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Datasheet for the decision of 10 February 2021

Case Number: T 2697/16 - 3.3.08

Application Number: 08838661.0

Publication Number: 2202307

IPC: C12N15/09, C12N5/10, C12P21/02

Language of the proceedings: EN

Title of invention:
METHOD FOR PRODUCTION OF ANTIBODY

Patent Proprietor:
Chugai Seiyaku Kabushiki Kaisha

Opponents:
Lonza AG
Sölch, Günter

Headword:
Antibody production/CHUGAI SEIYAKU KABUSHIKI KAISHA

Relevant legal provisions:
EPC Art. 123(2), 123(3), 84, 56
RPBA Art. 12(4)
RPBA 2020 Art. 25(2)

Keyword:
Admission of new evidence and new ground for opposition (no);
Main request fulfils the requirements of the EPC (yes);
Appeal dismissed (yes);

Decisions cited:
G 0010/91, G 0003/14, T 0190/99, T 2091/13, T 0688/14, T 1005/15, T 1715/15

Catchword:

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Case Number: T 2697/16 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 10 February 2021

Appellant: (Opponent 1)	Lonza AG Lonzastrasse 3930 Visp (CH)
Representative:	Wohlfahrt, Jan Gleiss Große Schrell und Partner mbB Patentanwälte Rechtsanwälte Leitzstrasse 45 70469 Stuttgart (DE)
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Party as of right: (Opponent 2)	Sölch, Günter Nordring 27 83624 Otterfing (DE)
Representative:	Lederer & Keller Patentanwälte Partnerschaft mbB Unsöldstraße 2 80538 München (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 17 October 2016 concerning maintenance of the European Patent No. 2202307 in amended form.**

Composition of the Board:

Chairman	B. Stolz
Members:	P. Julià
	D. Rogers

Summary of Facts and Submissions

I. European patent no. 2 202 307, based on European patent application no. 08 838 661.0, was granted with 10 claims. Two oppositions were filed on the grounds set forth in Articles 100(a), 100(b), and 100(c) EPC. The opposition division did not admit Article 100(b) EPC as a ground for opposition and considered the main request not to fulfil the requirements of Article 84 EPC. Auxiliary request 1 was considered to fulfil all the requirements of the EPC.

II. Opponent 01 (appellant) lodged an appeal and, with the statement setting out the grounds of appeal, filed new evidence (document (39)). The appellant requested to admit this evidence as well as Article 100(b) EPC as a ground for opposition into the appeal proceedings. Objections were raised under Articles 123(2), 123(3), 84, 83 and 56 EPC against the request upheld by the opposition division.

III. In response thereto, the patent proprietor (respondent) filed a main request (the request upheld by the opposition division) and auxiliary requests 1 to 11. The respondent requested to admit neither the new evidence nor Article 100(b) EPC, into the appeal proceedings.

IV. As an auxiliary measure, oral proceedings were requested by both, the appellant and the respondent.

V. The board summoned the parties to oral proceedings. In a communication pursuant to Article 15 of the Rules of Procedure of the Boards of Appeal (RPBA 2020), they

were informed of the board's provisional opinion on some of the issues of the case.

VI. None of the parties filed any substantive response to the board's communication. With letter dated 20 August 2020, opponent 02 (party as of right) informed the board, without making any substantive submissions, of its intention not to attend the oral proceedings. There were no other submissions on file from the party as of right.

VII. Oral proceedings were held by video conference on 10 February 2021 in presence of the appellant and the respondent.

VIII. The following documents are cited in this decision:

(1) : WO 2007/014162 (publication date: 1 February 2007);

(2) : L. Norderhaug *et al.*, J. Immunol. Methods, 1997, Vol. 204, pages 77 to 87;

(20): S. Schlatter *et al.*, Biotechnol. Prog., 2005, Vol. 21, pages 122 to 133;

(26): J. Li *et al.*, Protein Engineering, Design & Selection, 2007, Vol. 20, No. 10, pages 491 to 496;

(39): D. Luo and W.M. Saltzman, Nature Biotechnology, 2000, Vol. 18, pages 33 to 37.

IX. Claim 1 of the main request (request upheld by the opposition division) reads as follows:

"1. A method of producing an IgG1 antibody or a fragment thereof, comprising allowing an animal cell to produce the antibody or the fragment, wherein the animal cell contains a larger number of copies of an exogenous DNA encoding the light chain or a fragment thereof of the antibody than the number of copies contained in the animal cell of an exogenous DNA encoding the heavy chain or a fragment thereof of the antibody and is an animal cell into which a vector comprising one copy of a DNA encoding the heavy chain or a fragment thereof of the antibody and two or more copies of a DNA encoding the light chain or a fragment thereof of the antibody has been introduced, wherein said vector comprises an expression unit consisting of a promoter, said exogenous DNA encoding the heavy chain or a fragment thereof, and a poly A signal, and wherein said vector comprises two or more expression units consisting of a promoter, said exogenous DNA encoding the light chain or a fragment thereof, and a poly A signal."

