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Datasheet for the decision of 14 September 2021

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Language of the proceedings: EN

Title of invention:

Monoclonal antibodies capable of reacting with a plurality of influenza virus A subtypes

Patent Proprietor:

Pomona Ricerca S.r.l.

Opponents:

Strawman Limited
James Poole Limited

Headword:

Cross-neutralsing antibodies/POMONA RICERCA

Relevant legal provisions:

EPC Art. 83
RPBA Art. 12(2), 12(4)

Keyword:
Main request - sufficiency of disclosure (no);
auxiliary request 1 - admitted (no)

Decisions cited:
T 0431/96, T 0877/03

Catchword:

Europäisches Patentamt
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Beschwerdekammern

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Case Number: T 2416/18 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 14 September 2021

Appellant: (Patent Proprietor)	Pomona Ricerca S.r.l. Corso Einaudi 1 10128 Torino (IT)
Representative:	Germinario, Claudio Società Italiana Brevetti S.p.A. Piazza di Pietra 39 00186 Roma (IT)
Respondent I: (Opponent 1)	Strawman Limited Orchard Lea Horns Lane Combe, Witney Oxfordshire OX29 8NH (GB)
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Respondent II: (Opponent 2)	James Poole Limited One Southampton Row London WC1B 5HA (GB)
Representative:	Carpmaels & Ransford LLP One Southampton Row London WC1B 5HA (GB)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 12 July 2018 concerning maintenance of the European Patent No. 2274335 in amended form.**

Composition of the Board:

Chair	G. Alt
Members:	R. Morawetz
	R. Romandini

Summary of Facts and Submissions

I. The appeal of the patent proprietor (appellant) is against the interlocutory decision of the opposition division, which stated that, account being taken of the amendments in the form of auxiliary request 7, the patent and the invention to which it related met the requirements of the EPC (Article 101(3)(a) EPC).

II. The patent is entitled "*Monoclonal antibodies capable of reacting with a plurality of influenza virus A subtypes*". Claims 1, 2 and 4 of the patent as granted read as follows:

"1. A human monoclonal antibody directed against influenza A virus hemagglutinin antigen, characterized in that it is capable of binding to and neutralizing a plurality of subtypes of the influenza A virus, wherein said plurality of subtypes comprises at least one influenza A virus subtype containing hemagglutinin H1 and at least one influenza A virus subtype containing hemagglutinin H3.

2. A monoclonal antibody according to claim 1, comprising at least one heavy chain variable domain and at least one light chain variable domain, with the heavy chain variable domain having amino acid sequence SEQ ID NO:1 and the light chain variable domain having amino acid sequence SEQ ID NO:2.

4. The monoclonal antibody according to claim 1, which is capable of binding the hemagglutinin conformational epitope specifically recognized by the monoclonal antibody according to claim 2."

III. Two oppositions were filed against the patent in its entirety. The opposition proceedings were based, *inter alia*, on the ground for opposition under Article 100(b) EPC. Opponents 1 and 2 are respondents I and II in these appeal proceedings.

IV. The decision under appeal dealt with sets of claims according to a main request and according to auxiliary requests 1 to 7. The opposition division held, *inter alia,* that there was no evidence in the patent that, when following the selection method disclosed in paragraph [0055] of the patent, an antibody as claimed in claim 1 of the main request (which was identical to claim 1 as granted) could be reliably obtained from the individuals selected according to the selection method described. It concluded that the invention claimed in claim 1 of the main request did not meet the requirements of Article 83 EPC.

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

D7 Throsby M. et al., PLoS ONE (2008), Vol. 3, pages 1 to 15

D29 Burioni R. et al., New Microbiologica (2009), Vol. 32, pages 319 to 324

D30 Burioni R. et al., Virology (2010), Vol. 399, pages 144 to 152

D35 Clementi et al., PLoS ONE (2011), Vol. 6, pages 1 to 10 (D4, 12 February 2016)

D40 Corti D. et al., Science (2011), Vol. 333, pages 850 to 856

VI. With the statement of grounds of appeal, the appellant filed sets of claims according to a main request and according to auxiliary requests 1 to 3 and submitted arguments to the effect that, *inter alia*, the invention claimed in claim 1 of the main request (which was identical to claim 1 as granted) met the requirements of sufficiency of disclosure.

