)	GlaxoSmithKline Biologicals S.A. Rue de l'Institut, 89 BE-1330 Rixensart (BE)
(Patent Proprietor 2)	GlaxoSmithKline Biologicals, Niederlassung der SmithKline Beecham Pharma GmbH & Co. KG Zirkusstrasse 40 D-01069 Dresden (DE)
Representative:	Andrew Teuten Sagittarius IP Three Globeside Fieldhouse Lane GB-Marlow SL7 1HZ (GB)
Respondent: (Opponent)	Sanofi Pasteur, Inc. 1 Discovery Drive, Knerr Building 1 Swiftwater, PA 18034 (US)
Representative:	William Gwyn Cole avidity IP Kestrel House Falconry Court Baker's Lane Epping, Essex CM16 5DQ (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 15 December 2008 revoking European patent No. 1216053 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chair: M.-B. Tardo-Dino
Members: B. Claes
M. Montrone

Summary of Facts and Submissions

I. The appeal was lodged by the patent proprietors (appellants) against the decision of the opposition division, whereby the European patent No. 1 216 053 with the title "*Influenza vaccine*" and published as WO 01/22992 was revoked.

II. The sole opponent (respondent) had opposed the patent under Article 100(a) EPC, on the grounds of lack of novelty (Article 54 EPC) and lack of inventive step (Article 56 EPC), and under Articles 100(b) and 100(c) EPC.

III. The decision of the opposition division was based on a main request (patent as granted) and two auxiliary requests. The opposition division decided that the subject-matter of claim 17 of the main request was based on added matter (Article 100(c) EPC) and the subject-matter of claim 1 of both auxiliary requests lacked an inventive step (Article 56 EPC).

Claim 1 of auxiliary request 1 before the opposition division, which was identical to claim 1 of the patent as granted, read:

"1. A monovalent influenza vaccine composition comprising an influenza virus component which is a low dose of egg-derived influenza virus antigen from an influenza virus strain that is associated with a pandemic outbreak, or has the potential to be associated with a pandemic outbreak, in combination with a suitable adjuvant, wherein the low antigen dose is less than 15 µg of haemagglutinin per dose or no

more than 15 µg per combined dose of vaccine and wherein the adjuvant is a combination of aluminium hydroxide and aluminium phosphate."

Claim 1 of auxiliary request 2 before the opposition division read:

"1. A monovalent influenza vaccine composition comprising an influenza virus component which is a low dose of egg-derived influenza virus antigen from an influenza virus strain that is associated with a pandemic outbreak, or has the potential to be associated with a pandemic outbreak, in combination with a suitable adjuvant, wherein the low antigen dose is less than 15 µg of haemagglutinin per dose or no more than 15 µg per combined dose of vaccine and wherein the adjuvant is a combination of aluminium hydroxide and aluminium phosphate, **and wherein the antigen is selected from an H2 antigen such as H2N2 and an H5 antigen such as H5N1.**" (emphasis added by the board)

IV. With the statement of the grounds of appeal dated 10 April 2009 the appellants requested that the decision under appeal be set aside and the patent be maintained based on either a main request (identical to auxiliary request 1 before the opposition division), an auxiliary request 1 (identical to auxiliary request 2 before the opposition division) or a new auxiliary request 2.

Claim 1 of the new auxiliary request 2 read:

"1. A monovalent influenza vaccine composition comprising an influenza virus component which is a low dose of egg-derived influenza virus antigen from an influenza virus strain that is associated with a pandemic outbreak, or has the potential to be associated with a pandemic outbreak, in combination with a suitable adjuvant, wherein the low antigen dose is less than 15 µg of haemagglutinin per dose or no more than 15 µg per combined dose of vaccine and wherein the adjuvant is a combination of aluminium hydroxide and aluminium phosphate, **and wherein the antigen is an H5 antigen such as H5N1**." (emphasis added by the board)

V. In the reply dated 4 September 2009, the respondent requested that the appeal be dismissed and argued, *inter alia*, that the subject-matter of claim 1 of each request on file lacked inventive step (Article 56 EPC).

VI. The board summoned the parties to oral proceedings scheduled to take place on 4 April 2013.

VII. With a letter dated 4 March 2013 the appellants submitted a new main request and a new auxiliary request 1.

Claim 1 of the new main request read:

"1. Use of an influenza virus component which is a low dose of egg-derived influenza virus antigen from an influenza virus strain that is associated with a pandemic outbreak, or has the potential to be

associated with a pandemic outbreak, in combination with a suitable adjuvant, wherein the low antigen dose is less than 15 µg of haemagglutinin per dose and wherein the adjuvant is a combination of aluminium hydroxide and aluminium phosphate in the manufacture of a monovalent influenza vaccine composition for prevention of pandemic influenza virus infection in humans."

