Internal distribution code:

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

Datasheet for the decision of 20 July 2022

Case Number: T 0804/19 - 3.3.08

Application Number: 07765049.7

Publication Number: 2041259

IPC: C12M1/12, C12M3/06, C12N5/07, C12N5/073, C12N5/079

Language of the proceedings: EN

Title of invention:
Improved process for the culturing of cells

Patent Proprietor:
Patheon Holdings I B.V.

Opponents:
Boehringer Ingelheim Pharma GmbH & Co. KG/
Boehringer Ingelheim International GmbH
Repligen Corporation
Baxalta GmbH

Headword:
Cell culturing/PATHEON

Relevant legal provisions:
EPC Art. 54, 56, 83, 84, 87, 123(2)
RPBA Art. 12(4)

Keyword:
Main request - admitted (yes)
Main request - requirements of the EPC - (yes)
Late-filed facts - admitted (no)

Decisions cited:
G 0001/03, G 0001/15

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 0804/19 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 20 July 2022

Appellant: (Opponent 03)	Baxalta GmbH Thurgauerstrasse 130 8152 Glattpark (Opfikon) (CH)
Representative:	N. Muncke Hoffmann Eitle Patent- und Rechtsanwälte PartmbB Arabellastraße 30 81925 München (DE)
Respondent: (Patent Proprietor)	Patheon Holdings I B.V. Herengracht 540 1017 CG Amsterdam (NL)
Representative:	C. Schlörb and D. Günther Vossius & Partner Patentanwälte Rechtsanwälte mbB Siebertstrasse 3 81675 München (DE)
Party as of right: (Opponent 01)	Boehringer Ingelheim Pharma GmbH & Co. KG/ Boehringer Ingelheim International GmbH Binger Straße 173 55216 Ingelheim am Rhein (DE)
Representative:	Höfer, Friederike Dreikönigsgasse 10 D-89073 Ulm (DE)

Party as of right: (Opponent 02) Opposition withdrawn	Repligen Corporation 41 Seyton Street, Building No. 1, Suite 100 Waltham, MA 02453 (US)
Representative:	Burda, Martin Robert Fish & Richardson P.C. HighLight Business Towers Mies-van-der-Rohe-Straße 8 80807 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 11 January 2019 rejecting the opposition filed against European patent No. 2041259 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairman	B. Stolz
Members:	M. Montrone
	D. Rogers

Summary of Facts and Submissions

I. The appeal lies against the decision of an opposition division to reject the oppositions against the European patent No. 2 041 259. This patent is based on European patent application No. 07765049.7 published as International patent application WO 2008/006494 ("patent application").

II. With their statement of grounds of appeal, opponent 03 ("appellant") submitted objections against the subject-matter of the claims as granted under added subject-matter, insufficiency of disclosure, lack of priority entitlement, lack of novelty and inventive step. In support of their case new documents D64 to D67 were submitted.

III. In reply, the patent proprietor ("respondent") submitted auxiliary requests I to VIII which correspond to the set of claims submitted during the first instance proceedings.

IV. In reply, the appellant submitted further arguments and documents.

V. In reply to the summons, opponent 01 informed the board that they would not attend the oral proceedings. Opponent 02 had already withdrawn their opposition during the first instance proceedings.

VI. The appellant requested a re-scheduling of the present case, and of the two related cases T 875/19 and T 513/20 to dates that were closer together. This request was not granted due to the board's workload.

VII. In a communication in preparation of oral proceedings, the parties were informed of the board's provisional, non-binding opinion.

VIII. In reply, the appellant informed the board that they will not attend the oral proceedings.

IX. Oral proceedings before the board were held on 20 July 2022, in the absence of the appellant and of opponent 01 as announced. During the oral proceedings, the respondent withdrew all of their claim requests, except auxiliary request VI, which became their main request.

X. Claim 1 of the main request (filed as auxiliary request VI under cover of a letter dated 4 October 2019) reads:

"1. Process for the culturing of eukaryotic cells in a reactor in suspension in a cell culture medium, wherein the cells produce a biological substance, wherein the biological substance is an IgG with a molecular weight of 150 kDa, wherein the cell culture comprising the cells, the biological substance and cell culture medium is circulated over a hollow fiber filter using a tangential flow resulting in a liquid outflow and a flow which contents are kept in or fed back into the reactor, wherein at least one cell culture medium component is fed to the cell culture, wherein the filter has a pore size characterized by a molecular weight cut-off of at most 50 kDa, suitable to separate the biological substance from substances having a lower molecular weight than the biological substance, wherein the liquid outflow from the filter essentially only contains components having a molecular weight lower than that of the biological substance and wherein the biological substance is retained in or fed back into the reactor".

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

D4: US 6,544,424 (published 8 April 2003;

D5: Furey J., Genetic Engineering News, 2002, Vol. 22(7), 62-63;

D7: WO2005/095578 (published 13 October 2005);

D9: US 5,286,646 (published 15 February 1994);

D10: US 4,806,484 (published 21 February 1989);

D15: Takazawa Y. *et al*., Cytotechnology, 1988, Vol. 1, 171-178;

D19: Matsumura M. and Nayve F.R., Cytotechnology, 1995, Vol. 18, 35-50;

D20: Refine Technology, Co., "ATF system", Operating Manual for Models ATF-4 and ATF-6, 2000;

D21: WO2008/152075 (published 14 January 2009);

D23: EP2343362 (divisional of the patent in suit);

D24: EP2634242 (divisional of the patent in suit);

D25: EP2634243 (divisional of the patent in suit);

D26: EP2634250 (divisional of the patent in suit);

D27: Presentation "The human PER.C6® manufacturing platform", 10 May 2007;

D33: Koros W. J. *et al.*, Pure & Applied Chemistry, 1996, 1479-1489;

D35: Millipore Technical Brief "Protein Concentration and Diafiltration by Tangential Flow Filtration", 2003;

D36: DE 10120835 (published 7 November 2002);

D38: Flickinger M.C. *et al.*, Bioprocess Engineering, 1990, Vol. 5, 155-164;

D42: Comparison of the claimed process using TFF vs. ATF with a monoclonal antibody producing CHO cell;

D51: Declaration John Bonham-Carter, dated 19 December 2017;

D52: Vidarsson G. *et al.*, Frontiers in Immunology, 2014, Vol. 5, 1-17.