VII. In its reply, respondent II provided its counter-arguments.

VIII. In response, the appellant withdrew the main request and auxiliary request 1 which had been filed with the statement of grounds of appeal. Auxiliary requests 2 and 3, also filed with the statement of grounds of appeal, became the new main request (referred to in the following as the main request) and the new auxiliary request 1 (referred to in the following as auxiliary request 1), respectively.

Claim 1 of the main request is identical to claim 1 as granted (see section II above).

Claim 1 of auxiliary request 1 reads as follows (wherein the amendments over claim 1 of the main request are underlined):

"1. A human monoclonal antibody directed against influenza A virus hemagglutinin antigen, characterized in that it is capable of binding to and neutralizing a plurality of subtypes of the influenza A virus, wherein said plurality of subtypes comprises at least one influenza A virus subtype containing hemagglutinin H1 and at least one influenza A virus subtype containing hemagglutinin H3, <u>characterized in that said antibody is capable of binding the hemagglutinin conformational</u>

epitope specifically recognized by the monoclonal antibody whose heavy chain variable domain has the amino acid sequence SEQ ID NO:1 and whose light chain variable domain has the amino acid sequence SEQ ID NO:2."

IX. The board summoned the parties to oral proceedings, as requested by the appellant and respondent II, and issued a communication under Article 15(1) RPBA 2007, in which it indicated its preliminary opinion with respect to, *inter alia*, the sufficiency of disclosure of the invention claimed in claim 1 of the main request. With respect to auxiliary request 1, the board indicated that it was inclined to hold the request inadmissible under Article 12(4) RPBA 2007 for lack of substantiation and because it could have been presented in the opposition proceedings.

X. In response, respondent I announced that it would not be represented at the oral proceedings, while the appellant and respondent II made further submissions with respect to the format of the oral proceedings.

XI. Oral proceedings before the board were held in the videoconference format and in the absence of respondent I in accordance with Rule 115(2) EPC and Article 15(3) RPBA.

XII. At the end of the oral proceedings, the Chair announced the board's decision.

XIII. The appellant's arguments, submitted in writing and during the oral proceedings, are summarised as follows:

Main request - claim 1

Claimed invention - claim construction

The claimed antibody had to bind to an epitope shared at least by haemagglutinin of influenza viruses of subtypes H1 and H3.

Sufficiency of disclosure (Article 83 EPC)

Teaching of the patent

The fact that individuals having B cells capable of producing the claimed cross-reactive antibodies were rare was immaterial in assessing the sufficiency of disclosure since the patent described in paragraph [0055] selection criteria that allowed for the reliable identification of individuals who were highly likely to produce the antibody of claim 1.

Individuals who fulfilled the pre-selection criteria (1), (2) and (6) potentially produced antibodies against various influenza strains. Individuals who additionally fulfilled the selection criteria (3) to (5) produced polyclonal antibodies directed against epitopes from various vaccinia strains and therefore were thought to have a higher probability of producing antibodies capable of recognising at least one antigenic site that was not subject to changes, i.e. a conserved part of haemagglutinin. Individuals fulfilling all the selection criteria (1) to (6) were therefore highly likely to produce the antibody of claim 1.

Satisfying the selection criteria described in paragraph [0055] of the patent necessarily meant producing a strong polyclonal heterosubtypic antibody response.

That the patent provided the skilled person with the technical information necessary to put the claimed invention into practice was evidenced by the fact that following the procedure disclosed in the patent, one antibody, Fab28, with the claimed properties, was obtained. The patent thus described, inclusive of an example, one way of carrying out the claimed invention, in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.