Claim 1 of the new auxiliary request 1 read:

"1. The use of below 10 µg or below 8 µg, or from 1 - 7.5 µg or from 1 - 5 µg of egg-derived influenza virus haemagglutinin antigen from a single strain of influenza associated with a pandemic outbreak or having the potential to be associated with a pandemic outbreak and of a combination of aluminium hydroxide and aluminium phosphate, in the manufacture of a vaccine lot for protection against pandemic influenza virus infection in humans."

Auxiliary requests 1 and 2 filed with the statement of the grounds of appeal (see section II, above), were renumbered as auxiliary requests 2 and 3, respectively.

VIII. With a subsequent letter dated 27 March 2013, the appellants submitted yet another new auxiliary request 1 (labelled as "Main Request Auxiliary A").

Claim 1 of this new auxiliary request 1 read:

"1. Use of an influenza virus component which is a low dose of egg-derived influenza virus antigen from an influenza virus strain that is associated with a

pandemic outbreak, or has the potential to be associated with a pandemic outbreak, in combination with a suitable adjuvant, wherein the low antigen dose is less than 15 µg of haemagglutinin per dose and wherein the adjuvant is a combination of aluminium hydroxide and aluminium phosphate in the manufacture of a monovalent influenza vaccine composition for prevention of pandemic influenza virus infection in an individual from a human population which is immunologically naïve to the haemagglutinin antigen subtype of said virus strain."

IX. Oral proceedings took place on 4 April 2013. The final requests of the parties at the end of the oral proceedings were as follows:

The appellants (patent proprietors) requested that the decision under appeal be set aside and that the patent be maintained on the basis of the claims of the following requests in the following order:
As the main request: the main request filed with the letter dated 4 March 2013 (see section VII, above);
As auxiliary request 1: auxiliary request 1 (Main Request Auxiliary A) filed with the letter of 27 March 2013 (see section VIII, above);
As auxiliary request 2: auxiliary request 1 filed with the statement setting out the grounds of appeal of 10 April 2009 (see sections III and IV, above);
A auxiliary request 3: auxiliary request 2 filed with the statement setting out the grounds of appeal of 10 April 2009 (see sections III and IV, above);
As auxiliary request 4: auxiliary request 1 filed with the letter dated 4 March 2013 (see section VII, above).

The respondent requested that the appeal be dismissed.

X. The following documents are cited in the present decision:

D5: Kistner *et al.* (1998), Vaccine, Vol. 16, No. 9/10, pages 960-968.

D5a: Kistner *et al.* (1999), in "*Inactivated Vaccines prepared in cell culture*", Brown *et al.* (Eds.), Dev. Biol. Stand., Basel, Krager, Vol. 98, pages 101-110.

D41: Nicholson *et al.* (1979), J. Biological Standardization, Vol. 7, pages 123-136.

D42: Declaration of Dr E. Neumeier dated 9 April 2009.

XI. The appellants' arguments can be summarised as follows:

Main request and auxiliary request 1 - admissibility

The requests had been filed in response to the summons for oral proceedings and complied with the principle of procedural economy and served the interests of procedural efficiency. Auxiliary request 1 was filed to overcome an objection raised by the respondent in its letter of 22 March 2013 about the uncertainty in the meaning of "pandemic influenza" virus. The scope of both requests was narrower and complied with Article 123(2) EPC in view of numerous references to prevention of influenza virus infection, in humans, in the application as filed. All the claims contained an explicit limitation to "pandemic" influenza strains and

the use of the vaccine in humans. The claims were now in the "Swiss-type" claim format. Parts in the main claim directed to multiple doses had been deleted as well as the claims to a kit.

The claims of these requests rendered the issues to be dealt with less complex as they eliminated discussion about priority issues. The use of the "Swiss-type" claim format rendered any issue of claim construction moot and certain contentious issues were no longer relevant.

The amendments in the claims of the main request and auxiliary request 1 did not create new substantive problems such as added matter or clarity.

The respondent had not requested the adjournment of the oral proceedings for reasons that insufficient time was available do deal with the requests.

The board had no obligation to follow decision T 162/09, but was to apply the principles of the Rules of Procedure of the Boards of Appeal (RPBA).

Auxiliary requests 2 and 3 - claim 1 - inventive step

Document (D41) did not represent the closest prior art, but rather document (D5a) which disclosed approaches to solving problems with production of antigen for pandemic influenza vaccines. The document therefore addressed a common purpose with the patent.

Document (D41) reported results of a clinical study in primed and unprimed subjects, shortly after the re-

emergence of the H1N1 subtype in 1977, with four types of monovalent influenza vaccines: one inactivated whole virus vaccine, two non-adsorbed purified surface antigen subunit vaccines, and one $Al(OH)_3$ adsorbed surface antigen subunit vaccine. As explained in document (D42), the H1N1 virus was however circulating at the time of the study. Inevitably therefore interference occurred between immune responses caused by a natural infection, and those induced by vaccination. None of the volunteer populations could be regarded as entirely without previous immunological experience to the H1N1 virus at the time of vaccination.

