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Datasheet for the decision of 16 September 2022

Case Number: T 2007/17 - 3.2.02

Application Number: 11767067.9

Publication Number: 2605792

IPC: A61B17/20, A61B17/00, A61K39/00, A61K39/145, A61K9/14, A61M37/00

Language of the proceedings: EN

Title of invention:
SOLUBLE NEEDLE ARRAYS FOR DELIVERY OF INFLUENZA VACCINES

Patent Proprietor:
Seqirus UK Limited
Theraject, Inc.

Opponents:
Ahrens, Gabriele
GlaxoSmithKline Biologicals SA

Headword:

Relevant legal provisions:
EPC Art. 54, 56

Keyword:

Novelty - (yes)
Inventive step - (yes)

Decisions cited:

Catchword:

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

Boards of Appeal

Chambres de recours

Boards of Appeal of the
European Patent Office
Richard-Reitzner-Allee 8
85540 Haar
GERMANY
Tel. +49 (0)89 2399-0
Fax +49 (0)89 2399-4465

Case Number: T 2007/17 - 3.2.02

D E C I S I O N
of Technical Board of Appeal 3.2.02
of 16 September 2022

Appellant: (Opponent 1)	Ahrens, Gabriele Patentanwälte Einsel & Kollegen Jasperallee 1a 38102 Braunschweig (DE)
Representative:	Ahrens, Gabriele Patentanwälte Einsel & Kollegen Jasperallee 1A 38102 Braunschweig (DE)
Respondent: (Patent Proprietor 1)	Seqirus UK Limited Point Level 3, 29 Market Street Maidenhead, Berkshire SL6 8AA (GB)
Respondent: (Patent Proprietor 2)	Theraject, Inc. 39270 Paseo Padre Suite 112 Fremont, CA 94608-2916 (US)
Representative:	Carpmaels & Ransford LLP One Southampton Row London WC1B 5HA (GB)
Party as of right: (Opponent 2)	GlaxoSmithKline Biologicals SA Rue de l'Institut 89 1330 Rixensart (BE)
Representative:	Goddard, Carolyn Janice GlaxoSmithKline Global Patents (CN925.1) 980 Great West Road Brentford, Middlesex TW8 9GS (GB)

Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted on 7 July 2017 rejecting the opposition filed against European patent No. 2605792 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairman M. Alvazzi Delfrate
Members: S. Böttcher
C. Schmidt

Summary of Facts and Submissions

I. Opponent 1 filed an appeal against the decision of the opposition division to reject the opposition.

II. Oral proceedings before the board took place on 16 September 2022.

III. The appellant (opponent 1) requested that the decision under appeal be set aside and that the patent be revoked.

Opponent 2, who had the status of a party as of right, did not file any requests and did not take part in the oral proceedings.

The respondent (patent proprietor) requested that the appeal be dismissed and the patent be maintained as granted.

IV. Claim 1 of the patent as granted reads as follows.

"A skin patch comprising a plurality of solid biodegradable microneedles, wherein the microneedles comprise a mixture of (i) a biosoluble and biodegradable matrix material and (ii) a purified influenza virus surface antigen vaccine, wherein the vaccine comprises hemagglutinin and 5-30 µg of detergent per µg of hemagglutinin."

Claim 2 of the patent as granted reads as follows.

"A process for preparing a skin patch comprising a plurality of solid biodegradable microneedles, comprising steps of: (i) mixing a biosoluble and

biodegradable matrix material with a purified influenza virus surface antigen vaccine, wherein the vaccine comprises hemagglutinin and 5-30 µg of detergent per µg of hemagglutinin; and (ii) adding the mixture from step (i) to a mould containing cavities for forming microneedles."

Claim 3 of the patent as granted reads as follows.

"A skin patch comprising a plurality of solid biodegradable microneedles, wherein the microneedles comprise a mixture of (i) a biosoluble and biodegradable matrix material and (ii) a purified influenza virus surface antigen vaccine comprising hemagglutinin, wherein the amount of influenza virus hemagglutinin per patch is ≤ 16 µg per strain, wherein the patch comprises 5-30 µg of detergent per µg of hemagglutinin."