The skilled person was able, following the teaching in the patent supplemented with their common general knowledge and with a reasonable amount of trial and error but without applying inventive step, to carry out the claimed invention across the whole scope claimed.

No experimental results had been provided to prove that repeating the selection procedure described in paragraph [0055] of the patent failed to lead to the claimed result.

Post-published evidence

Document D40 (see page 851, left-hand column, end of second paragraph), document D7 (see page 2, last paragraph, and page 3, third paragraph), document D29 (see page 320, left-hand column, second paragraph 3) and document D30 (see page 145, left-hand column, first paragraph) provided post-published confirmation of the suitability of the screening concept set out in paragraph [0055] of the patent.

Case law

It was accepted in the case law of the boards of appeal that the isolation of mAbs was a matter of routine (see e.g. decisions T 431/96 and T 877/03). In the case at hand, the virus isolates served as the antigen. Binding and neutralisation were readily testable.

Auxiliary request 1

Admittance (12(4) RPBA 2007)

The request had been filed at the earliest stage of the appeal proceedings in order to overcome the objections relating to the main request under Article 100(b) EPC which had been raised in the appealed decision. Claim 1 had been rendered more precise based on claim 4 as granted. It was more limited than the main request and should be admitted.

Whether or not the request could have been presented before the opposition division was a consideration within the framework of the RPBA 2020 but not under Article 12(4) RPBA 2007.

XIV. Respondent II's arguments, submitted in writing and during the oral proceedings, are summarised as follows:

Main request - claim 1

Claimed invention - claim construction

The claim defined the antibody using entirely functional language and was directed to a mere *desideratum*.

Sufficiency of disclosure (Article 83 EPC)

Teaching of the patent

Individuals producing cross-neutralising antibodies were extremely rare (see paragraphs [0012], [0021] and [0023] of the patent). Pursuant to paragraph [0055] of the patent, the selection of such rare individuals was based on the concept of healthy donors and on serological testing.

There was no evidence on file supporting the healthy donor concept reflected in criteria (1), (2) and (6) of the selection method and there were several reasons why the serological tests mentioned in criteria (3) to (5) could not provide a useful selection for individuals that produced cross-neutralising mAbs.

These tests were dilution tests performed with polyclonal sera, i.e. with a heterogenous mixture of antibodies recognising different epitopes. These tests could not distinguish between antibodies that had cross-reactivity and antibodies that had no cross-reactivity.

Moreover, sera were tested against entire virus isolates and not against the haemagglutinin antigen specifically. There was no assay for cross-reactive monoclonal antibodies (mAbs) in the entire selection process described in paragraph [0055] of the patent.

The serological tests simply provided a read-out for individuals who had been exposed to the influenza strains tested for and produced antibodies against these strains. These antibodies were most likely separate antibodies recognising different epitopes.

There was no scientifically credible reason why the selection criteria in the patent provided any meaningful selection of the "rare individuals" on which the patent relied, and so these criteria appeared to be arbitrary with respect to the selection of cross-neutralising antibodies.

There was no evidence on file supporting the appellant's assertion that individuals fulfilling criteria (1) to (6) had an increased chance of producing cross-reactive mAbs.

The fact that a single antibody, Fab28, had been identified from the blood of a patient selected according to the criteria in paragraph [0055] of the patent did not mean that the antibody was identified because the patient was identified using those criteria. There were no comparative data in the patent to show that the patient selection criteria recited in the patent increased the skilled person's chances of finding a cross-neutralising antibody, versus "brute force" screening of large numbers of samples.

The arbitrary nature of the screening was demonstrated by the properties of antibody Fab28, the one antibody disclosed in the patent. The antibody did not

detectably neutralise any modern H3N2 strain circulating after 1975 (see document D35, Table 1), showing a disconnect between the tests in paragraph [0055] of the patent.

Fab28 represented a "*single lucky event*" and finding other cross-neutralising antibodies was a chance event. Relying on chance for reproducibility amounted to an undue burden in the absence of evidence that such chance events occurred frequently enough and could be identified to guarantee success.