Claims 2 to 4 relate to particular embodiments of claim 1. Claims 5 and 6 are directed, respectively, to a recombinant vector as defined in claim 1, and to an animal cell having the vector of claim 5 for use as a production system for preparing or expressing an IgG1 antibody. Claim 7 is directed to a cultured animal cell for the use defined in claim 6. Claim 8 is directed to the method according to any of claims 1 to 4, wherein the cell is stably expressing the antibody or the fragment thereof. Claim 9 is directed to the animal cell according to claims 6 or 7, which is stably expressing the antibody or the fragment thereof.

X. The arguments of the appellant, insofar as they are relevant for the decision, can be summarised as follows:

Admission of document (39) into the appeal proceedings

Document (39) referred to the term "vector" used in the claims and was filed in direct response to a discussion under Articles 84 and 123(2) EPC that took place for the first time at the oral proceedings before the opposition division. Thus, it was not late filed.

Admission of the ground for opposition under Article 100(b) EPC (Article 83 EPC) into the appeal proceedings

The term "expression unit" was not present in the granted claims. The introduction of this term in the claims upheld by the opposition division resulted in serious problems under Article 83 EPC. Whilst the orientation of the encoding DNA was not relevant in the subject-matter of the granted claims, it became relevant for the claims in appeal due to the introduction of this term. In this context, reference was made to document (26) for the definition of this term as well as to document (39) and to the contested patent as providing no guidance on how to perform the invention with vectors other than (circular) plasmids.

Main request
Article 84 EPC

The opposition division considered the term "expression unit" to exclude functional elements other than those mentioned in the claims, but not small sequences of a few nucleotides such as those used for joining the

elements of such unit. The presence of these small sequences rendered this term unclear because neither the size nor the function of these small sequences were limited. Thus, the term "expression unit" was not clearly defined. Moreover, by using the term "comprising" in the definition of the vector, the claims did not exclude the presence of more than one copy of a DNA encoding the heavy chain. Although this objection had not been originally raised under Article 84 EPC, it was also relevant under this article. In addition, whilst all examples of the patent were exemplified with (circular) plasmids, the claims were not limited thereto but referred to a vector in general. Furthermore, claims 8 and 9 required the animal cell to stably express the IgG1 antibody. According to the patent, stable expression was achieved by integration of the vector comprising the DNA encoding the heavy and light chains of the antibody into the genome of the cell. However, it was not clear whether animal cells resulting from a partial integration (only the encoding DNA) or from the integration of several different vectors, fell also within the scope of these claims.

Article 100(c) EPC; Article 123(2) EPC

By using the term "comprising" in the definition of the vector, the claims embraced vectors having more than one copy of a DNA encoding the heavy chain. These vectors had no basis in the patent application, wherein only a 1:2 heavy chain:light chain (HC:LC) gene ratio was disclosed. The claims contained also several intermediate generalisations that had no basis in the patent application. A first generalisation arose from the definition of the expression unit in the claims because it was not limited to the (circular) plasmids

disclosed in the examples and figures 1 and 3 of the patent application. None of the specific elements and features disclosed therein (promoters, polyA signal) were present in the claims. There was no basis in the patent application for a generalisation of the exemplified specific circular plasmids to a vector in general. A second generalisation arose from the orientation of the three expression units mentioned in the claims because it was not limited to that shown in the examples of the patent application; orientations other than the disclosed one were not supported by the patent application. A third intermediate generalisation arose from claims 8 and 9 requiring the animal cell to stably express the antibody but without limiting the vector to a linear plasmid. The disclosure of a stable expression in the patent application was based on the use of linear plasmids. Thus, the subject-matter of claims 8 and 9 had no basis in the patent application.

Article 123(3) EPC

Claims 6 and 7 of the main request covered not only (first generation) cells resulting from the introduction of the vector defined in the claims but also (second generation) cells having this vector from cell duplication. These (second generation) cells were not covered by granted claims 7 and 8 because these claims explicitly referred to the introduction of the vector into the cells.

Article 100(a) EPC; Article 56 EPC

The closest prior art document (2) disclosed a vector comprising a DNA sequence encoding a heavy chain of an antibody and a DNA sequence encoding a light chain of an antibody, wherein each DNA sequence was an element

of an expression unit having a promoter and a polyA signal. The advantages of using a single vector for antibody production were disclosed in document (2), such as simple cloning steps, easy cell transformation and high yields of antibody production. The technical difference between the claimed subject-matter and document (2) was the presence of two or more expression units with a DNA sequence encoding the light chain of the antibody in the single vector. Since the claims of the main request comprised embodiments that provided no improvement over the constructs disclosed in document (2), the technical problem to be solved was the provision of an alternative method for the production of IgG1 antibodies. In view of the prior art, in particular documents (20) and (1), the skilled person would have arrived at the claimed subject-matter in an obvious manner.