The difference between the claimed invention and the teaching in document (D41) resided in: 1) the selection of the strains; and 2) the adjuvant. The technical effect obtained with the claimed vaccine composition was the successful induction of an immune response against a potentially pandemic strain, in an unprimed population.

Starting from document (D41), the skilled person would at least attempt to maintain the efficacy of the vaccine as disclosed therein. Document (D41) demonstrated that, when comparable doses of the four vaccines under study were administered, similar responses were obtained within each group, i.e. the aluminium adsorbed subunit vaccine did not perform any better than the conventional whole virus vaccine or the non-adsorbed subunit one. The skilled person would therefore have no incentive to modify commercially available non-adjuvanted influenza vaccines (e.g. FluvirinTM or AdmuneTM as used in document (D41) both

of which are non-adsorbed vaccines) and explore approaches relying on more complex manufacturing processes. Based on the data disclosed in document (D41) the skilled person would rather continue working with the whole virus vaccine and have no incentive to look for adjuvant alternatives, let alone a combination of aluminium adjuvants in order to optimise the vaccine formulation.

There was not much teaching in document (D41) that the skilled person could rely on, other than that a low dose vaccine was effective - whether as a whole virus vaccine or an $Al(OH)_3$ adsorbed subunit vaccine - in a population which was likely to be already primed against the vaccine strain.

The patent convincingly demonstrated that the claimed composition was effective against H2N2, in a naive population, at a low dose. This data had been provided for the first time by the present inventors. This demonstrated a technical effect over the prior art and a valuable development in the field of pandemic influenza vaccines. Example 5 demonstrated that a monovalent whole virus vaccine with an HA antigen from an H2 strain and at a content of as low as 1.9 µg/dose was capable of eliciting an immune response equivalent to the control group (15 µg HA/dose, no aluminium) in the unprimed study group (< 30 years). The adjuvant had thus a bearing on the H2 strain, specifically when used at a low dose. It was the precise combination of these features that enabled the low dose adjuvanted vaccine to work in the unprimed population and therefore suitable in a pandemic situation. The same approach

should be used when the strain was H5.

Claim 1 was to a low-dose monovalent vaccine composition comprising H2 or H5 and adjuvanted with a combination of $Al(OH)_3$ and aluminium phosphate adjuvant. The prior art disclosed neither a human influenza vaccine comprising such an adjuvant nor a human influenza vaccine comprising an H2 or H5 strain nor a combination of said adjuvant and H2 or H5.

Starting from document (D41), the technical problem to be solved was how to design a low dose H2 or H5 based vaccine composition which was effective in its target population, i.e. a population of unprimed subjects.

Neither the respondent nor the opposition division had provided any tangible evidence to establish that the choice of the specific adjuvant as claimed and the choice of the specific influenza strain were obvious.

The adjuvant was neither taught nor suggested by the prior art. Moreover, no document on file taught or suggested to the skilled person to make an influenza vaccine using two sorts of aluminium adjuvants combined together.

Likewise, the prior art did not actually point to the specific H2 or H5 strains as obvious choices. It was not denied that H2 and H5 were among the non-circulating strains and were therefore available to the skilled person to choose from when looking at non-circulating strains. But in fact all the influenza strains currently known were already known to the skilled person at the priority date, i.e. the 14 non-

circulating strains including H2, H5, H7, H9 and the 2 currently circulating ones. The fact that these particular strains were among the strains known to the skilled person was not enough to establish obviousness of a vaccine as that claimed. There was nothing in document (D41) or in any of the prior art on file that motivated the skilled person to try to make a vaccine for a pandemic or potential pandemic threat that uses one or other of the claimed strains, let alone these strains with the claimed combination of adjuvants.

Document (D25), table 3, listed influenza landmarks in humans in this century. H2 was not present in the bottom half of Table 3 of document (D25). Therefore it was not responsible for recent human incidents of new influenza. H5 which was present in the bottom half of the table, was not the last strain to be associated with incidents in humans (it was followed by H9) and was reported in document (D25), page 38, third paragraph, as a "false alarm". Therefore at the time the patent was filed H2 and H5 would not have been obvious choices for the skilled person.

If nothing further had happened in terms of incidents of H5 in the human population since the filing date of the patent, it would certainly now be considered an unobvious choice for a pandemic vaccine. In order to find that H5 was an obvious choice in 1999 therefore, one would have to use impermissible hindsight knowledge of events that have taken place after the invention was made.

Auxiliary request 4 – admissibility

This request further simplified the case and was the last opportunity to maintain the patent.

XII. The respondent's arguments can be summarised as follows:

Main request and auxiliary request 1 – admissibility

Following the principles established in decision T 162/09 neither the main request nor auxiliary request 1, which was filed even later, should be admitted into the proceedings.