Since the patent had been revoked, the onus was on the patent proprietor, as the appellant, to present a detailed line of argument as to why the decision under appeal was wrong (see also decision T 30/15).

Based on the technical teaching of the patent, the skilled person would not have been able to obtain further antibodies of claim 1 without undue burden.

Post-published evidence

Document D40 referred to donors who had been previously found to produce a strong heterosubtypic antibody response (see page 851, left-hand column) but did not disclose what the selection criteria had been. Reference (9) of document D40 mentioned in that context was not in the appeal proceedings.

Document D7 (see page 2, page 3) looked at a different cell type, memory B cells, and used donors that had been recently vaccinated, contrary to the selection criteria in paragraph [0055] of the patent.

The selection criteria in document D29 (see page 320, left-hand column) and document D30 (see page 145, left-hand column, and page 149, right-hand column) did not match the criteria set out in paragraph [0055] of the patent either.

Therefore, none of documents D40, D7, D29 or D30 provided evidence of an increased probability of finding cross-reactive mAbs when following the teaching of paragraph [0055] of the patent.

Case law

There was a fundamental difference between the cases relied on by the appellant and the patent. Each of these cases related to a single antigen and the steps required to identify antibodies to that single antigen.

Auxiliary request 1

Admittance (Article 12(4) RPBA 2007)

Auxiliary request 1 should be held inadmissible. It differed from the main request by the introduction of the subject-matter of claim 4 as granted into claim 1. Claim 4 as granted had been deleted from the claim requests pursued by the appellant in the opposition proceedings. If the appellant had wanted to defend that subject-matter, it could and should have done so in the opposition proceedings.

No supporting arguments as to why this request overcame a lack of sufficiency of disclosure were provided in the statement of grounds of appeal, or in response to the respondent's reply, or in response to the board's preliminary opinion. The re-introduction of the

subject-matter of dependent claim 4 as granted could not be considered a response to any aspect of the decision under appeal.

XV. Respondent I did not submit any arguments or requests during the appeal proceedings.

XVI. The appellant requested that the decision under appeal be set aside and that the patent be maintained in amended form on the basis of the set of claims of the main request, filed as auxiliary request 2 with the statement of grounds of appeal, or alternatively, that the patent be maintained in amended form on the basis of the set of claims of auxiliary request 1, filed as auxiliary request 3 with the statement of grounds of appeal.

XVII. Respondent II requested that the appeal be dismissed.

Reasons for the Decision

1. The appeal complies with Articles 106 to 108 and Rule 99 EPC and is admissible.

Main request - claim 1

Claimed invention - claim construction

2. The claim relates to a human monoclonal antibody (mAb) directed against influenza A virus haemagglutinin antigen capable of binding to and neutralising at least one influenza A virus subtype containing haemagglutinin H1 and at least one influenza A virus subtype containing haemagglutinin H3. In other words, the claim is directed to a human mAb functionally characterised in that it displays a heterosubtype

cross-neutralising activity for influenza A virus subtypes H1 and H3. It is undisputed that the claimed antibody has to recognise an epitope that is shared between haemagglutinins H1 and H3.

Sufficiency of disclosure (Article 83 EPC)

3. Article 83 EPC requires that the application disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art. In the case at hand, to carry out the claimed invention, the skilled person must be able, on the basis of the disclosure in the application and of common general knowledge, to obtain the claimed human mAbs without undue burden (see Case Law of the Boards of Appeal of the European Patent Office, 9th edition 2019, (CLBA), section II.C.4.1).

4. The parties referred in their submissions to the patent and not the application as filed. The board ascertained that there is no difference in disclosure in the relevant passages between the application and the patent and, therefore, saw no need to correct the parties' references.

5. The board agrees with the appellant that the skilled person in the case at hand consists of a team of an immunologist, a virologist and a biotechnologist expert in antibody production. This was not contested by the respondents.