Document (20) disclosed a single (dual-gene, pcB72.3) vector similar to that disclosed in document (2), and showed the relevant role of the HC:LC gene ratio in the production of the antibody. Document (20) made the skilled person aware of the advantageous presence of an excess of light chain in the production of the antibody (low HC:LC, <1:2), in particular for stably transfected CHO cells (less than 1:7.5). Likewise, according to document (1), for antibody production, it was advantageous to have twice as many light chain than heavy chain coding sequences. The reference in document (1) to a possible disadvantageous effect associated with a method using two promoters in a single vector, would not have prevented the skilled person from considering such a method when looking for a mere alternative. The more so, since document (2) already taught the use of more than one promoter in a single vector. Therefore, in order to have an

advantageous excess of light chain, it would have been obvious for a skilled person to modify the single vector disclosed in document (2) so as to have two or more expression units with a DNA sequence encoding a light chain of the antibody. Such a modification was in line with the teachings of document (2), namely to have an expression unit for each DNA sequence encoding either the heavy chain or the light chain of the antibody.

XI. The arguments of the respondent, insofar as they are relevant for the decision, can be summarised as follows:

Admission of document (39) into the appeal proceedings

According to the case law, late-filed evidence could only be exceptionally admitted into the proceedings if it was *prima facie* relevant. This was not the case for document (39). Moreover, this document was submitted in support of an inadmissible clarity objection and an inadmissible fresh ground of opposition.

Admission of the ground for opposition under Article 100(b) EPC (Article 83 EPC) into the appeal proceedings

The opposition division considered document (26) not to be relevant for the reproducibility of the claimed subject-matter and the objections under Article 83 EPC not to be *prima facie* relevant. Therefore, this ground for opposition was not admitted into the proceedings at first instance. Thus, in line with decision G 10/91 (OJ EPO 1993, 420), this ground for opposition could not be admitted into the appeal proceedings.

Main request
Article 84 EPC

The term "expression unit" and the functional elements of such unit were clearly defined in the claims. This definition and the reference made by the opposition division to the possible presence of a few (joining) nucleotides, was also in line with the teachings of the patent and the common general knowledge of a skilled person. The granted claims already referred to a vector defined also by the term "comprising", and to the introduction of a vector into an animal cell. Thus, in line with decision G 3/14 (OJ EPO 2015, A102), an objection of lack of clarity based on these features had to be disregarded. The more so since the patent provided guidance on how to introduce the DNA encoding the heavy and light chains of the antibody into cells and evidence of gene delivery systems other than the exemplified (circular) plasmids, as well as a clear teaching on the ratio of DNA encoding the heavy chain and the light chains. Claims 6 and 7 required the animal cell to have a vector with the expression units defined in these claims. Accordingly, any reasoning based on the integration of a vector into the genome was inappropriate. Moreover, claims 8 and 9 were not amended and therefore, any alleged unclarity was already present in the granted claims and had to be disregarded according to decision G 3/14 (*supra*).

Article 100(c) EPC; Article 123(2) EPC

The HC:LC gene ratio defined in the claims was identical to the ratio disclosed in the patent application, namely one heavy chain and two or more light chains. As regards the first generalisation, the disclosure of the patent application was not limited to

the specific vectors used in the examples. A skilled person recognised that the specificities described in the examples, such as the vector, were not essential for achieving the technical effect and could be replaced by known alternatives. This was also the case for the orientation of the three units mentioned in the claims (second intermediate generalisation). As regards the third generalisation, points (12) and (13) in paragraph [0009], and paragraph [0031] of the patent application, provided a basis for claims 8 and 9.

Article 123(3) EPC

The disclosures in paragraphs [0041] and [0042] and Example 3 of the patent application concerning the culture of (clone) cells transfected with the exemplified vector, showed that granted claims 7 and 8 comprised not only (first generation) cells directly transfected with the vector, but also their (second generation) progeny cells. Thus, claims 6 and 7 of the main request did not contravene Article 123(3) EPC.

Article 100(a) EPC; Article 56 EPC

The technical difference between the claimed subject-matter and the closest prior art document (2) was the presence in a single vector of two or more expression units with a DNA encoding a light chain, instead of only one. The examples of the patent showed that cells transfected with a single vector having a 1:2 HC:LC gene ratio were more efficient in IgG1 production than cells transfected with a single vector having a 1:1 HC:LC gene ratio. Therefore, the technical effect of this difference was to improve the production of antibody. Thus, the technical problem to be solved was the provision of an improved method for antibody

production. The problem was solved by the claimed subject-matter across the whole scope of the claims.

According to the case law, the claims had to be read with a mind willing to understand and taking into account the whole disclosure of the patent, so as to arrive at a technically sensible interpretation of the claims (T 190/99). The embodiments referred to by the opposition division and the appellant, namely the use of different promoters for expressing the heavy and the light chains (a strong and a weak promoter, respectively), were contrary to the whole disclosure of the patent and the prior art on file, all of them using always the same promoter for both the heavy and the light chains. Moreover, the number of possible expression units within a single vector was limited; the upper range of expression units encoding the light chain in the claims was thus not open. In the present case, due to structural constraints of the single vector, it could not be higher than four (HL:LC gene ratio of 1:4). There was no evidence on file showing that the improvement disclosed in the patent could not be achieved up to this ratio. According to the case law (*inter alia*, T 2091/13, T 1005/15), in the absence of such evidence, there was no reason to doubt that the effect disclosed in the patent was not achieved across the whole scope of the claims. A mere likelihood, in absence of verifiable facts, was not enough to justify the absence of the improvement shown in the patent and the reformulation of the objective technical problem as the provision of an alternative method instead of an improved method for antibody production.