The amendments amounted to a fresh case. They were not foreseeable by the respondent and introduced for the first time the "Swiss-type" claim format for the prevention of pandemic influenza virus infection in humans. Furthermore, the amendments to the "Swiss-type" claim format did not conform to the format as endorsed in the decision G 5/83 of the Enlarged Board of Appeal. The amendments complicated the case and introduced a number of new issues for examination such as *inter alia* added matter and clarity.

The amendments resulted in a set of requests which could not be considered as converging.

Auxiliary requests 2 and 3 – claim 1 – inventive step

The similarities of the disclosure in document (D41) and the patent in suit were striking. Table 4 disclosed the vaccination of 24 vaccinees younger than 25 years with 3 µg doses of $Al(OH)_3$ adsorbed H1N1 virus. In 58%

of these vaccinees the subsequent H1 antibody response was satisfactory (≥ 40). Document (D41) therefore represented the closest prior art.

The patent in suit did not demonstrate any technical effect. It was known that if an influenza vaccine was adjuvanted with $Al(OH)_3$ in phosphate buffer, the resulting vaccine would only need to be administered at a dose containing one tenth the standard dose of haemagglutinin in order to be as effective as the non-adjuvanted vaccine (see document (D5a). The patent showed that the vaccine composition of Example 5, comprising 1.9 µg HA, was as effective as a dose of 15 µg of HA without adjuvant (that is about one eighth as much HA is required). From document (D5a) the skilled person, seeing that Example 5 employed $Al(OH)_3$ in phosphate buffer, would expect the vaccine to be ten times as effective as the non-adjuvanted equivalent, even if solid aluminium phosphate had not been added. Example 5 of the patent showed therefore no technical effect resulting from the additional use of a solid aluminium phosphate adjuvant as well as $Al(OH)_3$ in phosphate buffer adjuvant, as no enhancement in effectiveness was demonstrated over what occurred as a result of the use of $Al(OH)_3$ in phosphate buffer alone. No example was provided in the patent of the use of $Al(OH)_3$ and aluminium phosphate in the absence of phosphate buffer.

Claim 1 contained no limitation on the ratio of $Al(OH)_3$ to aluminium phosphate. If a technical effect was relied upon to support an argument that a claim met the requirements of Article 56 EPC, then this technical effect should be present over the whole scope of the

claim. The patent however did not demonstrate that any enhancement of effectiveness occurred by using a mixture of $Al(OH)_3$ and aluminium phosphate where the ratio of $Al(OH)_3$ to aluminium phosphate was very small (e.g. 1:100 or 1:1000). In such a case the burden of proof fell to the appellants and not the respondent to convince the board that a technical effect extended across the whole scope claimed.

The skilled person was already aware that $Al(OH)_3$ and aluminium phosphate together could be used to adjuvant an influenza vaccine, and this would have been an obvious way of solving the problem.

Document (D41) disclosed that effective influenza vaccines could be produced using $Al(OH)_3$ as adjuvant. The doses employed to administer to humans were below 15 µg HA in document (D41). The skilled person was aware that using $Al(OH)_3$ and aluminium phosphate would lead to a particularly effective influenza vaccine.

The limitation to H2 and H5 strains could not introduce an inventive feature. Example 3 of the patent carried out experiments on strains H1N1, H3N2 and B. At the end of paragraph [0105] the patent noted that the data on these strains allows the conclusion that low dose absorbed vaccine is suitable for use in a pandemic situation. If it was possible to generalise from H1N1, H3N2 or B to all possible strains, it also followed that the selection of any particular strain could not be inventive.

Document (D5) at page 961, left hand column referred to viral strains under consideration. The strains included

H1N1, H3N2 and B and, at lines 10 and 11, A/Singapore/1/57 (H2N2). Hence, the skilled person reading document (D5) would be aware that, when considering low dose vaccines that employ $Al(OH)_3$ and phosphate adjuvant, the H2N2 strain was considered appropriate in the same manner as H1N1, H3N2 and B. An analogous disclosure occurred in document (D5a) on page 102, heading "Virus strains", in line 6 of this passage. The skilled person would additionally have concluded that H2N2 was to be viewed in the same manner as H1N1, H3N2 and B.

Nothing "special" or "different" about the specific strain categories was derivable from the specification as originally filed or as granted. The limitation to H5 strains could not introduce an inventive feature for analogous reasons.

The patent contained no data relating to H5N1. Hence, the skilled person would not regard the disclosure of the patent plausible with regards to strain H5N1.

Auxiliary request 4 - admissibility

This request should not be admitted into the proceedings as claim 1 did not comply with the requirements of Article 84 EPC with respect to the definition of pandemic influenza virus in humans. The request was not convergent and reverted to a broader scope.

Reasons for the Decision

1. The appeal is admissible.

Main request and auxiliary request 1 - admissibility

2. These requests were filed one month and one week before the oral proceedings, respectively. Accordingly, they amount to an amendment of the case in the sense of Article 13 RPBA and in particular, since the changes occurred after arranging oral proceedings, the requests fall within the ambit of Article 13(3) RPBA. The board agrees with the appellants that the board's discretion is to be exercised with respect to the circumstances of each case.