V. The following documents are referred to in this decision.

D1 Intradermal influenza vaccine delivery using skin-penetrating dissolvable vaccine microneedles, S. Oh et. al., Annual Meeting and Exposition, The AAPS Journal, Vol. 8, 2006

D2 Dissolving polymer microneedle patches for influenza vaccination, S. Sullivan et. al., Nature Medicine 16, 915 to 920, 2010

D9 WO 2011/151726

D10 WO 2001/151723

D14 WO 2004/105729

D15 Prescribing information for FLUZONE®

D16 Intradermal delivery of vaccines: A review of the literature and the potential for development for use in low- and middle-income countries. (2009)

Program for Appropriate Technology in Health.

D17 Summary of Product Characteristics for OPTAFLU™

D18 WO 2008/130587

D26 Flucelvax US Package Insert

VI. The arguments of the appellant may be summarized as follows.

Novelty over D9 and D10

D9 related to methods of administration of vaccines using biodegradable microneedles (page 1, line 13; page 6, lines 16 to 19 and line 27 to page 8, line 21; page 11, lines 33 to 34; claims 11 and 12). The vaccine could be an influenza vaccine (page 2, lines 8 to 9; page 4, lines 7 to 9; page 12, lines 7 to 29), for instance a purified surface antigen influenza vaccine comprising hemagglutinin, such as FLUVIRIN, AGRIPPAL and INFLUVAC (page 12, lines 12 to 16).

It was also mentioned that inactivated vaccines, i.e. whole virus, split virus and surface antigen, were suitable for intradermal injection (page 12, lines 9 to 10). Surface antigen vaccines contained fewer viral components than split virus or whole virus vaccines (page 12, lines 12 to 13). Since the person skilled in the art knew that fewer viral components reduced the risk of side effects, surface antigen vaccines would be preferred.

Hence, D9 disclosed a microneedle patch comprising a surface antigen vaccine as a preferred embodiment. Furthermore, the surface antigen vaccines mentioned in D9 contained a considerable amount of detergent (point 4.51 of the respondent's letter dated 3 April 2018).

D9 referred to detergents as a further component of vaccine products on page 20, first paragraph. In addition to a general range of detergent level (0.01 to 50 µg per µg of hemagglutinin), three examples of a high level of the detergent polysorbate 80 were explicitly mentioned (5 to 40 µg per µg, 5 to 30 µg per µg and 8 to 25 µg per µg). Hence, the person skilled in the art would have derived that the surface antigen vaccine of the microneedle patch of D9 could comprise 5 to 30 µg detergent per µg hemagglutinin, as claimed in claims 1 to 3. Since the claimed range was not narrow and not sufficiently far removed from the specific examples (5, 8, 25 and 30 µg per µg) of the whole range (0.01 to 50 µg per µg), it could not be considered as novel.

D10 contained essentially the same disclosure as D9 (page 7, lines 1 to 21; page 12, lines 14 to 31; page 20, second paragraph). With regard to the combination of claims 1, 10 or 11 and 17, D10 even disclosed a microneedle preparation from a liquid composition including a detergent. D10 also anticipated the claimed range of 5 to 30 µg per µg (page 20, lines 4 to 12). Hence, the above-mentioned conclusions also applied to D10.

Consequently, the subject-matter of claims 1 to 3 lacked novelty over D9 and D10.

Inventive step starting from D1 or D2

D1 related to administration of the influenza vaccine Fluzone by means of a biodegradable microneedle patch. According to D15 (page 5, third paragraph), Fluzone was a split virus antigen comprising hemagglutinin.

D2 also related to dissolving microneedle patches for influenza vaccination using an inactivated whole virus vaccine (page 916, left column, first paragraph; page 915, right column, last paragraph).

The subject-matter of claim 1 differed from the skin patches of D1 and D2 in that the vaccine was a purified surface antigen vaccine and in that the vaccine comprised 5 to 30 µg of detergent per µg of hemagglutinin.

These two distinguishing features solved the objective technical problem of providing an alternative microneedle skin patch.