In the light of the prior art, the claimed subject-matter was not obvious. Document (20) disclosed cells co-transfected with two single gene vectors and cells

transfected with a dual-gene vector encoding both heavy and light chains. For a 1:1 HC:LC gene ratio, the latter cells provided more antibody than the former cells and resulted in an excess of light chain polypeptide both in transient and stable antibody production. Document (20) concluded that an excess of light chain polypeptide was necessary but not sufficient for antibody production, with heavy chain polypeptide availability being a key limiting factor. There was thus no incentive for a skilled person to increase the number of light chain genes in the vector used in the method of document (2) because the amount of light chain polypeptide was already increased with the dual-gene vector with 1:1 HC:LC gene ratio. There was no incentive for a skilled person to increase the number of light chain genes and, if (s)he would have considered it, (s)he would not have done so in the expectation of any improvement or advantage. Likewise, the skilled person would have considered the disclosure of document (1) not to be persuasive because it described a different approach (polycistronic vector), taught away from the claimed subject-matter (problems associated with a single vector having separate promoters due to promoter interference), and referred only to hypothetical experiments.

XII. The appellant (opponent 01) requested that the decision under appeal be set aside and the patent be revoked.

XIII. The respondent (patent proprietor) requested that the appeal be dismissed (main request) or, in the alternative, that the decision under appeal be set aside and the patent be maintained on the basis of any of auxiliary requests 1 to 11.

XIV. There were no submissions or requests on file from the party as of right (opponent 02).

Reasons for the Decision

Admission of document (39) into the appeal proceedings

1. Document (39) is a review article concerning the definition of the term "vector". According to the appellant, the filing of this document was a direct response to a discussion under Articles 84 and 123(2) EPC that took place for the first time at the oral proceedings before the opposition division. However, in the statement of grounds of appeal, document (39) was cited only in the context of Articles 84 and 83 EPC for illustrating the common general knowledge of a skilled person, in particular that "there are several other kinds of vectors beside circular plasmids". This fact has never been contested neither at first instance nor in appeal proceedings and it is well-known in the art.

2. The relevance of document (39) is thus limited to appellant's objections raised under Articles 83 and 84 EPC, in particular when these objections relate to the term "vector". However, the objection raised under Article 83 EPC was not admitted into the proceedings by the opposition division and the admissibility of the objection under Article 84 EPC is questioned by the respondent (with reference to decision G 3/14, OJ EPO 2015, A102). Therefore, in the communication pursuant to Article 15 RPBA 2020 (hereafter the boards communication), the board informed the parties that the admission of document (39) into the appeal proceedings would be considered only if any of the appellant's

objections raised under these two articles were admitted into the appeal proceedings. In that communication, the parties were also informed that, in the board's opinion, none of these objections could be admitted into the appeal proceedings.

3. Since the board has no reason to deviate from its provisional opinion as regards the non-admission of appellant's objections raised under Articles 83 and 84 EPC (*infra*), there is no need for the board to consider the admission of document (39) into the appeal proceedings.

Admission of the ground for opposition under Article 100(b) EPC (Article 83 EPC) into the appeal proceedings

4. The opposition division considered the ground for opposition under Article 100(b) EPC not to be substantiated in the notice of opposition and thus, to be a fresh ground. After consideration of the parties' arguments, the opposition division decided that this fresh ground of opposition was not relevant and thus, it was not admitted into the proceedings (cf. page 10, point 7 *et seq*. of the decision under appeal).

5. As stated by the respondent with reference to decision G 10/91 (*supra*), fresh grounds for opposition may be considered in appeal proceedings only with the patent proprietor's approval. In the present case, this approval is lacking.

6. Therefore, as stated in its communication, the board understands appellant's request to admit the objection raised under Article 83 EPC into the appeal proceedings to be a request for the board to review the opposition

division's discretionary decision not to admit the ground for opposition under Article 100(b) EPC into the proceedings. The criteria for such review are set out in the case law and require the board to assess whether the opposition division exercised its discretion in accordance with the wrong principles or in an unreasonable way (cf. "Case Law of the Boards of Appeal of the EPO", 9th edition 2019, V.A.3.5.1.b), 1198, and V.A.3.5.5, 1205).

7. In the board's communication, the parties were also informed that, in the light of the facts of the present case and the reasons given in the decision under appeal, the board was of the opinion that the opposition division exercised its discretion neither in an unreasonable way nor according to the wrong principles. In the board's view, appellant's arguments submitted in appeal on this issue neither indicated nor supported that this was the case. This was not contested at the oral proceedings before the board.

8. Therefore, the board saw no reason to deviate from its provisional opinion and decided not to admit the fresh ground for opposition (Article 100(b) EPC/ Article 83 EPC) into the appeal proceedings.

Main request

9. The main request is identical to the auxiliary request 1 upheld by the opposition division and underlying the decision under appeal. Thus, the main request already forms part of the appeal proceedings.