3. The board observes that the main request was neither filed in response to new submissions by the respondent nor to a communication of the board and that no particular reasons were indicated by the appellants to justify the filing of the request at such a late stage. Furthermore, the newly introduced terms "pandemic influenza virus infection" - which was interpreted in various ways by the appellants during the proceedings - and "in humans" generated an issue if not of clarity, at least of claim construction demonstrating that amended claim 1 neither served the principle of procedural economy nor the principle of procedural efficiency. Moreover, the change of category of claim 1 - contrary to the appellants' contention - neither serves the principle of procedural economy nor the principle of procedural efficiency since it equally generates further issues to be discussed. Indeed, besides a change of category of the claim, the amended wording no longer covers the "use of a composition" but rather the "use of components of a composition" which, *inter alia*, could be interpreted as covering vaccines

containing more than 15 µg of haemagglutinin as opposed to the granted claims which were restricted to vaccines in which the amount of haemagglutinin was limited to 15 µg in total. Accordingly, the change in the scope of protection gives rise to an issue under Article 123(3) EPC.

4. The board accepts that auxiliary request 1 represents a response of the appellants to a submission of the respondent. However, the board notes that, as argued by the respondent, the introduced wording "individual from a human population" in claim 1 adds a further issue of clarity relating to the population concerned. Furthermore the change of category of claim, the change from "use of a composition" to "use of components of a composition" gives rise to the same issue under Article 123(3) EPC as mentioned in point 3 above.

5. In view of the above considerations the board decided not to admit the main request and auxiliary request 1 into the proceedings pursuant to Article 13(3) RPBA.

Auxiliary request 2 - claim 1

Formal matters and novelty (Article 54 EPC)

6. Despite the objections raised by the respondent in the appeal proceedings, both in writing and orally during the oral proceedings, the board decided that claim 1 of auxiliary request 2 complied with the requirements of Articles 84 and 123 EPC, thereby confirming the decision of the opposition division in this respect. In view of the board’s negative findings with respect to

inventive step (see further) however the board sees no necessity to reason its decision on these points.

7. The opponent had no novelty objections against the subject-matter of claim 1 of auxiliary request 2. The board has none either. The subject-matter of claim 1 is therefore considered to be novel (Article 54 EPC).

Inventive step (Article 56 EPC)

Construction of claim 1

8. Claim 1 concerns a monovalent influenza vaccine composition which comprises i) a low dose (less than 15 µg haemagglutinin) of an egg-derived influenza virus antigen from an influenza virus strain that is associated with a pandemic outbreak or has the potential to be associated with a pandemic outbreak, being H2 or H5, which are in combination with ii) a suitable adjuvant being a combination of aluminium hydroxide and aluminium phosphate.

9. Paragraph [0008] of the patent in suit defines the features of an influenza virus strain which provide it with the potential to cause a pandemic outbreak, i.e. such a virus strain: "*(...) contains a new haemagglutinin compared to the haemagglutinin in the currently circulating strains; it is capable of being transmitted horizontally in the human population; and it is pathogenic for humans. A new haemagglutinin may be one which has not been evident in the human population for an extended period of time, probably a number of decades, such as H2. Or it may be a haemagglutinin that has not been circulating in the*

human population before, for example H5, H9 or H6 which are found in birds. In either case the majority, or at least a large proportion of, or even the entire population has not previously encountered the antigen and is immunologically naïve to it."

10. The appellants have given great weight to the fact that the claimed vaccine is based on an influenza virus antigen which is from an influenza virus strain *that is associated with a pandemic outbreak or has the potential to be associated with a pandemic outbreak*. In view of paragraph [0008] of the patent, the board can concur with the appellants' view that therefore the claimed vaccine composition is to be considered effective to provide protection at low dose in human populations which are immunologically naive or unprimed with respect to the antigen used in the vaccine.

Closest prior art

11. In assessing whether or not a claimed invention meets the requirements of Article 56 EPC, the boards of appeal apply the "problem and solution" approach, which requires as a first step the identification of the closest prior art.

12. In the decision under appeal the opposition division considered document (D41) to represent the closest prior art in respect of the claim under consideration. The appellants have argued however that the closest prior art in this context was rather represented by the disclosure in either of documents (D5) or (D5a).

13. In accordance with the established case law of the boards of appeal, the closest prior art is a teaching in a document conceived for the same purpose or aiming at the same objective as the claimed invention and having the most relevant technical features in common, i.e. requiring the minimum of structural modifications to arrive at the claimed invention.