XII. The appellant's written submissions, insofar as relevant to the present decision, may be summarised as follows:

Admission into the appeal proceedings of the main request (submitted as auxiliary request VI), of document D20, and a new argument under insufficiency of disclosure based on document D38

The auxiliary requests filed in reply to the statement of grounds were not convergent, and should thus not be admitted into the proceedings.

Document D20 was not admitted by the opposition division into the proceedings. The opposition division applied the "up-to-the-hilt" standard, and not the appropriate balance of probabilities standard for deciding on the public availability of document D20. The document was a power point presentation on alternating tangential flow (ATF) technology given every month in the years 2000-2004 during sales presentations to companies in the UK and Ireland. The audience was under no confidentiality constraints as confirmed by the declaration of Mr. Bonham-Carter (see D51). While document D20 was not a commercial brochure *per se*, it served the same purpose, i.e. the promotion of ATF.

Main request

Added subject-matter - claim 1

Claim 1 comprised added subject-matter because the application as filed provided no basis for the combination of features "*eukaryotic cells*", "*IgG with a molecular weight of 150 kDa*", "*filter*", "*tangential flow*", and *"wherein the filter has a pore size characterised by a molecular weight cut-off of at most 50 kDa*". These features were selected from different lists that were not disclosed in combination.
While page 3, lines 7 to 13 of the application as filed disclosed "*eukaryotic cells*", this passage indicated that the cells "*may*" be eukaryotic cells only.
Page 5, lines 9 to 10 of the application as filed disclosed the feature "*IgG with a molecular weight of 150 kDa*". However, it was not disclosed in combination with the other features of the claim.

Page 5, lines 11 to 12 of the application as filed disclosed the term "*filter*". However, the filter was selected from a list of alternative separation systems. The term "*tangential flow*" was mentioned on page 6 of the application as filed, however, in a list of two alternatives.
The feature "*the filter has a pore size characterized by a molecular weight cut-off of at most 50 kDa*" was selected from another list disclosed on page 5, lines 5 to 10 of the application as filed.
Likewise "*hollow fiber*" was selected from a list of filters disclosed on page 5, lines 21 to 26 of the application as filed.
None of these features were disclosed in individualised form in the application as filed, contrary to the criteria set out in the case law.

Furthermore, the cell lines cited in the dependent claims represented selections from a list.

Lack of clarity and insufficiency of disclosure

The introduction of the feature "*molecular weight of 150 kDa*" into claim 1 made the case more complex because new issues under Articles 83 and 84 EPC arose. The patent application contained no teaching on how an IgG of 150 kDa was produced. Human IgG1, IgG2 and IgG4 had a molecular weight of 146 kDa, IgG3 a molecular weight of 170 kDa (see document D52, Table 1).

Furthermore, the claimed process comprised non-working embodiments. Document D15 disclosed a process that fell within the scope of claim 1. However, the document reported that in initial experiments the culture supernatant circulating over the filter caused membrane

clogging despite the use of tangential flow filtration (see page 176, column 1, second paragraph).
Document D38 disclosed a further process that fell within the claimed process. The document disclosed a tangential flow filtration of the cell culture over a membrane filter. The filter's effective pore size was continuously reduced due to the presence of serum proteins in the medium that caused gel polarisation. This ongoing pore size reduction necessarily resulted in filter clogging.

Priority

The second priority document ("P2"-document) did not provide a basis for the combination of the features cited in claim 1 for the same reasons set out above under added subject-matter. The main request was not entitled to the second priority date, and the relevant date was thus the filing date of the patent application, i.e. 4 July 2007.

Novelty

Figure 1 of document D15 disclosed the claimed process.

Documents D23 to D26 were divisional applications of the patent in suit. As the claimed subject-matter was not entitled to the priority date, these four published divisional applications formed part of the prior art ("poisonous divisionals").

Document D36 described the production of monoclonal antibodies from mammalian cells, including IgG. The cells were cultured in suspension. Fresh medium was added while waste products were removed via a hollow fiber filter in the culture medium characterised by a

MWCO below the molecular weight of an antibody, preferably in the range of 3 kDa to 10 kDa (see paragraphs [0001], [0010], [0015], [0028] and [0035]). The fresh medium circulated inside the filter. Alternatively an alternating flow direction of the fresh/waste medium was disclosed based on a reversed pressure gradient across the filter membrane (see column 3, lines 25, 26, paragraph [0010], point (c), and [0031]). The cell culture inside the reactor was continuously moved by an impeller (see paragraph [0023]). Since the filter was immersed in a culture medium that was in a rotational movement it was "*inevitable that there is a tangential flow when circulating the medium over the filter*", as likewise implied by the German verb "*umfließt*".

Figure 2 of document D38 disclosed the claimed process.

Inventive step

Each of documents D9, D10, D15, D19, D36, and D38 represented the closest prior art.

Document D9 used a very similar cell culturing system to that of document D10 for producing monoclonal antibodies (see Figure 2). Accordingly, the same reasoning applied.

Document D10 disclosed an airlift bioreactor for culturing suspended hybridoma cells producing a monoclonal antibody (see column 1, lines 19 to 29, column 2, second and third paragraph). The reactor set-up used an external hollow fiber filter, designated as "*external cross flow filter*", for the exchange of nutrients and waste products from the cell culture (see column 1, third paragraph, and Figure 1). Figure 1

disclosed that the fresh medium and the culture medium were pumped through the filter in a tangential flow. Due to the hollow fiber's different cross-sectional area of the lumen and shell space it was inevitable that the pumps created a pressure gradient across the membrane which caused the nutrient/waste exchange. This pressure gradient resulted in a tangential flow filtration, and not in a dialysis-based exchange. The difference between the claimed process and document D10 resided in the explicit reference to the production of an IgG instead of a monoclonal antibody. This was not inventive since the production of IgGs was already known in the art.

Document D15 disclosed a perfusion culturing of hybridoma cells for producing an IgG antibody. The cell culture was run through a membrane filter (Pellicon cassette) with a MWCO of 10 kDa, and the concentrated product was fed back into the reactor (see abstract, Figure 1, page 173, column 1, second paragraph). In initial experiments solely a cell settling zone within the reactor was used to reduce the amount of circulating cells. The cell culture's supernatant leaving the reactor comprised about 5% of the total cells and caused filter clogging (see page 176, column 1, second paragraph). A second experimental set-up used an additional cell trap to prevent filter clogging. This trap did not remove all cells from the cell culture. Even if it did, it was obvious to replace the cell trap with an ATF system, since this system was established, commercially available, and known to prevent filter clogging (see e.g. document D4, column 1, lines 49 to 57, column 3, lines 42 to 67). The claimed method was an obvious alternative to the second experimental set-up in document D15.