Article 84 EPC

10. Claim 1 defines the vector used in the method of producing an IgG1 antibody as comprising several expression units, wherein these units are further defined as consisting of a promoter, an exogenous DNA encoding either the heavy chain of the antibody or the light chain of the antibody (or a fragment thereof), and a polyA signal. The term "consisting" used in the definition of these expression units has a clear and accepted meaning in the case law which, as acknowledged by the opposition division, excludes the presence in these units of components other than those explicitly mentioned in the claim (cf. "Case Law", *supra*, II.A. 6.2, 308, and II.E.1.15, 499). The comment made by the opposition division in the decision under appeal regarding the possible presence of small sequences joining the three components of these units mentioned in claim 1, reflects only what is already known by a person skilled in the relevant technical field. It neither changes the definition of these expression units and the components of these units as defined in claim 1 nor does it go beyond what a skilled person would normally understand to fall within such a definition.

11. The vector used in the method of claim 1 is first defined as "comprising" one copy of a DNA encoding a heavy chain of the antibody (or a fragment thereof) and two or more copies of a DNA encoding the light chain of the antibody (or a fragment thereof). Although the term "comprising" is used, the board considers this definition to require the vector to have only a single (one) copy of a DNA encoding the heavy chain of the antibody and clearly excluding vectors with more than one copy of a DNA encoding the heavy chain. In this

context, the term "comprising" allows the presence of other components within the vector (such as promoters, signal sequences, etc.) but not variations or changes in the specific amount or proportion defined in the claim for the DNA encoding the (one) heavy chain and the DNA encoding the (two or more) light chain. Otherwise, the term "comprising" would render this relation completely meaningless and superfluous. This interpretation extends to, and necessarily limits and constrains also, the further definition of the vector as "comprising" an expression unit with an exogenous DNA encoding the heavy chain of the antibody and two or more expression units with a DNA encoding the light chain of the antibody. The presence in the vector of further expression units with an exogenous DNA encoding the heavy chain of the antibody is therefore clearly excluded from the scope of claim 1.

12. Whilst appellant's first objection under Article 84 EPC arises from a comment made by the opposition division in the decision under appeal, this is not the case for the second objection concerning the ratio of DNA sequences encoding the heavy chain and the light chain of the antibody in the vector. Indeed, as acknowledged by the appellant at oral proceedings before the board, this objection was originally raised at first instance under Article 123(2) EPC, not under Article 84 EPC (cf. page 3, point 3.1.3 of appellant's submissions dated 5 August 2016 at first instance). However, there is no evidence in the Minutes of the oral proceedings before the opposition division and in the decision under appeal that the appellant further pursued this objection under Article 123(2) EPC at the oral proceedings at first instance. There is no decision of the opposition division thereupon, neither under Article 123(2) EPC nor under Article 84 EPC. In any

case, in view of the presence in the granted claims of the term "vector comprising", the examination of such objection under Article 84 EPC is more than questionable (*infra*). Be that as it may, the board, as stated above, does not consider this objection to be relevant since the term in the context of claim 1 does not allow for more than one (single) DNA sequence encoding the heavy chain of the antibody.

13. As regards appellant's objections arising from the definition of the vectors in the claims not being limited to the (sole) linear vectors exemplified in the patent, in particular for claims 8 and 9 which require the (animal) cell to stably express the antibody but without any limitation to linear vectors, the board observes that this limitation was already not present in the vectors mentioned in the granted claims, in particular claims 9 and 10 as granted. Claims 8 and 9 of the main request, apart from the correction of their claim dependencies and the addition of the term "animal" in claim 9, are literally identical to claims 9 and 10 as granted. Thus, appellant's objections under Article 84 EPC do not arise from an amendment of the granted claims. In line with decision G 3/14 (*supra*) which states that the claims of an amended patent may be examined for compliance with the requirements of Article 84 EPC only when, and then only to the extent that, the amendment introduces non-compliance with this article, appellant's objections based upon the term and definition of "vector" cannot be examined by the board.

14. Thus, the main request fulfils the requirements of Article 84 EPC.

Article 100(c) EPC; Article 123(2)EPC

15. The appellant argued that there is no basis in the patent application for embodiments comprising more than one copy of a DNA encoding a heavy chain or a fragment thereof of the antibody.

15.1 These embodiments are also the basis of an objection raised by the appellant for an objection of lack of clarity. The substance and merits of this objection have been assessed by the board under Article 84 EPC above and considered not to be relevant. In the board's view, the claims of the main request are clearly limited to a method using vectors which have only one (single) copy of a DNA encoding the heavy chain of the antibody and, correspondingly, only one (single) expression unit with an exogenous DNA encoding such a heavy chain. Since appellant's embodiments upon which the objection raised under Article 123(2) EPC is based do not fall within the scope of the claims of the main request, the appellant's objection is not relevant.