14. Documents (D5) and (D5a) have very similar disclosures and have the same authors. They disclose, as an alternative for the production of egg-derived influenza virus antigens for use in influenza vaccines, the production of such antigens in a serum-free cell culture system based on Vero cells (a continuous monkey kidney cell line). The documents disclose that the system is capable of producing high titre influenza virus on an industrial scale and the development of a candidate inactivated influenza whole virus vaccine utilising this system (see document (D5), page 961, left-hand column, lines 12 to 17; document (D5a), page 102, lines 6 to 9). Vero cell production is reported for a number of influenza A virus subtypes including H1N1, H2N2 and H3N2 (see e.g. document (D5), Table 2 and document (D5a), table 1). Both documents compare the immunogenicity of Vero cell- and egg-derived vaccine strains including subtypes H1N1 and H3N2 in mice (see document (D5), page 965 and (D5a), page 105, section "*Comparison of the immunogenicity of Vero cell and egg-derived vaccine strains*") and disclose the production of influenza vaccines which were in use for the seasonal vaccination in 1995/1996 and 1996/1997 (see document (D5), page 965 ff. and (D5a), page 105, ff., sections "*Influenza vaccine obtained using the serum-free Vero cell technology*" and

"*Further characterisation of the Vero cell derived vaccine*"). The vaccines disclosed are based on serial PBS 1:4 dilutions of a stock vaccine having an HA-antigen content of 15 µg/ml in PBS and $Al(OH)_3$ (aluminium hydroxide) as the adjuvant (see document (D5), page 962 and document (D5a), page 103, section "*Determination of the effective dose 50 (ED_{50}) of vaccine preparations*"). These vaccines are reported as the basis of clinical trials that had been initiated in the UK and Austria (see document (D5), page 967, right-hand column and document (D5a), page 108, both last sentence). In addition to the disclosure in document (D5), document (D5a) refers, in the introduction and in the context of possible shortfalls in influenza vaccine supply production in the case of a major pandemic, to certain drawbacks of egg-produced antigen (see page 101, section "*Introduction*", lines 7 to 10) and discloses successful immunogenicity studies in chimpanzees based on Vero cell produced low dose vaccines, including the H1N1 and H3N2 subtype, containing $Al(OH)_3$ as adjuvant (see pages 106 and 107, section "*Immunogenicity studies in chimpanzees*").

15. Document (D41) is an older document published in 1979 disclosing influenza vaccine production based on a H1N1 type A influenza strain which caused, as of the season 1977-1978, the so-called "Russian flu" pandemic which spread widely amongst persons then aged 23 years or younger in many countries both in the northern and southern hemisphere (see page 124, lines 2 to 9). The respondent has stressed the pandemic character of this outburst of H1N1 infection. Indeed, subtype H1N1 had not been detected anymore since 1957 so that only a large portion of the population of 23 or older in 1977

had experienced infection by viruses of the H1N1 subtype in the period 1947-1957 (see page 124, lines 9 to 20). Document (D41) discloses the production and use of *inter alia* the monovalent $Al(OH)_3$ adsorbed egg-derived subunit vaccine "Fluvirin" in individuals of the age group 12 to 25 years and the group being 26 years or older (see Table 4 and page 124, lines 42 to 44). The vaccines used to collect the data for Table 4 included low dose vaccines containing 3 or 9 µg HA per dose administered subcutaneously to both groups of volunteers. The 3 µg HA per dose vaccines led to HI titres which are considered as protective (≥ 40) in 58% of the tested young group of volunteers (24 individuals) after a single dose and reached 93% after a second dose. Similar results were obtained with 9 µg HA per dose.

16. The appellants have argued that the disclosure in document (D41) could not represent the closest prior art because the experiments disclosed therein were not conducted with a population which was naive or unprimed relative to the relevant virus strain. In fact the spread of the virus had already started as was also shown in document (D42). Document (41) concerned therefore a different objective.

16.1 The board notes, however, that the authors of document (D41) seem to have been well aware of this problem. In particular in the section entitled "*Serological studies, pre-existing antibody*" it is reported that indeed there were indications, based on HI titres before vaccination, that one school population had recently been exposed to H1N1 virus. However, all results from this school had been excluded from further analysis (see page 130, lines 9 to 12). Document (D41) then continues that:

"*HI antibody was infrequent in the serum of volunteers aged ≤25 years in all other centres, whereas 18% of the older volunteers had titres ≥ 40 (Table 1) (...) Although none of the volunteer populations could be regarded as entirely without previous immunological experience of H1N1 virus at the time of vaccination, volunteer* ***groups comprising individuals aged ≤ 25 years probably contained mainly unprimed individuals.*** *Since the H1N1 virus was in circulation during the period that the trial was in progress, the detection of high antibody titres in response to the first dose of vaccine in a few young volunteers, who were seronegative before vaccination, might be attributable to immunological "priming" brought about by natural infection before or around the time of vaccination*." (see page 130, lines 11 to 25, emphasis added by the board). The board concludes therefore from these passages in document (D41) that, although the authors admit a certain interference of the ongoing new spread of the H1N1 virus at the time of the experiments forming the basis for the published results, the tested and recorded population of volunteers aged ≤ 25 years, was mainly **unprimed**.

