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**Datasheet for the decision
of 1 October 2014**

Case Number: T 1493/09 - 3.3.04

Application Number: 03712047.4

Publication Number: 1492562

IPC: A61K39/12

Language of the proceedings: EN

Title of invention:

Virus-like particles of human papillomavirus

Applicant:

GlaxoSmithKline Biologicals S.A.

Headword:

Human papillomavirus vaccines/GLAXOSMITHKLINE

Relevant legal provisions:

EPC Art. 56

Keyword:

Inventive step - main request (no) - auxiliary request (no)

Decisions cited:

Catchword:

see points 20 to 22



**Beschwerdekammern
Boards of Appeal
Chambres de recours**

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Case Number: T 1493/09 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 1 October 2014

Appellant: GlaxoSmithKline Biologicals S.A.
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted on 16 February 2009 refusing European patent application No. 03712047.4 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairwoman G. Alt
Members: A. Chakravarty
M. Blasi

Summary of Facts and Submissions

- I. The appeal lies from the decision of the examining division to refuse European patent application No. 03 712 047 which was published as international application WO 03/077942.
- II. The decision under appeal dealt with a main and three auxiliary requests.
- III. The examining division took the view that the main request lacked novelty over prior art document D10 (see point 2.1 of the decision under appeal), the first auxiliary request lacked inventive step over closest prior art document D8 in combination with document D10 (see point 2.2(ii) of the decision under appeal). The second and third auxiliary requests were found to lack inventive step for the same reasons as auxiliary request 1.
- IV. With the statement of grounds of appeal, the appellant (applicant) submitted a main and only claim request.
- V. Following a communication of the board setting out its preliminary appreciation of the substantive and legal matters concerning the appeal, the appellant submitted a new main request and an auxiliary request, replacing the previous main request.

Claim 1 of the main request reads:

"1. A vaccine composition comprising VLPs containing L1 proteins or functional L1 protein derivatives from HPV16, HPV18, HPV 31 and HPV 45 genotypes wherein the immune response generated by the vaccine is at a level in which the protective effect of each VLP type is

still seen and wherein the vaccine composition comprises an adjuvant which is an aluminium salt".

This claim is identical to claim 1 of auxiliary request 1 considered by the examining division in its decision.

Claim 1 of the auxiliary request reads:

"1. A vaccine composition comprising VLPs containing L1 proteins or functional L1 protein derivatives from HPV16, HPV18, HPV 31 and HPV 45 genotypes wherein the immune response generated by the vaccine is at a level in which the protective effect of each VLP type is still seen and wherein the vaccine composition comprises an adjuvant which is an aluminium salt for use in the prevention or treatment of a disorder related to HPV infection".

This claim was not considered by the examining division.

VI. Oral proceedings before the board took place on 1 October 2014. The requests of the appellant were that the decision under appeal be set aside and that a patent be granted on the basis of the new main request filed with the letter dated 10 September 2014, or alternatively on the basis of auxiliary request 1 (sole auxiliary request) filed with the same letter.

At the end of the oral proceedings, the Chairwoman announced the decision of the board.

VII. The following documents are mentioned in this decision:

D8: Vaccine, vol. 19, 2001, pages 3733-3743, Palker, T. J. et al.

D10: Journal of the National Cancer Institute, vol. 93(4), 2001, pages 284-292, Harro, C. D. et al.

Annex 1, A and B: Abstracts from the 29th International Papillomavirus Conference, held August 21-25, 2014 in Seattle, USA

VIII. The arguments of the appellant can be summarised as follows:

Main Request

Inventive step (Article 56 EPC)

Claim 1

Document D10 disclosed vaccines directed to the same purpose as the invention, namely vaccines against human papilloma virus (HPV) providing protection against HPV associated cervical cancer. It also related to a human clinical trial of these vaccines.

Document D8 addressed a different problem, provision of a vaccine against both cervical cancer and genital warts and reported data from monkey studies. Since the animal model used could not support efficacy of a human vaccine, document D8 did not disclose an effective vaccine.

It followed, that for assessment of inventive step, document D10 should be regarded as closest prior art.