Teaching of the application

6. The present invention lies in the field of human mAbs directed against the haemagglutinin antigen of influenza A virus. Within influenza A viruses, subtypes

are distinguished based on the antigenic features of two viral surface proteins, haemagglutinin and neuraminidase. Subtypes that have affected humans in the course of recent history are subtypes H1N1 and H3N2 (see also paragraph [0009] of the patent). Immunity against influenza A virus subtypes is distinguished as follows: (i) homologous immunity relating to the individual isolate, e.g. to isolate A/PR/8/34 of subtype H1N1; (ii) homosubtype immunity relating to isolates belonging to the same subtype, e.g. to isolate A/PR/8/34 and isolate A/SC/1918, both of subtype H1N1; and (iii) heterosubtype immunity relating to isolates belonging to different subtypes, e.g. to isolate A/PR/8/34 of subtype H1N1 and to isolate A/PC/1/73 of subtype H3N2 (see also paragraph [0012] of the patent). After an infection or vaccination, homologous or homosubtype immunity is seen in humans, but heterosubtype immunity to influenza A viruses is "*extremely rare both in case of natural infection and in case of vaccination*" (see paragraph [0012] of the patent) and achieving mAbs with such properties has so far proved to be "*extremely difficult*" (see paragraph [0021] of the patent).

7. The patent discloses antigen binding fragment 28 (Fab28), which has a heterosubtype cross-neutralising activity against the reference isolates of virus A/PR/8/34 (H1N1) and virus A/PC/1/73 (H3N2) (see paragraphs [0067] and [0068] and Figures 1 and 2) and thus possesses the functional properties defined in claim 1. The patent thus discloses one way of carrying out the claimed invention. This is not disputed.

8. At issue is whether the patent, when considered alone or in combination with common general knowledge, provides guidance which allows the skilled person to

obtain substantially all the embodiments falling within the ambit of the claim without undue burden.

9. The patent proposes obtaining the claimed human mAbs by way of a process comprising the following steps: (i) selection of individuals for the generation of human mAbs by following the inclusion criteria defined in paragraph [0055] of the patent, (ii) vaccination of the individuals selected accordingly and (iii) cloning of monoclonal cross-reactive anti-influenza antibodies from their EBV-transformed peripheral blood B lymphocytes (see experimental section, paragraphs [0055] ff).

10. Furthermore, the patent states that "*in particular, it is described that some individuals, despite continuous exposure to influenza virus (sometimes for professional reasons, as physicians, pediatricians, people working in kindergartens and schools), do not contract the disease. These rare individuals were thought to be less susceptible to influenza virus infection due to the development, for still unknown reasons, of an effective heterosubtype immunity. For this reason they were thought to be the best candidates for the generation of human mAbs*" (see paragraph [0055]).

11. In examining the issue of sufficiency of disclosure in the case at hand, a question of particular relevance is whether or not it can be accepted that the patent, as submitted by the appellant, describes selection criteria that allow for the reliable identification of individuals who are highly likely to produce the antibody of claim 1.

12. The following inclusion criteria are disclosed in the patent for the selection of these individuals:

"(1)- *between 25 and 55 years of age;*

(2)- *recent pathological medical history, for the ten years preceding the study, negative for clinical influenza syndromes;*

(3)- *antibody titer higher than 1:1000 against virus isolates, subtypes HlNl and H3N2 responsible for the annual epidemics during the five years preceding the study;*

(4)- *high neutralizing titer (IC50 >= 1:400) against virus isolates, subtypes HlNl and H3N2 responsible for the annual epidemics during the five years preceding the study;*

(5)- *detectable neutralizing titer (IC50 >=1:20) against two reference subtype A virus isolates (A/PR/8/34 subtype HlNl; A/PC/1/73 subtype H3N2);*

(6)- *no prior anti-influenza vaccination;*

(7)- compliance to receive anti-influenza vaccination"

(see paragraph [0055] of the patent; numbering (1) to (7) has been added by the board for ease of reference).