Document D19 disclosed a process for culturing mouse hybridoma cells producing an IgG antibody (see page 36, column 1, second but last paragraph). The cells and the IgG were retained in the reactor by a membrane filter with a MWCO of 10 kDa that was fixed at the bottom of the reactor. This resulted in a dead-end filtration. The difference between the claimed method and document D19 was the use of a tangential flow instead of a dead-end filtration. Since no effect could be ascribed to this difference, the technical problem to be solved remained the provision of an alternative method. The use of TFF instead of a dead-end filtration was well known, and therefore obvious for the skilled person.

Document D36 disclosed a perfusion culturing of cells for the production of antibodies. The claimed method differed therefrom in using a tangential flow for filtration. The use of a tangential flow was not inventive for the same reasons outlined above for document D19.

Document D38 disclosed a perfusion culturing of cells for the production of an antibody (see abstract). The process used a membrane filter operated by tangential flow for retaining the cells and the antibodies in the cell culture (see Figures 2 and 15). The filter had a pore size of 0.20 micron, or 0.65 micron. The effective pore size, however, was smaller because serum proteins in the medium caused a gel polarisation on the filter surface so that the filter's retention properties were similar to those of the 10 kDa ultrafiltration membrane disclosed in document D15 (see page 163, column 1, second paragraph).
The claimed method differed from document D38 by using a filter with a MWCO of at most 50 kDa instead of a 0.2 micron pore size with a reduced effective pore size due

to gel polarisation. Since there was no beneficial effect associated with this difference, the problem to be solved remained the provision of an alternative process.
The claimed process encompassed the culturing of cells in serum-free medium. This embodiment lacked an inventive step, since the skilled person merely had to use an alternative filter, including a hollow fiber, with a smaller MWCO size as already suggested. Even if serum-containing medium was used, the skilled person would have encountered no problems in using filters with a smaller pore size. This was so because the skilled person would in this situation have used a filter operated in an ATF mode which prevented an excessive gel polarisation (see e.g. document D5, page 1, column 3, first paragraph). Since the solution merely required the use of an alternative, the skilled person needed no motivation to change the filter type, even in the absence of any filter problems reported in document D38. Different filters for retaining an antibody were commercially available. The selection of one of them as an alternative did not require any inventive skills.

XIII. The respondent's submissions, insofar as relevant to the present decision, may be summarised as follows:

Admission into the appeal proceedings of the main request (submitted as auxiliary request VI), of document D20, and a new argument under insufficiency of disclosure based on document D38

The main request was submitted in reply to the appellant's statement of grounds as auxiliary request VI. Moreover, this claim request was already submitted

during the first instance proceedings. It should thus be admitted to the appeal proceedings.

The opposition division's decision was correct in not admitting document D20 into the proceedings. Document D20 was a product presentation by Refine Technology, i.e. opponent 02 in these proceedings. This document was not publicly available under Article 54(2) EPC because it stated on its front page "*Copyright 2000 - Confidential Information Enclosed*". The declaration D51 did not provide evidence to the contrary since Mr. Bonham-Carter was an employee of opponent 02. Document D20 was not a widely distributed commercial brochure since the presentation was given to potential customers under confidentiality constraints.

The appellant submitted under insufficiency that the continuous pore size reduction of the filter by gel polarisation as disclosed in document D38 led to non-working embodiments. This argument was raised for the first time in the appeal proceedings, and should not be admitted.

Main request

Added subject-matter - claim 1

Claim 1 comprised no added subject-matter. The claimed process had primarily a basis in claim 1 as filed, and the paragraph bridging pages 1 and 2 of the patent application.
In particular, the feature "*eukaryotic cells*" was disclosed on page 3, lines 7 to 13 of the patent application; the feature "*biological substance is an IgG with a molecular weight of 150 kDa*" was disclosed on page 5, lines 9 to 10, page 10, last paragraph, and

the working examples of the patent application; the features "*filter*", "*tangential flow*", and "*wherein the filter has a pore size characterised by a molecular weight cut-off of at most 50 kDa*" were disclosed on page 5, lines 4 to 11, page 6, line 26 of the patent application, as well as in claims 5 and 6 as filed.

Lack of clarity and insufficiency of disclosure

The amendments in claim 1 were clear (Article 84 EPC) and did not contravene the requirements of Article 83 EPC.

Priority

The claimed process was at least entitled to the second priority right originating from European application EP 07002571.3 filed on 6 February 2007. Thus, documents D21 and D27 were not prior art (Article 54 EPC).

Novelty

Document D15 disclosed a membrane filter, not a hollow fiber filter. Thus, the claimed process was novel.

The divisional applications D23 to D26 were not detrimental to the process of claim 1, since G 1/15 allowed partial priorities (see headnote).

Document D36 disclosed a perfusion culturing of cells for the production of an antibody. The process used *inter alia* a hollow fiber module immersed into the cell culture for a nutrient/waste exchange. The culture medium in document D36 did not flow in a tangential direction over the filter surface, because the flow encompassed perpendicular and turbulent elements.

Document D38 disclosed a reactor with a membrane filter, not a hollow fiber filter. Thus the claimed process was novel.

Inventive step

Document D7 represented the closest prior art. The claimed process differed from the process of document D7 solely in the pore size of the hollow fiber filter used. While the filter in the claimed process retained the cells and the antibody within the cell culture, the pore size in document D7 was so large that antibodies and some cells passed through the filter. The product resulting from the claimed process was more concentrated compared to the process of document D7 (11.1 g/l IgG see Example 2 of the patent vs 0.47 g/l of IgG in document D7). The technical problem to be solved was thus the provision of an improved process for the culturing of suspended cells producing a desired biological substance in a cell medium. This problem was solved by using a hollow fiber filter with a MWCO pore size of at most 50 kDa.

Documents D9 and D10 did not represent the closest prior art since their filtration was based on dialysis, i.e. a fundamentally different system.

Document D15 disclosed a perfusion culturing of suspended cells producing an IgG antibody in a reactor with a cell settling zone (see abstract and Figure 1). This settling zone prevented the circulation of the majority of cells over an external membrane filter. The document mentioned that in preliminary experiments flow-out cells in the supernatant of the reactor's cell culture caused filter clogging. Thus the supernatant of

document D15 differed from the cell culture in claim 1 in not comprising substantially all cell culture cells. The filter clogging problem was solved in document D15 by using an additional cell trap. Due to the combined use of a settling zone and a cell trap, cells were no longer circulating over the membrane filter.