Document D10 disclosed a study of the safety and efficacy in humans of a HPV16 L1 virus like particle (VLP) vaccine. The efficacy of HPV16 L1 VLPs formulated

at different doses and used either as an unadjuvanted vaccine, with MF-59 as adjuvant or with alum as adjuvant was compared. The authors of document D10 reported that a high dose non-adjuvanted HPV16 L1 VLP vaccine was the most effective of the formulations tested. The equivalent vaccine adjuvanted with alum was not chosen for further clinical trials. The authors of document D10 concluded with the observation that the *"question of whether systemic administration with a VLP vaccine can confer protection under natural conditions must await the outcome of controlled efficacy trials"* (see page 291, final paragraph of the "Discussion" section).

At the end of the "Discussion" section of document D10, the authors remarked that a multivalent cancer vaccine would be needed to achieve broad protection and that *"a vaccine composed of the four HPV types seen most frequently in cervical cancer cases (types 16, 18, 31 and 45) would theoretically be able to protect against approximately 80% of cervical cancers"*.

Given the high risks and costs associated with vaccine development, the skilled person, aware of the disclosure of document D10, would not have risked departing from its preferred teaching and would have proceeded with a high dose unadjuvanted vaccine as an obvious next step. Even if the skilled person had considered preparing a multivalent vaccine including antigens from HPV serotypes 16, 18, 31 and 45, neither the choice of an L1 VLP based vaccine nor the choice of an alum adjuvant could be seen as suggested to the skilled person by the last sentence of document D10. In particular, alum as adjuvant would have been connected with too many uncertainties. The skilled person faced with the problem of provision of a vaccine capable of

protecting against the HPV types most frequently associated with cervical cancer, would not have modified the vaccines disclosed in document D10 to arrive at the claimed vaccine composition.

Furthermore, the claimed subject-matter would not have been obvious to the skilled person when starting from document D8. Document D8 disclosed a composition consisting of HPV L1 VLPs from serotypes 6, 11, 16 and 18 adjuvanted with alum. However, this was in the context of animal studies which represented an earlier step in the development of a vaccine than the "in human" studies of document D10. The skilled person knew that the animal model used was not predictive of efficacy in humans. Thus, the skilled person seeking to solve the problem of provision of an effective multivalent vaccine against HPVs would not have modified the composition disclosed in document D8 to arrive at the claimed vaccine because the (starting) composition was not known to be an effective vaccine in humans. Motivation to alter the composition of document D8 would have needed to have come from a further document. Should the skilled person have turned for instance to document D10 for further guidance, he would have been discouraged from maintaining alum as adjuvant since here it was reported that an unadjuvanted high dose vaccine was preferred.

Auxiliary Request 1

Inventive step (Article 56 EPC)

Claim 1

This claim was formulated as a second medical use claim in the "use limited product" format foreseen by Article

54(5) EPC. This format specifically required that the vaccine be for use in the prevention or treatment of a disorder related to HPV infection and as such set a higher bar with respect to evidence of ability to provide effective protection under natural conditions (i.e. in the cervical mucosa in the case of HPV cancer protection). Therefore, the problem to be solved was the provision of a multivalent HPV vaccine which is effective to prevent or treat HPV related disorders caused by each of the HPV serotypes included in the vaccine. Data in the application showed that a mixed L1 VLP vaccine of HPV serotypes 16, 18, 31 and 45 elicited a strong antibody response in a preclinical mouse model. Post published evidence, Annex 1, A and B, provided clinical efficacy data that had recently become available for a 9-valent HPV vaccine containing HPV LI VLPs of serotypes 6, 11, 16, 18, 31, 33, 45, 52 and 58 adjuvanted with an aluminium salt, *in casu* amorphous aluminum hydroxyphosphate sulphate. The data reported on phase III efficacy trials that had been submitted with the regulatory agencies for the product targeted to come to the market early 2015. The abstracts reported that a 9-valent HPV L1 vaccine comprising the serotypes mentioned in the present claims, showed efficacy and immunogenicity in humans.

Starting from document D10, and in the absence of any teaching in the prior art of immunogenicity of multivalent HPV vaccines in man, the skilled person would have had no expectation of achieving the solution to the objective technical problem of providing a multivalent HPV vaccine which is effective to prevent or treat HPV related disorders caused by each of the HPV serotypes included in the vaccine, due i.a. to the doubts about the alum adjuvant for the reasons given in relation to the main request.