To solve this problem, the person skilled in the art would resort to the commercially available vaccine Optaflu (D17) (or its US-equivalent Flucelvax (D26)), which was a surface antigen vaccine comprising about 8 to 26 µg detergent per µg hemagglutinin (paragraphs [0093] and [0094] of the patent, and D26, page 7). Optaflu was prepared from viruses which were grown in cell culture. The person skilled in the art was aware that this was advantageous over viruses grown in eggs, which could be allergenic (paragraph [0032] of the patent). Apart from that, as a surface antigen vaccine, Optaflu provided the advantage that the risk of side effects was reduced. Hence, the person skilled in the art would have chosen Optaflu as an alternative to the vaccine Fluzone used in D1 or the vaccine of D2.

D14 disclosed microneedles coated with a vaccine containing a certain amount of surfactant, i.e. detergent (paragraphs [00019] and [00020]). The requirement of mechanical stability was mentioned in paragraph [00018]. Based on the teaching of this

document, the person skilled in the art would have expected that a larger amount of detergent would have a positive effect also in solid microneedles.

D18 disclosed a microneedle patch, wherein the needles contained an influenza vaccine and a detergent.

Contrary to the statement in paragraph [0026] of the patent, D16 did not teach that biodegradable microneedle patches were incompatible with surface antigen vaccines having a high level of detergent. From D16, the person skilled in the art rather derived that solid, biodegradable microneedles offered several advantages and that microneedle devices had considerable promise (page 56, points 8.1 and 8.2). Furthermore, it was mentioned on page 34, first paragraph on the right, that biodegradable microneedles with sufficient strength had been achieved in preclinical studies. Thus, D16 did not convey a prejudice against a microneedle array made from a surface antigen vaccine having a large amount of detergent.

Hence, the large amount of detergent in Optaflu would not have discouraged the person skilled in the art from using this vaccine in a microneedle patch according to D1 or D2, despite D17 only disclosing the administration of Optaflu as an intramuscular injection (page 12, points 4. and 5.).

Therefore, the subject-matter of claim 1 lacked an inventive step.

VII. The arguments of the respondent may be summarized as follows.

Novelty over D9 and D10

D9 did not disclose the use of a purified surface antigen influenza vaccine, in combination with a high level of detergent, in a skin patch comprising a plurality of solid biodegradable microneedles.

To arrive at the subject-matter of the claims, the person skilled in the art would have to select features from the following three lists of equally preferred alternatives.

1. The vaccines could include no detergent at all, a low level of detergent or a high level of detergent, e.g. between 5 and 30 µg per µg (page 20, lines 1 to 3).

2. Suitable solid formulations of the vaccine could include biodegradable microneedles, coated microneedles or thin oral films (page 6, lines 18 to 29, page 6, line 26 to page 11, line 17, claims 11, 13 and 17).

3. Inactivated vaccines suitable for intradermal injection could be whole virus, split virus or surface antigen vaccines (page 12, lines 9 to 10).

D9 did not mention any advantage of a large amount of detergent over a low or zero amount, of biodegradable microneedles over coated microneedles or oral films, or of surface antigen vaccines over whole virus or split virus vaccines.

Hence, there was no specific pointer in D9 that would have led the person skilled in the art to directly and unambiguously derive the combination of features recited in claim 1 of the main request. The subject-

matter of claim 1 was therefore novel over D9.

Like D9, D10 did not express any preference for the particular combination of a high detergent level and solid, biodegradable microneedles when using purified surface antigen influenza vaccines. Although D10 mentioned a microneedle formulation containing detergent, it was silent as to the amount of detergent, and there was no hint that a high level of detergent was preferred. Hence, the subject-matter of claim 1 was also novel over D10.

Inventive step starting from D1 or D2

Starting from either D1 or D2, the objective technical problem was to provide a skin patch comprising a plurality of solid, biodegradable microneedles for intradermal delivery of a further influenza vaccine.

It was surprising that the solid, biodegradable microneedle format was also effective when it was used to deliver influenza vaccines containing high levels of detergent since none of the prior art documents provided any evidence to show that solid biodegradable microneedles were effective in these circumstances.

D16 taught that preparing suitable formulations for solid, biodegradable microneedles constituted a significant challenge for intradermal delivery, requiring further development work (page vii, third bullet point; page 43, Figure 9; pages 33 to 34, Table 12). Thus, the person skilled in the art would have been aware that formulating biodegradable microneedles with sufficient strength was not straightforward.