The processes of documents D19 and D36 did not represent the closest prior art. Document D19 used a dead-end filtration, i.e. the filtration resulted from a perpendicular flow of the culture medium relative to the filter surface. Document D36 used likewise a different filtration system. Due to the rotational movement of the cell culture relative to an immobilised filter, the cell culture did not flow substantially parallel to the filter surface but in a perpendicular and turbulent manner.

Document D38 disclosed a further perfusion culturing of suspended cells in serum-containing medium for the production of an IgG antibody. The process used an external membrane filter with a pore size of 0.22 or 0.65 microns (see abstract, page 157, column 1, fourth paragraph and Figure 2). The serum proteins of the medium caused a so called gel polarisation of the filter membrane. This reduced the filter's effective pore size to an extent resembling an ultrafiltration membrane without disclosing it's actual pore size. No indications were derivable from document D38 whether this effect was reproducible for other filter types, in particular hollow fibers. The claimed process differed from the process of document D38 in the use of a different filter with a different pore size.

The differences of the claimed process vis-à-vis the processes of documents D15 and D38 resulted in a

production of IgG at higher yields. This was shown in Example 2 of the patent and the supplementary experimental data of document D42. The technical problem to be solved was thus the provision of an improved process for the production of IgG in suspended cells.

The use of a tangential flow filtration and a hollow fiber filter in the claimed process solved this problem. This solution was inventive, even if the technical problem to be solved was the provision of an alternative process for the production of IgG in suspended cells.

This was so because even if the skilled person used a hollow fiber filter instead of the membrane filters disclosed in documents D15 or D38, he or she would not have automatically arrived at a solution that fell within the scope of claim 1. The skilled person replacing the membrane filter of document D15 with a hollow fiber filter did not arrive at a process falling within the scope of claim 1 because cells were no longer circulating over the filter. In document D38 the replacement of the membrane filter with a hollow fiber filter did not necessarily result in gel polarisation since the surfaces of the two filters differed. Even if gel polarisation occurred, the filter's effective pore size remained unknown. Thus the skilled person using a hollow fiber filter arrived not automatically at a pore size that fell within the claimed pore size range.

XIV. The appellant requested that the decision under appeal be set aside and the patent be revoked.

XV. The respondent requested that the decision under appeal be set aside and the patent be maintained on the basis

of the main request submitted as auxiliary request VI under cover of a letter dated 4 October 2019. Furthermore, the respondent requested not to admit into the appeal proceedings a new argument of the appellant under insufficiency of disclosure based on document D38.

Reasons for the Decision

Admission into the appeal proceedings of the main request (submitted as auxiliary request VI), document D20, and a new argument under insufficiency based on document D38

1. According to the established case law the function of an appeal is to give a judicial decision upon the correctness of a separate earlier decision taken by an examining or opposition division. The admission (consideration) of new claim requests or lines of argument into the appeal proceedings is at the board's discretion (Article 114(2) EPC and Articles 12(4) and 13(1) RPBA 2007; see Case Law of the Boards of Appeal of the EPO, 9th edition 2019 ("Case Law"), V.A.1, 1133 and V.A.4, 1206).

2. The main request (former auxiliary request VI) was filed on 4 October 2019 in reply to the appeal. Accordingly, the requirements of Article 12(4) RPBA 2007 apply (see also Article 25(2) RPA 2020). The principal criterion on admission under Article 12(4) RPBA 2007 is whether a claim request could have been filed earlier.

3. The appellant objected to the admission of the auxiliary requests into the appeal proceedings, because they lacked convergence.

4. In reply to the appeal, the respondent filed *inter alia* auxiliary request VI (i.e. the main request in the appeal proceedings), and explained the reasons for its filing and the amendments introduced therein. This request is identical to auxiliary request VI already filed at first instance. None of the auxiliary requests were examined at first instance because the opposition division decided in the patent proprietor/respondent's favour on the basis of the claims as granted.

5. The main request is the sole request in the appeal proceedings. Already for this reason, lack of convergence cannot apply. The features "*with a molecular weight of 150 kDa*" and "*hollow fiber*" were introduced to address objections under added subject-matter and lack of novelty raised by the appellant against the claims as granted. Accordingly, the main request complies with Rule 80 EPC.

5.1 In light of these considerations, the board considers that the main request represents an adequate reaction of the respondent to the course of the appeal proceedings.

5.2 The main request is thus admitted into the appeal proceedings (Article 12(4) RPBA 2007).

6. Document D20 was not admitted by the opposition division into the proceedings because it was held not to be publicly available (see decision under appeal, point 5.4).

6.1 The board shares this view. Based on a balance of probabilities it is not convincing that the presentation of document D20 is publicly available. Document D20's front page states explicitly that the

presentation is confidential. This statement contradicts Mr. Bonham-Carter's declaration (see D51), who is an employee of an opposing party (opponent 02).

6.2 Furthermore, other evidence, for example, from at least one attendant of the sales presentations is not available that supports Mr. Bonham-Carter's view that the presentation was given to the public in the years 2002-2004 under no confidentiality constraints.

6.3 Thus document D20 is not prior art under Article 54(2) EPC, and will be disregarded in these proceedings.

7. As regards the admission of the appellant's line of argument under insufficiency based on document D38, this argument was not submitted during the first instance proceedings, although insufficiency was a ground for opposition from the onset of the proceedings. Therefore, this argument could, and should have been submitted by the appellant already during the first instance proceedings. This line of argument is therefore not admitted into the appeal proceedings (Article 12(4) RPBA 2007).

Main request

Claim construction - claim 1

8. The process of claim 1 aims at the production of an immunoglobulin G (IgG) with a molecular size of 150 kDa in a reactor through the culturing of suspended eukaryotic cells in a medium circulated over a hollow fiber filter using a tangential flow. The filter is further characterised by a pore size with a maximum molecular weight cut-off (MWCO) of at most 50 kDa. Thereby medium components of 50 kDa and smaller pass

the filter and are removed in a liquid outflow, while components larger than 50 kDa, including IgG and cells, are retained in the culture medium. Furthermore, at least one medium compound is constantly replaced.