Reasons for the Decision

1. The appeal is admissible.

Main request

Inventive step (Article 56 EPC)

Claim 1

The closest prior art

2. To assess 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. 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.
3. The examining division considered document D8 to represent the closest prior art for the subject-matter of claim 1 but this was disputed by the appellant who considered document D10 as closest prior art. The board concurs with the examining division for the following reasons.
4. The subject-matter of claim 1 is an at least tetra-valent vaccine composition comprising VLPs containing L1 proteins or functional L1 protein derivatives from

HPV 16, 18, 31 and 45 ("at least", see the term "comprising") which composition comprises an aluminium salt as adjuvant. The description discloses that the vaccine is intended to prevent cervical cancer (page 2, 5th full paragraph), preferably 80% or more of cervical cancers should be effectively protected against (page 4, 4th paragraph). It is further stated that the vaccine may be optionally formulated with VLPs which provide protection against genital warts (page 5, 2nd full paragraph). The purpose of the claimed composition can then be seen as providing a broad protection against HPVs, in particular those causing cervical cancer.

5. The vaccine disclosed in document D8 is composed of HPV L1 VLPs from serotypes 6, 11, 16 and 18 and adjuvanted with alum (see for example the abstract). According to said document, serotypes 16 and 18 are associated with cervical cancer and serotypes 6 and 11 with genital warts (page 3733, column 1 - column 2). It is further explained at page 3734 (column 1, 2nd full paragraph) that the study described sought to determine whether a combination vaccine can induce neutralising antibodies to more than one VLP type, which was reported to be possible (see for example the abstract).
6. Document D10 on the other hand is concerned with a study of the safety and efficacy in humans of an HPV16 L1 VLP vaccine (see title) and compares the effect of different adjuvants on protection (see the section on page 284, "Background").
7. Considering therefore that both the subject-matter of present claim 1 and the disclosure of document D8 concern multivalent HPV L1 VLP vaccines providing broad protection against HPVs including in particular those

causing cervical cancer, whereas document D10 is primarily concerned with a monovalent HPV L1 vaccine, the board concludes that document D8 discloses subject-matter conceived for the same purpose. Therefore the board decides that document D8 represents the closest state of the art for the purpose of the assessment of inventive step of the subject-matter of claim 1.

Technical problem and solution

8. The subject-matter of claim 1 differs from the composition disclosed in document D8 (page 3734, column 2, section 2.1, "*Preparation of virus-like particles*") in that it comprises VLPs containing L1 proteins from HPV serotypes 31 and 45 which are associated with cervical cancer, in addition to those from HPV serotypes 16 and 18. The claimed vaccine compositions may include further L1 (or other) proteins (see the term "comprising"). For instance, a composition further comprising L1 VLPs from HPV serotypes 6 and 11 (present in the vaccine disclosed in document D8) falls within the ambit of the claim.
9. The technical effect of this difference is that the claimed vaccine composition provides protection against HPV serotypes 31 and 45 in addition to protecting against those HPV serotypes present in the closest prior art composition.
10. In view of the closest prior art disclosed in document D8, the difference thereto and the technical effect of this difference and further considering the disclosure of the application for example at page 2, paragraphs 2 and 3, the problem to be solved by the claimed subject-matter is formulated as the provision of a broadly

effective vaccine against HPV, especially providing broad protection against cervical cancer.

11. In its decision refusing the application, the examining division did not question whether the subject-matter claimed effectively solves the problem. The board sees no reason to depart from the approach of the examining division.

Obviousness

12. The HPV serotypes associated with various disease conditions were known in the art. Document D8 at page 3733 in the introduction, states i.a. *"HPV types infecting the genital tract can be subdivided into 'low-risk' or 'high-risk', according to their association with cervical carcinoma [-]. Low risk HPV types -6, -11, -42, -43 and -44 are frequently associated with low-grade cervical intraepithelial neoplasia (CIN) and genital condyloma. [-] High-risk types of HPV, notably HPV-16, -18, -31, -33, -45 and others, are associated with nearly 100% of premalignant dysplasias and cervical cancer"*. This teaching is echoed in document D10 at page 291, last sentence which reads *"A vaccine composed of the four HPV types seen most frequently in cervical cancer (types 16, 18, 31, and 45) would theoretically be able to protect against approximately 80% of cervical cancers"*.
13. In the board's view, the skilled person seeking to solve the problem formulated in point 10 above and starting from the closest prior art document D8 would have considered it obvious to adapt the vaccine disclosed therein to additionally include L1 VLPs of HPV serotypes 31 and 45, known to be associated with cervical cancer because the resulting vaccine