16.2 In this context, the board furthermore refers to paragraphs [0008] to [0012] of the patent in suit which report *inter alia* on the circumstances of the experiments based on H2N2 on which the invention is based (for paragraph [0008] see point 10, above). Paragraph [0009] of the patent in suit states that "*H2N2 influenza viruses circulated between 1957 and 1968 when they were displaced by the H3N2 subtype which caused the last pandemic of the last century. Today people who have previously been exposed to H2N2 are*

likely to be are [sic] *over thirty years of age. It has been suggested that an H2-containing virus might cause a new pandemic because a growing portion of the world population that was born after 1968 must be expected to be immunologically naive. To investigate whether this theoretical dichotomy of the population regarding H2 immunity is a true fact, a sero-epidemiological study was conducted in 400 individuals and antibodies to H2 were measured.*" Paragraph [0010] continues that "[t]*he results confirm the immunologically naïve status of those under 30 years of age since only 7 out of 200 subjects had a measurable antibody titer in the low range of 10 to 20*" and paragraph [0011] that "*a significant proportion of those aged over 30 years is still seropositive for H2, 30 years or more after infection. The number of seropositives (I-UT ≥ 10) is 90%.* In paragraph [0012] it is then concluded that "[t]*hese observations confirm the possibility that an H2 virus could spread in the population under 30 years. Taking into account the current demographics and the fact that people younger than 30 years represent a large part of the world population, it is possible that an H2 virus could cause a pandemic again."* The board considers that these passages in the patent demonstrate the similar circumstances in which the experiments of the patent were conducted as compared to the experimental circumstances in document (D41). In particular, it must be concluded that the younger populations experimented on in both document (D41) and the patent may not have been completely devoid of individuals which cannot directly be considered as unprimed, but were in both cases considered as a model population for the study of influenza vaccines in a

population which is naive or unprimed for the strain used.

16.3 In view of the above considerations, the board therefore considers that the argument of the appellant cannot disqualify document (D41) from being a candidate to represent the closest prior art as, similarly to the patent, it aims at establishing low dose monovalent influenza vaccine compositions based on an influenza virus strain associated with a pandemic outbreak which are effective in human populations which are immunologically naive or unprimed.

17. On the basis of the requirements referred to by the board in point 13 above and the claimed invention analysed in points 8 to 10 above the board considers document (D41) to represent the closest prior art rather than either of documents (D5) or (D5a) as it explicitly refers to low dose egg-derived influenza vaccine production with an antigen, which is from an influenza virus strain that is associated with a pandemic outbreak (i.e. 1977) or which had the potential to be associated with a pandemic outbreak, whereby the adjuvant is $Al(OH)_3$ and the vaccine is used in a population which is immunologically naive or unprimed.

Technical problem

18. There are two technical differences between the vaccine composition disclosed in document (D41) and the claimed vaccine composition, namely

i) the use of a different haemagglutinin from an influenza virus strain that is associated with a pandemic outbreak or has the potential to be associated with a pandemic outbreak (i.e. H2 or H5 in the latter instead of H1 in the former); and

ii) the additional use of aluminium phosphate as adjuvant in the latter as compared to solely $Al(OH)_3$ used in the former.

19. The appellants have argued that the technical effect obtained by the claimed vaccine composition is the successful induction of an immune response against a potentially pandemic strain in an unprimed population. Accordingly, it was argued that the objective technical problem was the provision of a low dose vaccine composition comprising a pandemic or potentially pandemic influenza strain which was effective in its target population of unprimed subjects. The solution was to rely on H2 or H5 (of specific pandemic or potentially pandemic strains) and the combination of the two aluminium-based adjuvants.

20. Accordingly and in view of the above considerations, the board is satisfied that for the purpose of the assessment of inventive step the objective problem to be solved corresponds to the one postulated by the appellants, namely the provision of a low dose vaccine composition comprising a pandemic or potentially pandemic influenza strain which is effective in a target population of unprimed subjects.

21. The board is satisfied that the patent demonstrates that this problem is solved. Indeed in respect of the

H2 antigen example 5 provides experimental support, whereas for the H5 antigen the board considers it, in the absence of contrary arguments, plausible that analogous experimentation would come to similar results.

Obviousness

22. The two technical differences between the vaccine composition disclosed in document (D41) and the claimed vaccine composition have been identified in point 18 above.

23. As to the first difference the board notes that it has not been argued by the appellants that it was the specific choice of the H2 or H5 antigen which particularly resulted in the technical effect obtained. It was rather argued that H2 and H5, in this context, were merely suitable examples of haemagglutinins of influenza viruses which at the relevant date were associated with a pandemic outbreak or had the potential to be associated with a pandemic outbreak. Indeed, different influenza type A viruses appear not to differ from the perspective of immunogenicity or antigenicity and therefore also not in their suitability to form the active ingredient in a human vaccine composition. The board thus considers that the specific selection of the H2 and H5 antigens in the claim cannot contribute in itself to the inventive character of the solution to the objective problem.