8.1 This type of process is known as cell perfusion culturing, wherein waste products are constantly removed while at least one nutrient is replenished (see e.g. document D5, page 62, column 1, second paragraph).

8.2 The terms "*eukaryotic cell*", "*suspension*", and "*reactor*" are not further defined in claim 1. Hence, the claim encompasses the use of any eukaryotic cell grown in solution, i.e. not adhered to surfaces, and any reactor design/size suitable for producing IgG from suspended cells. This includes the use of reactors with "*pre-filters*" to prevent premature filter clogging caused by cells at a certain density. Pre-filters are mentioned in paragraph [0028] of the patent, and include, for example, the "*cell-trap*" and "*settling zone*" disclosed in document D15 (see page 173, column 1, third paragraph, and page 176, column 1, third paragraph).

8.3 The term "*cell culture*" in claim 1 is defined as containing at least eukaryotic cells, IgG, and medium, without excluding the presence of other components due to the use of the comprising language. The claimed process uses any such cell culture, irrespective of the cells' density/viability, the IgG's subtype, origin or concentration, and the medium composition (e.g. serum-free medium, or serum-containing medium).

8.4 The claim further requires that "*the cell culture* [...] *is circulated over a hollow fiber filter using a*

tangential flow resulting in a liquid outflow". The construction of this feature is contested.

8.4.1 It is established case law that terms in a claim have to be given their broadest sensible technical meaning. Since the term "*cell culture*" in claim 1 is not defined, except for the presence of eukaryotic cells, IgG, and medium as its minimum constituents, the claim encompasses the circulation of the cell culture as a whole, or any portion thereof that comprises at least these three constituents in any concentration.

8.4.2 A further issue is how the feature "*is circulated over a hollow fiber filter using a tangential flow resulting in a liquid outflow*" must be construed. Either narrowly as necessarily implying a tangential flow filtration, i.e. a limitation to a specific type of filtration (see paragraph [0028] of the patent), or more broadly by relating to any filtration resulting in a liquid outflow mediated by a tangential flow of a cell culture that circulates over the filter.

8.4.3 In the board's opinion, the skilled person would construe the term "*using tangential flow*" in claim 1 as a cell culture that flows substantially parallel to the filter surface. This must result in a liquid outflow containing components of 50 kDa and smaller, which necessarily implies the presence of a pressure gradient across the membrane. Contrary thereto dialysis-based filtrations have no net liquid outflow, because the compound exchange across the membrane follows a concentration gradient (see document D33, page 1487, point 66).

8.5 Moreover, since the flow direction of the culture medium is not defined in claim 1, the process

encompasses the use of unidirectional and bidirectional (alternating) parallel flows of the culture relative to the filter surface (see patent, paragraph [0028]).

Added subject-matter - claim 1

9. In the following all references to the application as filed refer to the patent application (WO 2008/006494).

10. The appellant submitted that claim 1 comprised added subject-matter because the application as filed provided no basis for the combination of the features "*eukaryotic cells*", "*IgG with a molecular weight of 150 kDa*", "*filter*", "*tangential flow*", and "*wherein the filter has a pore size characterised by a molecular weight cut-off of at most 50 kDa*". These features were selected from different lists.

11. The board does not agree.

11.1 Claim 1 as filed reads: "*Process for the culturing of cells in a reactor in suspension in a cell culture medium, wherein the cells produce a biological substance, wherein at least one cell culture medium component is fed to the cell culture and wherein the cell culture comprising the cells, the biological substance and cell culture medium is circulated over a separation system and wherein the separation system separates the biological substance from substances having a lower molecular weight than the biological substance and wherein the biological substance is retained in or fed back into the reactor*".

11.2 Claim 4 as filed reads: "*Process according to claim 1-3, wherein the biological substance is recombinant protein, preferably an antibody*".

11.3 Claim 5 as filed reads: "*Process according to any one of claims 1-4, wherein the separation system is a filter, preferably a membrane filter, more preferably a hollow fiber filter*".

11.4 Thus claims 1, 4 and 5 as filed disclose a process for the culturing of suspended cells which preferably uses a "*hollow fiber filter*" as the separation system, wherein an "*antibody*" as biological substance is preferably produced. The application as filed further discloses on page 5, lines 9 and 10: "*For example for an IgG with a molecular weight of 150kDa, a separation system having a MWCO of at most 50kDa is most preferred*", i.e. the preferred use of a filter with a MWCO of at most 50 kDa for retaining the IgG antibody cited in claim 1.

11.5 As regards the producer cell of the biological substance, the application as filed discloses two generic cell types only, a "*eukaryotic*" and a "*prokaryotic*" (see page 3, lines 5 to 7, and 11). The use of one of two equal alternatives requires no selection from a list.

11.6 The application as filed further discloses that the "*circulation of the cell culture over a filter may be a flow substantially perpendicular with respect to the filter surface, also known as dead-end flow or a flow substantially parallel to the filter surface, also known as tangential flow*" (see page 6, lines 24 to 26). Again two alternatives are disclosed for circulating a cell culture over the filter, a perpendicular flow and a parallel, i.e. tangential flow. The use of one of them requires no selection from a list.

11.7 Consequently, the passages of the application as filed referred to above directly and unambiguously disclose the subject-matter of claim 1.

12. The feature "*mammalian cells*" in claim 2 is disclosed in claim 3 as filed, and on page 3, lines 15 and 16 of the application as filed, which states that these cells are used "*in particular*".

13. The various cell lines mentioned in claim 3 are literally disclosed on page 3, lines 17 to 19 of the application as filed as a list of equal alternatives.

14. Furthermore, the cell lines mentioned in claims 4, 5, and 6 are indicated on page 3, lines 17, 18, and 19 of the application as filed, respectively.

15. Lastly, the process of claim 7 finds a literal basis in claim 11 as filed.

16. The main request therefore complies with the requirements of Article 123(2) EPC.

Lack of clarity and insufficiency of disclosure

17. The appellant submitted that the introduction of the feature "*a molecular weight of 150 kDa*" in claim 1 added further complexity to the case since new issues arose under Articles 83 and 84 EPC. The patent application and the prior art did not disclose the production of an IgG of exactly 150 kDa, but an IgG of approximately 150 kDa only.

18. The board does not agree. The standard to be applied for assessing clarity and insufficiency is how the skilled person being familiar with the production of

biological products in cell culture construes the contested feature in the claimed process. In the board's view, the skilled person construes the term "*150 kDa*" of claim 1 as IgG's approximate molecular weight, since it is commonly known in the art that the molecular weight of antibodies, like that of any other recombinant protein, varies slightly from production batch to batch due to culture conditions that are not exactly reproducible.