13. Although the patent provides no further information on the purpose of the various inclusion criteria, it can be inferred from the wording of criteria (1), (2) and (6) that these criteria serve to select individuals who, despite not having been vaccinated against

influenza virus, had not contracted the disease in the past ten years, referred to in the following as the "healthy donor" concept (see also point 10 above).

14. As evident from point 10 above, the healthy donor concept reflected in selection criteria (1), (2) and (6) is a mere hypothesis and it is unknown whether individuals fulfilling these criteria do indeed produce an effective heterosubtype immunity.

15. As for the remaining selection criteria, criteria (3) and (4) relate to serological binding and neutralisation tests against virus isolates of subtypes HlNl and H3N2 responsible for the annual epidemics in the recent past, while criterion (5) relates to serological neutralisation tests against older reference virus isolates of subtypes HlNl and H3N2. These tests are performed with sera, i.e. the portion of serum remaining after coagulation of blood. It is undisputed that sera comprise a heterologous mixture of antibodies directed at various different epitopes, also referred to as polyclonal antibodies.

16. While the purpose of the tests of criteria (3) to (5) is not immediately apparent, what is evident is that none of the tests assesses for the presence of cross-neutralising antibodies recognising a shared epitope of haemagglutinins H1 and H3. Indeed, since these tests are performed with a mixture of polyclonal antibodies they cannot distinguish between individuals producing antibodies binding to H1 haemagglutinin or H3 haemagglutinin (homosubtype immunity) and individuals producing antibodies binding to an epitope shared by both haemagglutinins (heterosubtype immunity), as binding of the mixture of polyclonal antibodies will be detected in both cases. Analogous considerations apply

to the neutralisation tests. Furthermore, since the tests are performed on intact viruses, the tests are unsuitable for distinguishing between antibodies binding to haemagglutinin and antibodies binding to neuraminidase.

17. The board therefore agrees with respondent II that the tests of selection criteria (3) to (5) provide a read-out for individuals who have been exposed to the tested virus isolates and produce antibodies against these isolates. Being polyclonal, these antibodies are most likely separate antibodies recognising different epitopes. Accordingly, producing a strong polyclonal antibody response cannot be indicative of the presence of cross-reactive mAbs recognising a shared haemagglutinin epitope.

18. A connection between selection criteria (3) to (5) and the presence of cross-neutralising antibodies recognising a shared epitope of haemagglutinins H1 and H3 is thus not apparent. Accordingly, the appellant's assertion that criteria (3) to (5) ensure the identification of individuals who are likely to produce antibodies capable of recognising at least one antigenic site that was not subject to changes, i.e. a conserved part representing a shared epitope of haemagglutinins H1 and H3, is not considered persuasive.

19. It is common ground that criterion (7) does not contribute to the selection of individuals having a higher probability of producing heterosubtype immunity. This criterion need not be considered further.

20. In view of the above consideration of selection criteria (1) to (6), the board concurs with

respondent II that there is no scientifically credible reason to accept that the selection method of paragraph [0055] of the patent ensures the selection of individuals having a higher probability of producing heterosubtype immunity.

21. While the patent states that heterosubtype immunity is "*extremely rare*", see paragraph [0012], it does not reveal, for example, how many individuals were screened to identify Fab28. As argued by respondent II, the patent provides no comparative data showing that the selection criteria set out in paragraph [0055] increase the chances of finding a cross-neutralising antibody versus mere "brute force" screening of a large number of individuals. In the absence of such comparative data, the provision of Fab28 (see point 7 above) cannot serve as evidence that the criteria set out in paragraph [0055] of the patent allow for the reliable identification of individuals who are highly likely to produce the antibody of claim 1.

22. Moreover, the board concurs with respondent II that document D35, a scientific article relating to the characterisation of PN-SIA28 (= Fab28, the sole antibody isolated in the patent), provides evidence that the serological criteria in paragraph [0055] of the patent are arbitrary. Thus, while criterion (4) in paragraph [0055] of the patent selects for neutralisation of modern H3N2 isolates, H3N2 isolates circulating after 1975 are in fact not neutralised by Fab28 (see page 2, right-hand column, first paragraph, and Table 1), showing a disconnect between the criteria set out in paragraph [0055] of the patent and the properties of the one antibody disclosed in the patent.