D14 discussed the potential effects of surfactants

(i.e. detergents) on vaccine formulations for coated microneedles. However, the structural properties of solid microneedles were different from those of coatings. Hence, D14 did not prompt the person skilled in the art to use a vaccine containing detergent in the range of 5 to 30 µg per µg for formulating a solid microneedle.

D18 did not teach how much detergent could be tolerated when formulating solid, biodegradable microneedles without a detrimental effect on the delivery of the vaccine.

The person skilled in the art would not consider using Optaflu since D17 did not mention that this vaccine was compatible with microneedles. Since there would have been no expectation of success with Optaflu, they would have chosen another commercially available vaccine (containing less detergent) or another administration route.

As the cited prior art did not contain any pointer towards the selection of a purified surface antigen vaccine with a high level of detergent for use in solid, biodegradable microneedles, the subject-matter of claims 1 to 3 was inventive.

Reasons for the Decision

1. The invention relates to the intradermal administration of a specific class of influenza vaccines containing large residual amounts of detergent using a specific intradermal administration route.

Claim 1 relates to a skin patch comprising a plurality

of solid biodegradable microneedles. The microneedles are made of a mixture of
(i) a biosoluble and biodegradable matrix material and
(ii) a purified influenza virus surface antigen vaccine.
The vaccine comprises hemagglutinin (HA) and 5 to 30 µg of detergent per µg of hemagglutinin.

2. Novelty over D9 or D10

D9 relates to a process for preparing a lyophilised vaccine antigen and to a vaccine formulated by this process.

It is mentioned that, among other vaccine formulations, a skin patch comprising a plurality of solid biodegradable microneedles can be prepared from the antigen vaccine by using a biosoluble and biodegradable matrix material (page 6, line 10 to page 7, line 10).

On page 12, lines 12 to 29, D9 discloses that a purified surface antigen influenza vaccine comprising hemagglutinin can be used in some embodiments of the invention, i.e. for preparing a lyophilised antigen and for the vaccine.

Further, it is mentioned that the vaccine products may include a detergent, for instance Polysorbate 80 at between 5 to 30 µg per µg of HA (page 20, first paragraph).

The board agrees with the respondent that, to arrive at the subject-matter of any of claims 1 to 3, the person skilled in the art would have to select features from the following three lists of alternatives.

1. Detergent level: The vaccines could include no detergent at all, a low level of detergent or a high level of detergent, e.g. between 5 and 30 µg per µg of HA (page 20, lines 1 to 3).

2. Vaccine formulation: Suitable solid formulations of the vaccine could include biodegradable microneedles, coated microneedles or thin oral films (page 6, lines 18 to 29, page 6, line 26 to page 11, line 17, claims 11, 13 and 17).

3. Vaccine type: Inactivated vaccines suitable for intradermal injection could be whole virus, split virus or surface antigen vaccines (page 12, lines 9 to 10).

There is no disclosure in D9 that one of the elements of the lists is preferred over the others.

The appellant asserted that surface antigen vaccines had the advantage of having fewer side effects than whole virus or split virus vaccines. However, no such advantage is mentioned in D9. Even if the person skilled in the art were aware of the advantage, they would not be prompted to select surface antigen vaccines for the preparation of microneedles.

The appellant further alleged that the claimed level of 5 to 30 µg detergent per µg of HA could not be regarded as novel as this range was not narrow and not sufficiently far removed from the specific examples (5, 8, 25 and 30 µg per µg) of the whole range (0.01 to 50 µg per µg). The board does not concur with this view since D9 does not disclose the range of 5 to 30 µg per µg as a selection from a broader range of 0.01 to 50 µg per µg. D9 rather discloses this range as an example of a high level of detergent. However, it cannot be

derived that this level of detergent is advantageous and should be preferred when preparing a vaccine for a microneedle patch.