19. The appellant further submitted under insufficiency that the claimed method encompassed non-working embodiments. Processes reported in the prior art, although comprising all the features of claim 1, suffered from filter clogging due to the presence of cells (see document D15, Figure 1 on page 172, and page 176, column 1, third paragraph).

20. According to decision G 1/03 (OJ EPO 2004, 413), if there is a lack of reproducibility of the claimed invention (i.e. a failure of the claimed features to deliver an aimed effect), this may be relevant under the requirements of sufficiency of disclosure or inventive step. If the technical effect is expressed in the claim, there is a lack of sufficiency of disclosure. Otherwise, there is a problem of inventive step (cf. G 1/03, *supra*, point 2.5.2 of the Reasons).

21. Claim 1 mentions as technical effect the use of a hollow fiber filter that results in a "*liquid outflow and a flow which contents are kept in or fed back into the reactor*" resulting from the circulation of culture medium using a tangential flow. Furthermore, the filter with a maximum MWCO of 50 kDa must be "*suitable*" for retaining IgG while separating components with a lower molecular weight therefrom. Accordingly, under

insufficiency it must be assessed whether or not the structural features in claim 1 achieve these effects, i.e. (i) a retention of culture components above 50 kDa in the medium, e.g. IgG and cells, and (ii) a removal of components of a maximum size of 50 kDa from the culture in the liquid outflow.

22. The board has no doubts that hollow fiber filters of the pore size defined in claim 1 are suitable for these purposes. This has also not been contested.

23. Rather the appellant's objection is that the filter while not in the beginning of the process but over time looses it's ability to remove components from the cell culture, because of filter clogging.

23.1 The claimed process does not define a cultivation time for the cells, or another end point of the process, for example, a minimum IgG concentration, or a certain cell viability/density. Accordingly, a clogging of the filter over time for whatever reason is irrelevant for assessing insufficiency in this case. The process merely requires that at least some IgG is produced by cultivating eukaryotic cells in solution using a hollow fiber filter under the conditions specified in claim 1, so that IgG is retained/fed back, while components of 50 kDa and smaller are removed, and at least one medium compound is fed to the culture.

23.2 There are no arguments submitted, let alone evidence that the claimed process is not in principle suitable for these purposes. Document D15 provides no evidence in this respect. The document discloses that a process using a filter can be further improved by, for example, using an additional cell trap (see page 176, column 1, second and third paragraph).

24. Thus claim 1 and, hence, the main request complies with the requirements of Articles 84 and 83 EPC.

Priority

25. The appellant contested the entitlement to the priority right originating from document EP2007005915.3 filed on 6 February 2007 ("P2 document"), for the same reasons as those submitted under added subject-matter.

26. It is uncontested that the description of the P2 document is identical to that of the patent application. Furthermore, as concluded above, the subject matter of the main request does not extend beyond the content of the patent application as filed.

27. Accordingly, and in analogy to the finding on added subject-matter, the process of claim 1 is entitled to the priority right arising from the P2 document, because the criteria for examining added subject-matter and priority entitlement are the same (see Case Law, II.D.3.1.2). The relevant filing date is therefore 6 February 2007.

28. As a consequence, documents D21 and D27 are not prior art because they are published on 14 January 2009 and 10 May 2007, respectively, i.e. later than the filing date of the P2 document (6 February 2007).

Novelty

29. Claim 1 of the main request combines the subject-matter of claim 1 of auxiliary requests I and III submitted in reply to the statement of grounds of appeal. The appellant submitted that the process of claim 1 of

auxiliary requests I and III lacked novelty for the same reasons as set out for the main request, i.e. the claimed process lacked novelty over the disclosure of documents D15, D23 to D26, D36, and D38.

30. Document D15 discloses a perfusion culturing of suspended mouse-human hybridoma cells in serum and serum-free medium for the production of IgG (see abstract). A membrane filter cassette with a MWCO of 10 kDa is used for retaining IgG and cells within the culture medium (see Figure 1 in conjunction with page 172, column 1, first paragraph). This membrane filter is not a hollow fiber filter.

31. The board agrees with the opposition division's conclusion in the decision under appeal (see point 6.1.1.1) that documents D23 to D26 do not represent "poisonous divisionals" for the subject-matter claimed. In decision G 1/15 (published in OJ 2017, 82) the Enlarged Board of Appeal has ruled that partial priorities can be claimed for a claim encompassing alternative subject-matter even if the claim comprises one or more generic expressions provided that said alternative subject-matter has been disclosed for the first time, directly, or at least implicitly, unambiguously and in an enabling manner in the priority document.

32. Document D36 discloses a process for the production of IgG from suspended mammalian cells in a reactor. Fresh medium is pumped through a filter immersed in the cell culture inside the reactor. This filter constantly supplies the culture medium with fresh nutrients while waste products are removed therefrom. *Inter alia* a hollow fiber filter is used characterised by a MWCO below the molecular weight of an antibody, preferably

in the range of 3 kDa to 10 kDa (see paragraphs [0001], [0010], [0015], [0028], and [0035]).

32.1 The nutrient/waste exchange within the filter results from the circular pumping of fresh medium through the lumen side of the filter in a substantially parallel flow direction mediated by a pressure gradient (see paragraphs [0010] and [0021]). The exchange is supported by a rotational movement of the culture medium within the reactor. An impeller forces the culture medium to flow around ("*umfließt*") the external side of the filter. This external movement of the culture medium is independent from the fresh medium's internal parallel circular flow inside the filter, or the medium's alternating dead end flow in filters with a single inlet (see paragraphs [0023], [0031], and [0034]).

32.2 The appellant submitted that the rotational flow of the culture medium around the immersed filter in document D36 inevitably resulted in a tangential flow of the culture medium over the filter's external surface.

32.3 The board does not agree. Rather it is inevitable that a constant rotational movement of the culture medium against an immobilised filter causes a flow which comprises perpendicular, tangential and turbulent elements over the filter's external surface. This prevents a substantially parallel flow of the culture medium over the filter surface, contrary to the requirements of the claim (see point 8.4.3 above).