23. In view of the above considerations, the board does not accept that the patent describes in paragraph [0055] selection criteria that allow for the reliable identification of individuals who are highly likely to produce the antibody of claim 1.

Post-published evidence

24. The requirements set out in Article 83 EPC must be met on the filing date of the application. This principle applies to any claim request filed in opposition appeal proceedings on the basis of which maintenance of the patent in an amended form is requested. Against this background, post-published documents may be used as evidence that the disclosure is reproducible without undue burden only under certain circumstances (see also CLBA, section II.C.6.8).

25. In the case at hand, the question of whether or not post-published evidence can be taken into account in assessing the sufficiency of disclosure need not be answered. Indeed, consideration of the documents relied on by the appellant would not lead to a different assessment of the board because none of the documents shows that the selection criteria in paragraph [0055] of the patent ensure the reliable identification of individuals who are highly likely to produce the antibody of claim 1. The board's reasoning in this respect is set out below (see points 26 to 28).

26. Document D40, in particular, concerns the isolation of broadly neutralising antibodies against influenza A viruses from plasma cells isolated from "*selected donors who had been previously found to produce a strong heterosubtypic antibody response (9), shortly after natural infection with influenza A or*

vaccination" (see page 851, left-hand column, end of second paragraph). However, how the donors producing a strong heterosubtypic antibody response were selected is not explained in document D40. This is the subject of a reference document, document (9), which is not on file.

27. Document D7, in turn, uses memory B cells isolated from recently vaccinated donors and antibody phage display to search for broadly neutralising H5N1 mAbs using combinatorial libraries (see paragraph bridging pages 2 and 3). Finally, document D29 (see page 320, left-hand column) and document D30 (see page 149, right-hand column) are silent about the healthy donor concept, and the antibody titer, neutralising titer and lack of prior anti-influenza vaccination mentioned in criteria (3), (4) and (6) of paragraph [0055] of the patent are not mentioned either.

28. In sum, the selection criteria employed for the identification of the donors of document D40 producing a strong heterosubtypic antibody response are unknown and the selection criteria employed in documents D7, D29 and D30 do not match the patient selection criteria set out in paragraph [0055] of the patent. Therefore, and contrary to the appellant's submissions, none of these documents provides confirmation of the suitability of the screening concept set out in paragraph [0055] of the patent.

Case law

29. As for the case law relied on by the appellant, it is not applicable to the facts of the present case. In contrast to the cases underlying decision T 431/96 (see Reasons, points 6, 7, 10 and 11) and decision T 877/03

(see Reasons, point 23), for example, a suitable antigen, i.e. an antigen representing an epitope shared by haemagglutinins H1 and H3, allowing the skilled person to screen for the claimed antibodies by applying routine methodology is not disclosed in the patent. Screening on the basis of different influenza strains is unsuitable for identifying individuals producing the claimed human mAbs (see points 16 and 17 above). For these reasons, the appellant's line of argument based on case law is not convincing.

Conclusion on sufficiency of disclosure (Article 83 EPC)

30. The board concludes from the above considerations with respect to the selection method provided in paragraph [0055] of the patent that this does not increase the skilled person's chances of finding a cross-neutralising antibody. Furthermore, the board agrees with respondent II that Fab28 represents a "*single lucky event*" and that finding other cross-neutralising antibodies by following the screening method disclosed in paragraph [0055] of the patent is at best a chance event. In the absence of any evidence that such chance events occur frequently enough and can reliably be identified by the selection criteria disclosed in the patent, and further considering that individuals producing such antibodies are acknowledged in the patent as being "*extremely rare*", the provision of the claimed antibodies amounts to an undue burden.