16. The appellant argued that there is no basis in the patent application for vectors or expression units other than the (sole) exemplified circular plasmids. According to the appellant, the absence of such a limitation represented an unallowable intermediate generalisation lacking any basis in the patent application. Moreover, the appellant also argued that, according to the patent application, linear vectors were necessary for obtaining (animal) cells that stably express the antibody. There was no basis in the patent application for a generalisation to cells obtained by using vectors other than linear vectors and thus, claims 8 and 9 of the main request contravened Article 123(2) EPC.

16.1 Without entering into the merits of these objections, the board, in its communication, informed the parties that these objections had never been raised under Article 123(2) EPC at first instance. Neither the decision under appeal, the Minutes of the oral proceedings at first instance nor the parties' submissions filed in preparation of those proceedings indicated that these objections were ever discussed at first instance. Thus, these were new objections under Article 123(2) EPC not raised at first instance.

16.2 In view thereof, the board also indicated in its communication that the question arose why these objections could not have been raised at an earlier stage of the proceedings. The parties' attention was drawn to Article 12(4) RPBA 2007 (in conjunction with Article 25(2) RPBA 2020) and the board stated that these objections could be admitted into the appeal proceedings only at the board's discretion. In view of the submissions on file, indeed, the lack of any reasons for explaining the introduction of these objections at this late stage of the proceedings, the parties were informed that the board was minded not to admit them into the appeal proceedings.

16.3 At the oral proceedings before the board, both parties referred to their written submissions and made no further submissions. In view thereof, the board saw no reason to deviate from its provisional opinion and therefore, in the exercise of its discretion, did not admit these objections into the proceedings.

17. The appellant further argued that there was no basis in the patent application for a generalisation of the specific components or elements of the expression units

and vectors other than those exemplified in the patent application, such as the promoter, signal sequences, etc. and, more particularly, for orientations within the vector of the expression unit with the exogenous DNA encoding the heavy chain of the antibody and the expression units with the exogenous DNA encoding the light chain of the antibody.

17.1 In the board's communication, the parties were informed that it agreed with the findings of the opposition division on this issue. The examples of the patent application instruct the skilled person how to construct the vectors with the expression units suitable for use in the method of claim 1. Although these vectors are exemplified with specific elements, such as the CAG promoter, mouse beta globin polyA, etc., and used for the production of specific antibodies, namely anti-human glypican-3 and anti-human IL6R, a skilled person would recognise these specific elements as not essential and being replaceable by known alternatives, such as those mentioned in the description of the patent application and referred to by the respondent in response to the statement of grounds of appeal.

17.2 In line with the case law which acknowledges that an intermediate generalisation may be justified if the extracted elements or features are recognised as being not inextricably linked with other (exemplified) elements or features (cf. "Case Law", *supra*, II.E.1.9, 482), the board considers the appellant's objection not to be relevant. The same applies also to the orientation of the expression units within the vector. As stated in its communication, the board sees no reason to deviate from the findings of the opposition division as regards this issue.

18. Therefore, the main request does not contravene Article 123(2) EPC.

Article 123(3) EPC

19. Appellant's objection under this article was raised against claims 6 and 7 of the main request. The appellant argued that, contrary to granted claims 7 and 8, they covered not only (first generation) cells "into which the vector has been introduced", but also (second generation) cells ("a cell which has a vector") wherein the vector was present due to cell duplication, and not by introduction.

19.1 In the board's communication, the parties' attention was drawn to the case law stating that, for the purpose of Article 123(3) EPC, it is the totality of the claims before the amendment in comparison with the totality of the claims after the amendment that has to be considered, i.e. it is necessary to assess the whole scope of the claims before and after the amendments (cf. "Case Law", *supra*, II.E.2.2, 502). In the board's view, the granted claims contemplated a culture of (first generation) cells into which the vector defined in the claims had been introduced. Cell cultures are known to have several phases (lag, log, stationary, decline) in which cells are grown and divided. This is also supported by the disclosure of the patent and the exemplified subject-matter. Thus, the scope of the granted claims - in their totality - encompassed cells with properties as those identified by the appellant, namely (second generation) cells having the vector as a result of said cell culture and not by direct introduction of the vector.

In this context, the parties' attention was also drawn to the case law on product-by-process claims (cf. "Case Law", *supra*, II.A.7, 315 and I.C.5.2.7, 133). According thereto, features related to the method of production may be relevant for a product, such as for establishing novelty, only if they cause it to have properties different from those of the product known from the prior art and obtained by other methods. In the present case, both first and second generation cells, are characterised only by the presence of a vector as defined in the claims; no technical differences - arising directly from their method of production and rendering each of these cell types distinct - have been put forward by the appellant. Therefore, the board sees no reason to deviate from the findings of the opposition division in the decision under appeal on this issue.

20. Thus, the main request does not contravene Article 123(3) EPC.

Article 100(a) EPC; Article 54 EPC

21. The decision of the opposition division acknowledging the novelty of the subject-matter of the main request has not been contested in appeal and thus, it is not the subject of the appeal proceedings.

Article 100(a) EPC; Article 56 EPC

22. In the decision under appeal, the opposition division considered document (2) to represent the closest prior art since this document has the same purpose as the patent, namely an efficient and high yield production of IgG antibodies. Thus, the selection of this closest

prior art document follows the criterion established in the case law (cf. "Case Law", *supra*, I.D.3, 178).