33. Document D38 discloses a perfusion culturing of a mouse hybridoma cell line producing an IgG_{2a} antibody grown in serum comprising medium (see abstract, page 156, column 1, second paragraph, and Figure 2). Cells and

IgG are retained in the cell culture by circulating in a tangential flow over a membrane filter that is connected to a backflush timer that periodically reverses the flow to minimise filter clogging (see page 157, column 1, third paragraph and Figure 2, Legend). The filter is "*equipped with either a 0.22 or 0.65 micron Durapore (millipore DVLP) membrane*" (see page 157, column 1, fourth paragraph), which is not a hollow fiber filter.

34. Consequently, the process of claim 1 and, hence, the main request is novel and complies with the requirements of Article 54 EPC.

Inventive step

Closest prior art and technical problem

35. The appellant submitted that any one of documents D9, D10, D15, D19, D36 and D38 represented the closest prior art. The respondent selected document D7, while the opposition division considered that documents D7, D19, or D38 represented the closest prior art.

36. According to the case law the closest prior art must be directed to the same purpose as the claimed invention, and, as a secondary consideration, should have most of the relevant technical features in common.

37. Document D7 discloses a process for a perfusion culturing of suspended eukaryotic cells in serum-free medium, wherein the cell culture is circulated over a hollow fiber filter in an ATF mode. The resulting liquid outflow has a lower cell density than the cell culture, i.e. a certain percentage of cells leaks through the filter (see page 1, lines 6 to 11, page 3,

line 33 to page 4, line 9, page 7, lines 30 and 31, and claim 1).

37.1 The hollow fiber filter has a pore size with a MWCO of "*0.2 micron*", i.e. 0.2 µm (see page 8, lines 11 to 16, page 10, line 20), which explains the cell leakage. The process produces preferably monoclonal antibodies, including IgG1, which are, due to the large filter pore size, constantly removed from the cell culture (see page 9, lines 14, 20, 26, 29 and 31, Examples 1 and 2, page 7, line 30, and page 11, line 14, and claim 14).

37.2 The claimed process therefore differs fundamentally from the process of document D7 since the filter with a smaller pore size (maximum of 50 kDa instead of 0.2 µm) retains, and thereby concentrates antibodies and cells within the culture medium instead of constantly removing them therefrom, in particular the antibodies.

38. Documents D9 and D10 disclose a dialysis-based filtration which differs fundamentally from a filtration using a tangential flow resulting in a liquid outflow (see point 8.4.3, above).

38.1 The appellant submitted that the different cross-sectional areas of the lumen and shell side of the hollow fiber filter used for nutrient/waste exchange in document D9 inevitably generated a pressure gradient which caused a cross flow of nutrients/waste products across the filter. The document disclosed therefore no dialysis-based filtration but a filtration that fell within the scope of claim 1.

38.2 The board does not agree. Document D9 designates the filter consistently as "*dialyser*" (see e.g. column 7, lines 43, 46, 56, and column 8, lines 34 to 41). This

is consistent with the filter's function as a dialyser since document D9 states that the exchange speed of nutrients/waste via the membrane is "*dependent upon the concentrations of the materials in question on both sides of the membrane and upon the membrane surface*" (see column 10, lines 10 to 16). Thus, the exchange of nutrients/waste depends solely on the presence of a concentration gradient (i.e. a classical dialysis), and not on a pressure gradient as required for an outflow resulting from a tangential flow (see point 8.4.3 above, document D33, page 1487, point 66, and document D35, page 1, column 1, second paragraph, and Figure 1).

38.3 The skilled person takes this disclosure in document D9 at face value. A pressure gradient does not allow a simultaneous exchange of nutrients/waste across a filter membrane along respective concentration gradients, but presses substances across the membrane along a pressure gradient - even against a concentration gradient. Pressure gradients within the hollow fiber filter can be avoided by synchronising the pumps. Therefore it is not inevitable that pumps in combination with different sectional areas of the lumen and shell sides of a hollow fiber filter generate pressure gradients across a membrane.

38.4 The same is true for document D10. Although this document designates the hollow fiber filter used for the nutrient/waste exchange as "*cross flow filter*", document D10 states that this filter allows the waste products to "*diffuse*" from the culture, and the nutrients to "*diffuse*" into the culture, while keeping antibodies and cells within the culture medium (see column 1, lines 20 to 40, column 2, lines 12 to 17).

38.5 Thus the nutrients/waste exchange over the filter is caused by diffusion which is a dialysis-based filtration along a concentration gradient (see column 1, lines 31 to 35, and claim 1, step (f)). The cross flow filter in document D10 is therefore operated in a dialysis mode.

39. Document D15 discloses a perfusion culturing of suspended cells for the production of IgG. In a preliminary experimental set-up about 95% of the cells are retained in the reactor mediated by a settling zone, while the "*supernatant*" fraction that contains about 5% of the cells circulates over a membrane filter cassette to retain IgG and cells within the reactor (see abstract, and Figure 1 in conjunction with page 172, column 1, first paragraph). Since filter clogging is still an issue, the final experimental set-up adds a cell trap to the process (see Figure 1, and page 176, column 1, third paragraph). These two means reduce the amount of circulating cells to such an extent that filter clogging is no longer a problem. Document D15 does not mention whether or not the supernatant contains cells. However, since the cell removal is so efficient, the supernatant does not necessarily contain cells contrary to the requirements of the claimed process (see point 8.4.1, above).

40. Document D19 discloses a perfusion culturing of a mouse hybridoma cell in serum-free medium that produces IgG (see abstract, and page 36, column 1, penultimate paragraph, and column 2, last paragraph). The cells and antibodies are retained inside the reactor by a filter with a MWCO of 10 kDa that is fixed to the reactor bottom. This set-up results in a so called "dead-end filtration" of the cell culture (see page 36, column 2, second paragraph). The claimed process differs thus

fundamentally from the process of document D19, since a tangential flow is used instead of a perpendicular flow resulting in a dead-end filtration.

41. Document D36 as indicated above (see point 32.3) discloses a further process for the production of IgG from suspended mammalian cells in a reactor. The culture medium is not circulated in a tangential flow over the filter surface, but in a flow comprising perpendicular, tangential, and turbulent elements.

42. Document D38 as indicated above (see point 33) discloses a perfusion culturing of suspended cells producing an IgG in serum-containing medium. The cell culture circulates over a membrane filter "*with either a 0.22 or 0.65 micron Durapore (millipore DVLP) membrane*" in a tangential flow. The serum proteins in the medium reduce through gel polarisation the effective pore size of the filter so that it has "*similar*" retention properties to a 10 kDa ultrafiltration membrane (see page 163, column 1, lines 7 to 12; Reference "*[5]*" is identical to document D15 in these proceedings). However, similar properties between filters allow no conclusions about the actual pore size of document D38's membrane filter. An IgG with an approximate size of 150 kDa might be similarly well retained by pore sizes larger than 10 kDa, for example, 55 kDa. Thus the filter in document D38 does not necessarily fall within the pore size range cited in claim 1.