31. The opposition division had decided to reject claim 1 as granted for lack of sufficiency of disclosure. Therefore, the onus was on the patent proprietor, as the appellant who pursues a claim identical to claim 1 as granted with its main request, to present a detailed line of argument as to why that decision was not

correct on the merits (see also CLBA, section III.G.5.1.2c). Contrary to the appellant's assertion, in the case at hand the respondents were under no obligation to provide experimental evidence to support the insufficiency attack.

32. The invention claimed in claim 1 of the main request does not meet the requirements of Article 83 EPC.

Auxiliary request 1

Admittance (Article 12(4) RPBA 2007)

33. Amended claim 1 of auxiliary request 1 is based on claim 4 as granted and differs from claim 1 of the main request in that the claimed antibody is further characterised as being capable of binding the haemagglutinin conformational epitope specifically recognised by a reference antibody (see section VIII).

34. The request was filed for the first time with the statement of grounds of appeal (VI and VIII) and its admittance is thus governed by Article 12(4) RPBA 2007. Pursuant to Article 12(4) RPBA 2007, the board has discretion to hold requests filed with the statement of grounds of appeal inadmissible if they "*could have been presented or were not admitted in the first instance proceedings*". The appellant's line of argument that the "*could have been presented*" consideration did not apply to the case at hand because this consideration was only relevant under the new RPBA, as in force from 1 January 2020, therefore cannot succeed.

35. Admittance of auxiliary request 1 hinges, *inter alia*, on the question of whether the appellant was in a

position to make its submissions earlier, and whether it could have been expected to do so under the circumstances (see CLBA, section V.A.4.11.1).

36. In response to the notice of opposition, the appellant had filed sets of claims according to a main request and according to auxiliary requests 1 to 3. In all of these claim requests, subject-matter corresponding to that of claim 4 as granted had been deleted in response to an objection under Article 83 EPC raised by the opponents (see appellant's letter dated 13 March 2018, page 1, last paragraph, to page 2, fourth paragraph). Subject-matter corresponding to that of claim 4 as granted had also been deleted in auxiliary requests 4 to 7 filed during the opposition proceedings.

37. Evidently, if the appellant had wanted to pursue the subject-matter of claim 4 as granted it should not have deleted claims directed to that subject-matter from all of its requests pending before the opposition division. The board therefore considers that the appellant could and should have presented auxiliary request 1 in the opposition proceedings.

38. Furthermore, a substantiation requirement applies to claim requests submitted in the appeal proceedings, see Article 12(2) RPBA 2007. In accordance with this requirement, when an auxiliary request is submitted the patent proprietor (or applicant) must also provide reasons as to the extent to which the objections raised in the decision under appeal are overcome by the amendments made, unless this is self-explanatory (see CLBA, V.A.4.12.5). Pursuant to Article 12(4) RPBA 2007,

claim requests filed with the statement of grounds of appeal that do not meet the substantiation requirement are not considered by the board.

39. In the case at hand, the appellant provided no reasoning in the statement of grounds of appeal as to why the amendment in auxiliary request 1 addressed the opposition division's finding of a lack of sufficiency of disclosure. Moreover, no reasoning was provided by the appellant in response to the respondent's reply or the board's communication, both objecting to the lack of substantiation of the amendments made in auxiliary request 1. Furthermore, the board concurs with respondent II that the re-introduction of the subject-matter of dependent claim 4 as granted cannot be considered a response to any aspect of the decision under appeal. Indeed, that in the present case an explanation was needed because it is not self-explanatory as to why the amendment was made has not been contested by the appellant.

40. In view of the above considerations, the board has decided to hold auxiliary request 1 inadmissible (Article 12(4) RPBA 2007).

Conclusion

41. The main request, which is the sole request in the appeal proceedings, does not meet the requirements of Article 83 EPC. Accordingly, the patent cannot be maintained in amended form on the basis of this request. Hence, the decision under appeal cannot be set aside and the appeal is to be dismissed, with the consequence that the opposition division's interlocutory decision becomes final.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chair:

A. Chavinier Tomsic G. Alt

Decision electronically authenticated