23. Document (2) discloses the (transient and stable) expression of an exogenous DNA sequence encoding a heavy chain and an exogenous DNA sequence encoding a light chain of an IgG antibody, either from two distinct expression vectors (pLNOH2 and pLNOK, respectively) or from a single (dual-gene) expression vector (pLNOH2K), wherein each exogenous DNA sequence is under control of its own specific (CMV) promoter (cf. pages 79 and 81, figures 1 and 2, respectively). Hence, document (2) discloses a vector comprising two expression units, one with an exogenous DNA sequence encoding the IgG heavy chain and one with an exogenous DNA sequence encoding the IgG light chain. The vector used in the method of claim 1 of the main request differs from this dual-gene vector by having an increased number (two or more) of expression units with an exogenous DNA sequence encoding the light chain of the IgG antibody.

24. Starting from this prior art, the respondent formulated the objective technical problem to be solved as the provision of an improved method for the production of IgG1 antibodies. This was contested by the appellant arguing that such an ambitious problem was not solved across the whole scope of the claims and thus, in line with the findings of the opposition division, the objective technical problem needed to be reformulated in less ambitious terms (cf. "Case Law", *supra*, I.D. 4.4, 192), namely as the provision of an alternative method for the production of IgG1 antibodies.

24.1 It is known in the art that the HC:LC gene ratio is highly relevant in the production of antibodies.

Indeed, both intracellular and extracellular abundance of the heavy and light chain polypeptides, even though not directly proportional to the HC:LC gene ratio, will eventually determine the yield of the antibody produced, as shown for instance in document (20). It is not contested that the examples of the patent show an improved, higher yield production of IgG1 antibody when using the exemplified vectors comprising one expression unit with an exogenous DNA sequence encoding the heavy chain and two expression units with an exogenous DNA sequence encoding the light chain of the antibody, compared with a vector such as the one disclosed in the closest prior art document (2) with only one expression unit for the heavy chain and one expression unit for the light chain of the antibody.

24.2 However, the opposition division observed that, whilst in the examples of the patent all expression units have the same promoter, this is not a limiting feature of the claims of the main request and thus, the claims encompass also vectors wherein the expression units may have different promoters, such as for instance a weak promoter for the expression units with the exogenous DNA sequence encoding the light chain of the antibody, whilst the expression unit with the exogenous DNA sequence encoding the heavy chain of the antibody may have a much stronger promoter. In that case, the intracellular and extracellular HC:LC ratio may not necessarily result in the improvement shown in the examples of the patent. This was contested by the respondent with reference to the examples of the patent and to the prior art on file which, the respondent argues, always use the same promoters for expressing both, the heavy and the light chain, in all constructs described therein. Therefore, the claims of the main request could not be read in any other way.

24.3 There is no evidence on file, and none has been put forward by the appellant, to show the effects on the level of antibody expression and production of the embodiments envisaged by the opposition division. However, the board understands respondent's argumentation not to contest these effects but to argue that, in the light of the teachings of the patent and the disclosures in the prior art, these embodiments would not be contemplated by a skilled person. In the board's view, this is a question different from that of whether or not the embodiments envisaged by the opposition division may fall within the scope of the claims. For answering this latter question, no evidence is needed.

24.4 In the board's view, it cannot be contested that the claims are not limited to vectors with expression units having all the same promoters. Although all the examples of the patent may describe such vectors, it is well established case law that, when assessing novelty and inventive step, there is no reason to use the description of the patent to interpret a broad claim more narrowly (cf. "Case Law", *supra*, I.C.4.8, 122, and II.A.6.3.4, 312). Thus, there is no reason for reading this restrictive feature or limitation, namely the use of the same promoter in all expression units, into the claims. Indeed, a suggestion to alter the HC:LC ratio by replacing and using a different promoter is found also in the prior art, even though it goes in a sense contrary to that referred to by the opposition division; document (20) suggests to use strong promoters - not weak ones - for expressing and increasing the amount of light chain of the antibody (cf. page 131, left-hand column, last sentence of second full paragraph). Nevertheless, this disclosure

shows that the interpretation of the opposition division and thus, the specific embodiments referred to by the appellant and the opposition division, makes technical sense and is not illogical (cf. T 190/99 of 6 March 2001).

24.5 Thus, the board agrees with the findings of the opposition division and considers that the objective technical problem needs to be formulated in the terms used by the opposition division and the appellant, namely the provision of an alternative method for the production of IgG1 antibodies.

25. It remains to be assessed whether, starting from the closest prior art document (2) and the above formulated less ambitious technical problem, a skilled person would have arrived at the claimed subject-matter in an obvious manner. For carrying out this assessment, the so-called "could-would approach" followed by the opposition division is appropriate (cf. "Case Law", *supra*, I.D.5, 197). In this context, the appellant referred to documents (20) and (1) as leading the skilled person, when starting from document (2), to the claimed subject-matter in an obvious manner.