D10 is very similar to D9. It relates to an antigen concentration procedure which does not involve lyophilisation and to a vaccine prepared by this process. The relevant passages cited by the appellant are even identical to those of D9 (page 7, lines 1 to 21; page 12, lines 14 to 31; page 20, second paragraph). However, although D10 discloses an influenza vaccine comprising a detergent for the preparation of solid biodegradable microneedles (combination of claims 1, 2, 10, 11 and 17), the person skilled in the art would still have to select the type of vaccine (surface antigen) and the amount of detergent comprised in the vaccine.

Consequently, the specific combination of a purified surface antigen influenza vaccine and a high level of detergent provided in the form of solid, biodegradable microneedles is not directly and unambiguously disclosed in D9 or D10. The subject-matter of claims 1 to 3 is therefore novel over D9 and D10.

3. Inventive step starting from D1 or D2

D1 relates to intradermal influenza vaccine delivery using dissolvable microneedles. The vaccine used (Fluzone) is a split virus vaccine and comprises HA and less than 2.2 µg of the detergent octylphenol ethoxylate per µg of HA (D15, table 5).

D2 also relates to dissolving microneedle patches for influenza vaccination using an inactivated whole virus vaccine (abstract).

As acknowledged by the appellant, D1 and D2 do not disclose that

1. the vaccine is a purified influenza virus surface antigen vaccine, and
2. the vaccine comprises 5 to 30 µg of detergent per µg of hemagglutinin.

These features jointly define a single class of vaccine. The objective technical problem may be considered that of providing intradermal delivery of a further different influenza vaccine.

The selection of a purified surface antigen vaccine comprising 5 to 30 µg of detergent per µg of HA for a microneedle patch was not rendered obvious by either of D14 or D18 and the common general knowledge of the person skilled in the art about the vaccine Optaflu (D17).

D14 discloses a patch of microneedles coated with a vaccine containing a certain amount of detergent to promote the solubilisation of the coating (paragraphs [00019] and [00020]). In paragraph [00018], it is mentioned that the coating should be homogeneous to provide for greater stability. D14 does not disclose any influence of the amount of detergent on the mechanical stability of the coating. Furthermore, the structural properties and the requirements with regard to mechanical stability of solid microneedles are different from those of coatings. Therefore, the person skilled in the art would not be prompted by the teaching of D14 relating to coated microneedles to change the vaccine used for the solid microneedles of D1 or D2.

D18 relates to producing microneedle patches. The biodegradable microneedles comprise a vaccine and a detergent (paragraphs [00032], [00036], [00042], [00086]), However, D18 is silent about the amount of detergent comprised in the vaccine. It would not be a matter of routine for the person skilled in the art to use a vaccine comprising the amount of detergent specified in the claims.

D17 and D26 provide evidence of the commercial availability of Optaflu and its US equivalent Flucelvax, respectively. Optaflu is a surface antigen vaccine comprising HA and about 8 to 26 µg of detergent per µg of HA.

The appellant mentioned some advantages of Optaflu over other commercially available vaccines and alleged that the person skilled in the art would have chosen this vaccine as an alternative to the one used in D1 or D2. However, the advantages referred to by the appellant relate to better patient compatibility due to fewer side effects. They would not prompt the person skilled in the art to choose Optaflu as an alternative vaccine in the microneedle patch of D1 or D2. Rather, the large amount of detergent, compared to Fluzone or to other commercially available vaccines, would discourage the person skilled in the art from using Optaflu. Furthermore, D17 discloses the administration of Optaflu solely as an intramuscular injection.

The board agrees with the respondent that the person skilled in the art would have been aware from D16 that preparing effective solid biodegradable microneedles containing a suitably formulated vaccine constituted a significant challenge (page vii, third bullet point,

table 12, pages 33, 34, "Weaknesses"). Hence, the teaching of D16 would have discouraged the person skilled in the art from considering the use of a different class of vaccines having a large amount of detergent in the microneedle patches of D1 or D2.

Hence, the prior art does not contain a pointer towards compatibility of a purified surface antigen vaccine containing a high level of detergent of 5 to 30 µg of detergent per µg of HA with the solid biodegradable microneedle format. Therefore, the subject-matter of claims 1 to 3 involves an inventive step.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

A. Chavinier-Tomsic M. Alvazzi Delfrate

Decision electronically authenticated