24. With respect to the second difference it has been argued by the appellants that the adjuvant as defined in claim 1, i.e. the combination of $Al(OH)_3$ and aluminium phosphate, had a bearing on the H2 strain

specifically when it was used in a low dose. It was in fact the precise combination of these features which made the invention: i.e. the low dose HA vaccines containing the combined adjuvant functioned in the relevant unprimed population and were therefore suitable in a pandemic situation. In this context the appellants referred to example 5 of the patent in suit, relating to low dose H2 based vaccines, to demonstrate the success of these vaccines. It has on the other hand been argued by the respondent that no specific technical effect was shown by the patent in suit which went beyond the technical effects known from the prior art when using low-dose influenza vaccines containing solely $Al(OH)_3$ as the adjuvant.

25. The board notes in this context, however, first, that the subject-matter of claim 1 is not restricted only to the H2 antigen, but as an alternative refers to the H5 antigen. Accordingly, any specific effects attributable to the adjuvant combination and the specific H2 antigen can only be relevant for a part of the subject-matter of this claim.

26. Furthermore and secondly, if the above arguments were relevant, the following considerations would seem of importance.

26.1 It was known in the prior art that an influenza vaccine composition comprising $Al(OH)_3$ was at least as effective at a dose of 1,5 µg HA as an analogous vaccine composition at a dose of 15 µg HA in the absence of $Al(OH)_3$ when tested in chimpanzees (see document (D5a), page 103, lines 14 to 19, page 108, lines 24 to 29 and table 5). Influenza vaccines comprising $Al(OH)_3$ as the

adjuvant could hence be administered at a dose comprising approximately a tenth of the standard dose of haemagglutinin and be still as effective as the vaccine comprising the standard dose but no adjuvant. The patent in suit similarly shows that the vaccine composition of example 5 comprising 1,9 µg HA and the $Al(OH)_3$ and aluminium phosphate combination adjuvant is about as effective as a dose of 15 µg HA without adjuvant (see the table contained in [0121]). Accordingly, example 5 of the patent in suit cannot be taken to provide evidence for a particular technical effect which results from the additional use of the aluminium phosphate in the adjuvant over the adjuvant comprising only $Al(OH)_3$ because no enhancement is demonstrated over what is expected to occur if $Al(OH)_3$ is used alone as an adjuvant. There is indeed no evidence or experiment in the patent in suit or even on file comparing the use of $Al(OH)_3$ alone or in combination with aluminium phosphate as an influenza vaccine adjuvant.

26.2 According to the established case law of the boards of appeal, features which do not contribute to the solution of the problem set are not to be considered in assessing the inventive step of a combination of features (see e.g. T 37/82, OJ EPO, 71 and Case law of the Boards of Appeal of the EPO, 7th Edition, 2013, I.D.9.5).

27. In view of the above considerations, the board has come to the conclusion that it has not been demonstrated that the adjuvant being a combination of $Al(OH)_3$ and aluminium phosphate has particular or general enhancing effects on the effectivity when aiming at reducing the

HA dose in the vaccine over the use of $Al(OH)_3$ alone as an adjuvant (see point 26.1 above). Accordingly, the board considers that the presence of the aluminium phosphate in the vaccines of the invention is a feature devoid of any technical effect and therefore without any technical relevance for the formulated solution (see point 21 above). Indeed the board considers that any technical feature in a claim that does not contribute to a technical effect cannot constitute a contribution which justifies an inventive activity (see point 26.2 above).

28. Accordingly, and in view of the fact that document (D41) itself discloses effective low dose influenza vaccines suitable for a pandemic outbreak comprising $Al(OH)_3$ as the adjuvant, the board comes to the conclusion that the subject-matter of claim 1 is plainly rendered obvious to a skilled person when looking for a solution to the problem formulated.

29. In view of the above considerations the subject matter of claim 1 lacks an inventive step (Article 56 EPC).

Auxiliary request 3 – claim 1

Formal matters and novelty (Article 54 EPC)

30. The board refers here to points 6 and 7 above which apply *mutatis mutandis* to claim 1 of auxiliary request 3.

Inventive step (Article 56 EPC)

31. The board refers here to the assessment of inventive step in the context of claim 1 of auxiliary request 2 which applies *mutatis mutandis* to claim 1 of auxiliary request 3. The subject-matter of claim 1 accordingly lacks inventive step (Article 56 EPC).

Auxiliary request 4 - admissibility

32. This request corresponds to auxiliary request 1 filed on 4 March 2013 and was presented by the appellant in an attempt to simplify matters (see section VII above).

33. The board notes however, that this request did not remove the issues related to the definition of pandemic influenza virus and, instead of comprising claims converging to subject-matter limited to take into account the contentious issues in the previous requests, reinstated subject-matter discussed in the context of the main request and auxiliary request 1.

34. In view of the above considerations the board decided not to admit the auxiliary request 4 into the proceedings.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar The Chair

P. Cremona M.-B. Tardo-Dino