25.1 Although the case law defines the skilled person as being cautious and having a conservative attitude (cf. "Case Law", *supra*, I.D.8.1.3, 205), it also acknowledges that furthering the state of the art belongs to the normal tasks of the skilled person and that routine adaptations as well as the use of known alternatives do not go beyond what may be normally expected from a skilled person (cf. *inter alia*, T 1715/15 of 27 February 2020, point 18 of the Reasons, and T 688/14 of 24 July 2019, point 25.1 and the case law cited therein). Indeed, even though the method

described in document (2) is said to provide a high yield of recombinant antibody, document (2) itself refers to an alternative for ensuring even higher levels of antibody expression. Thus, a skilled person would certainly be motivated by document (2) to look for possible alternatives. However, the alternative mentioned in document (2), namely the introduction of genomic introns or a genomic leader sequence (cf. page 85, left-hand column, penultimate paragraph), would not lead the skilled person to the method of claim 1, nor is there any other suggestion or indication in document (2) that would have led the skilled person thereto.

25.2 As stated above, document (20) shows that the transfected HC:LC gene ratio is not directly proportional to the intracellular level of the heavy and light chain polypeptides and that the presence of active antibody depends on both intracellular and extracellular abundance of the heavy and light polypeptides. In agreement with previous studies, document (20) acknowledges that an increased proportion or an excess of intracellular light chain polypeptide facilitates the assembly and secretion of the antibody and results thus in an improved production of the antibody (cf. *inter alia*, page 131, left-hand column, second full paragraph; and paragraph bridging left and right-hand columns). In line therewith, document (20) refers to advantageous expression vectors biased toward low HC:LC polypeptide ratios (<1:2) (cf. page 131, right-hand column, penultimate sentence of last full paragraph), and discloses HC:LC gene ratios falling within the HC:LC gene ratio of the vectors defined in the main request.

25.3 However, these HC:LC gene ratios are always achieved by increasing the amount of the expression vector with a (single) expression unit with an exogenous DNA sequence encoding the light chain of the antibody, not by increasing the number of exogenous DNA sequences encoding the light chain in the dual-gene expression vector disclosed in document (20) (pConk+VL and pcB72.3, respectively; see figure 1 on page 125). There is no suggestion in document (20) to modify the dual-gene expression vector in order to increase the number of the exogenous DNA sequence encoding the light chain, let alone to provide these additional exogenous DNA sequences as distinct, individual expression units within said vector. Indeed, as rightly observed by the respondent, the skilled person is taught away therefrom because document (20) already reports an excess of intracellular light chain over the heavy chain when using the dual-gene expression vector with a 1:1 HC:LC gene ratio (cf. figure 2 on page 126, and figure 6 on page 130). Moreover, as also stated above, if the suggestion made in document (20) would be followed, namely to use stronger promoters for the expression of the light chain (cf. page 131, left-hand column, last sentence of second full paragraph), this suggestion would lead the skilled person away from the vectors defined in the main request.

25.4 Likewise, it is also acknowledged in document (1) that an improved antibody expression is achieved when using two copies of an exogenous DNA sequence encoding the light chain and one copy of an exogenous DNA sequence encoding the heavy chain of the antibody (cf. page 83, first paragraph, last sentence; page 107, third paragraph, last sentence). However, the disclosure on page 83 is made after a reference to the advantageous use of the 2A and 2A-like sequences or other self-

processing sequences described in document (1) which facilitate the equimolar expression of two or more polypeptides by way of a single promoter.

25.5 Although HC:LC gene ratios like those of the subject-matter of the main request are disclosed in document (1) and are described as being advantageous for antibody expression, the exogenous DNA sequences encoding the heavy chain and the light chain are always separated by intervening sequences encoding cleavage sites, preferably the self-processed cleavage sites cited on page 83 (cf. *inter alia*, page 9, paragraphs [00021] and [00022]; page 29, paragraphs [00095] to [00097]). These intervening sequences are described as allowing the expression of the heavy and light chain coding sequences under the transcriptional control of a single promoter, i.e. as a polyprotein from a single transcript in a host cell (cf. *inter alia*, page 10, paragraph [00026] and page 11, paragraph [00027]).

25.6 Although document (1) refers also to prior art disclosing the use of two promoters within a single vector (cf. page 4, paragraph [00011], and page 5, paragraph [00013]), these references are cited only for describing the disadvantages and problems associated with such a single vector when compared to the advantages of the vectors with the intervening sequences disclosed in document (1). Therefore, in the board's view, the skilled person seeking to modify the dual-gene expression vector disclosed in document (2) would not contemplate these single vectors with multiple promoters explicitly referred to in document (1) as being disadvantageous but, if anything, the use of the advantageous intervening sequences disclosed in this document. Therefore, the skilled

person would also be led away from the subject-matter of the main request.

25.7 It follows from the above considerations that the claimed subject-matter is not rendered obvious by the disclosure of document (2) alone or in combination with those of either document (20) or document (1).

26. Therefore, the main request fulfils the requirements of Article 56 EPC.

Conclusion

27. Since the main request fulfils all requirements of the EPC, the appeal is to be dismissed.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

L. Malécot-Grob B. Stolz

Decision electronically authenticated