- composition comprising proteins from HPV serotypes 16, 18, 31 and 45 was directly suggested in document D10 and also in document D8. Moreover, the compositions disclosed in document D8 were already adjuvanted with alum.
14. The appellant has argued that the skilled person seeking to solve the above formulated problem and therefore seeking to provide a vaccine effective in humans would not have contemplated directly applying the teaching of document D8 with respect to adjuvantation. In particular, it was argued that since document D8 only concerns animal studies, not suitable to predict protective efficacy in humans, the skilled person would have needed to seek further teaching with respect to this. Document D10, which is concerned with a trial in humans, taught that a high dose unadjuvanted L1 VLP vaccine was the most effective (page 291, column 2, paragraph 2). The skilled person would therefore not have proceeded with an alum adjuvanted vaccine as described in document D8.
 15. In fact, document D8 discloses only animal experiments in relation to the efficacy of the vaccine compositions tested therein. It is not disputed either that "in human" trials provide a more accurate insight into the final protective efficacy of a vaccine in humans.
 16. However, in the board's opinion, the skilled person seeking to solve the problem formulated above under point 10, would not be limited to considering only formulations for immediate use in human clinical trials. Additional animal testing such as described in document D8 and indeed in the present description in Example 3, can realistically be considered by the

- skilled person as a possible purpose for the claimed composition.
17. Even if the skilled person was seeking vaccines for direct "in human" use, the board notes that document D10 at page 290, column 1, "Discussion" reports that "*[t]he results presented here indicate that three intramuscular doses of 10 or 50 µg of HPV16 L1 VLP vaccine with no adjuvant, with alum, or with MF59 were well tolerated and highly immunogenic in normal human volunteers. Regardless of dose and whether or not adjuvant was present in the vaccine, each of the volunteers who received the vaccine demonstrated a serum immune response by 1 month after the second immunization (i.e., at month 2). The third immunization induced a further elevation in end point serum antibody titers in most instances*" (emphasis added by the board). It follows that the skilled person would expect to obtain a highly immunogenic vaccine using any of the tested adjuvants and with no adjuvant, regardless of which combination was eventually preferred by the authors of document D10.
 18. In conclusion, the board can see no teaching in document D10 that would persuade the skilled person that alum would not be an effective adjuvant for an HPV L1 VLP vaccine and can find no teaching that would have caused the skilled person to alter the adjuvant used in document D8.
 19. In summary, taking into account the teaching of documents D8 alone or in combination with document D10, the person skilled in the art would have arrived at the solution proposed by claim 1 of the main request without exercise of an inventive step. The requirements of Article 56 EPC are therefore not fulfilled.

Auxiliary request 1

Inventive step (Article 56 EPC)

Claim 1

20. Claim 1 of this request differs from claim 1 of the main request in that it is directed to the second medical use of the vaccine composition, i.e. it is directed to a vaccine composition for use in the prevention or treatment of a disorder related to HPV infection, as opposed to the product as such. The appellant stated that this claim type set a higher bar with respect to evidence on the efficacy as a vaccine, in particular requiring evidence of effective protection in humans.

21. Claim 1 of auxiliary request 1 includes the therapeutic effect ("prevention or treatment of a disorder related to HPV infection") as an explicit feature, while claim 1 of the main request does not. In other words, claim 1 of auxiliary request 1 is directed to a "vaccine composition" characterised in that it comprises VLPs containing HPV-derived proteins which is capable of generating a protective immune response for each HPV L1 protein present in the VLPs in the composition. In the board's view, the wording of claim 1 of the main request already implies that the claimed composition is an effective vaccine for the treatment of HPV-related disorders. In fact, this effect (the same as the one as explicitly recited in claim 1 of the auxiliary request) was already taken into account by the board when evaluating the inventive step of the subject-matter of claim 1 of the main request (see in particular points 4 to 10 above). Hence, the board considers that the assessment of inventive step for the subject-matter of

claim 1 of the main request according to the problem and solution approach set out at point 2 to 19 above applies to the subject-matter of claim 1 of the auxiliary request without any change in the reasoning.

22. The subject-matter of claim 1 of auxiliary request 1 therefore lacks an inventive step for the same reasons as the subject-matter of claim 1 of the main request. The requirements of Article 56 EPC are not fulfilled.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar:

The Chairwoman:



P. Cremona

G. Alt

Decision electronically authenticated