43. Therefore, all documents referred to above are directed to the same purpose as the claimed process, namely a cell culture-based production of antibodies. As regards the distinguishing features, the processes reported in documents D7, D9, D10, D15, D19, and D38 differ from

the claimed process by two technical features (D7: filter with a larger pore size, no retention of antibodies within the culture medium, leakage of a substantial amount of cells; D9 and D10: dialysis-based filtration, no IgG mentioned; D15: membrane filter, and different cell culture composition circulating over the filter; D19: membrane filter, and dead-end filtration; D38: membrane filter, unknown pore size with properties similar to 10 kDa). The process of document D36 differs in one technical feature only, i.e. a cell culture that circulates in a non-tangential flow manner over the filter surface.

44. Irrespective of the differences in the number of technical features, documents D7, D9, D10, D19, and D36 for the reasons indicated above, use fundamentally different filtration systems in their processes which makes them unsuitable as closest prior art. For this reason the appellant's and the respondent's problem-solution approach arguments provided for these documents are not convincing, and will be disregarded. Accordingly, documents D15 and D38 represent the closest prior art.

45. The respondent submitted that the difference between the use of a hollow fiber filter used in the claimed process and a membrane filter disclosed in documents D15 and D38 resulted in the production of IgG with an increased yield. This was shown in Example 2 of the patent and in document D42.

45.1 According to the established case law, alleged advantages to which the patent proprietor merely refers, without offering sufficient evidence to support the comparison with the closest prior art, cannot be taken into consideration in determining the problem

underlying the invention and therefore in assessing inventive step (see Case Law, I.D.4.2).

45.2 No comparative experimental data of the claimed process using a hollow fiber filter versus a membrane filter have been provided by the respondent. Accordingly, neither the Examples in the patent nor the supplementary data of document D42 are suitable to support an increased IgG yield across the whole breadth of claim 1.

46. The technical problem to be solved is thus the provision of an alternative process of culturing suspended eukaryotic cells for the production of an IgG antibody.

47. In view of the working example of the patent, the board is convinced that the process of claim 1 solves this problem.

Obviousness

48. It remains to be assessed whether or not the skilled person, starting from documents D15 or D38 and facing the problem defined above, would have arrived at the process of claim 1 in an obvious manner.

49. The appellant submitted in a first line of argument that the claimed method was obvious for the skilled person in light of document D15's teaching alone since it merely required the replacement of a membrane filter by a hollow fiber filter. Alternatively, the claimed method lacked an inventive step when combining the process of document D15 with commercial ATF technology, for example, as disclosed in document D4.

50. The board does not agree. Starting from the first experimental set-up reported in document D15, the skilled person would not have merely replaced the membrane filter with a hollow fiber filter, since he or she would have expected that the indicated filter clogging problem remained the same irrespective of the type of filter used. In this situation, the skilled person would have followed the explicit teaching of document D15 for solving the clogging problem by using an additional cell trap. Since the filter clogging problem is solved, the skilled person has no reason to consider alternatives for solving the clogging problem, let alone the use of a hollow fiber filter together with ATF.

50.1 Starting from the second experimental set-up disclosed in document D15, i.e. the use of a settling zone and a cell trap, the board agrees with the appellant that the exchange of a membrane filter by a hollow fiber filter is obvious because both are equivalent filter alternatives in cell culturing processes.

50.2 However, the skilled person would not necessarily arrive at a process that falls within the scope of claim 1. The use of a settling zone together with the cell trap in the process of document D15 is so efficient at removing cells from the cell culture supernatant circulating over the filter, that the supernatant does not necessarily contain cells, contrary to the requirements of claim 1 (see point 39, above).

51. In a second line of argument the appellant submitted that the claimed method was obvious for the skilled person in the light of document D38's teaching. The claimed process comprised as one embodiment the

culturing of cells in serum-free medium for the production of IgG. This embodiment of claim 1 differed from the process of document D38 merely in the use of a filter with an appropriate pore size to retain IgG. In the absence of serum proteins the skilled person was free to choose any suitable filter. Document D38 referred in this context already to document D15 using a filter with a pore size of 10 kDa (see point 42 above). The selection of any suitable filter with this pore size, including a hollow fiber filter, was obvious for the skilled person. Similar arguments applied for the embodiment of claim 1 which used serum-containing medium for cell culturing. The skilled person would have considered any filter as suitable alternative that retained antibodies in the culture medium. This included any filter with a MWCO of 50 kDa or smaller.

52. The board does not agree. It is not convincing that the skilled person considered document D38 to represent the closest prior art for the culturing of cells in serum-free medium for the production of IgG.

52.1 The process of document D38 relies as an essential technical feature on the presence of serum proteins in the medium. Solely these proteins reduce the effective pore size of the microporous membrane filter to a size suitable for retaining antibodies in the culture medium. A cell culturing in serum-free medium is incompatible with this filtration system. Therefore, for any cell culturing in serum-free medium, the skilled person would have rather considered documents disclosing such a process as the appropriate closest prior art, for example, document D15 (see above).

52.2 As regards the process embodiment of claim 1 comprising culturing cells in serum-containing medium, the board

is of the opinion that the skilled person would have selected a hollow fiber filter instead of a membrane filter as an alternative. However, for the reasons set out above (see point 42), the skilled person using a hollow fiber filter would not necessarily arrive at an embodiment that falls within the scope of claim 1 since the actual cut-off size of the gel polarised hollow fiber filter remains unknown. Furthermore, it is unknown whether the retention properties of a gel polarised membrane filter are comparable to that of a hollow fiber filter since the surface properties of these filters might be different.

53. In light of these considerations, the process of claim 1 is not obvious over the prior art. The main request therefore involves an inventive step (Article 56 EPC).

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.
2. The case is remitted to the opposition division with the order to maintain the patent with the following claims and a description to be adapted:
   Claims:
   Nos 1 to 7 of the main request filed as auxiliary request VI under cover of a letter dated 4 October 2019.

The Registrar: The Chairman:

M. Schalow B. Stolz

Decision electronically authenticated