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Datasheet for the decision of 28 November 2019

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Application Number: 06753791.0

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Language of the proceedings: EN

Title of invention:
Method for the purification of Antibodies

Patent Proprietor:
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Opponents:
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Headword:
Antibody Purification/HOFFMANN-LA ROCHE

Relevant legal provisions:
EPC Art. 54, 56, 83, 84, 123(2)
RPBA Art. 12(2), 12(4), 13

Keyword:
Novelty - main and auxiliary request 1 (no)
Auxiliary requests 2 and 4 to 6 - Admission (no)
Auxiliary request 3 - clarity (no)
Auxiliary request 7 - allowable (yes)

Decisions cited:
G 0007/93, G 0003/14, T 0229/08, T 0197/10, T 2221/10, T 1931/14

Catchword:

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

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Case Number: T 1930/14 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 28 November 2019

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Decision under appeal:
Interlocutory decision of the Opposition Division of the European Patent Office posted on 24 July 2014 concerning maintenance of the European Patent No. 1888636 in amended form

Composition of the Board:

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

Summary of Facts and Submissions

I. European patent EP 1 888 636, entitled "*Method for the Purification of Antibodies*", derives from European patent application 06 753 791.0 which was filed as international application published as WO 2006/125599. The patent was opposed by seven parties (opponents 1 to 7).

II. In an interlocutory decision, the opposition division decided that, account being taken of the amendments in the form of auxiliary request 9, the patent and the invention to which it related met the requirements of the EPC (Article 101(3)(a) EPC). In that decision, the opposition division *inter alia* held that the subject-matter of claim 1 of the main request lacked novelty (Article 54 EPC). Claim 1 of auxiliary request 1 was held to lack clarity (Article 84 EPC). The subject-matter of claim 1 of auxiliary requests 3, 7 and 8 lacked an inventive step (Article 56 EPC). Auxiliary requests 2, 4, 5 and 6 were not admitted into the proceedings.

III. Appeals against the decision of the opposition division were filed by the patent proprietor (appellant) and opponent 5. Opponent 5 subsequently withdrew their appeal. Thus, opponents 1 to 7 are respondents I to VII, respectively.

IV. With the statement of grounds of appeal, the appellant re-filed the sets of claims of the main request and the 13 auxiliary requests pending before the opposition division at the end of their proceedings.

V. Claim 1 of the main request reads:

"1. Method for purifying a monoclonal antibody from aggregates thereof, wherein the method comprises

a) providing a solution comprising a monoclonal antibody, a buffer substance;

b) bringing the solution and a weak cation exchange material in contact under conditions whereby the monoclonal antibody binds to the weak cation exchange material;

c) recovering the monomeric monoclonal antibody from the weak cation exchange material in a single step by using a solution comprising a buffer substance and a salt,

wherein the method comprises purification of the monoclonal antibody by a protein A affinity chromatography before step a);

wherein the weak cation exchange material is a carboxy-methyl weak cation exchange material,

wherein the monoclonal antibody is a member of the immunoglobulin class G, wherein the solution in the recovering step c) has a pH value of from pH 3.0 to pH 7.0,

wherein the salt in step c) is selected from the group consisting of sodium chloride, sodium sulphate, potassium chloride, potassium sulfate, salts of citric acid, salts of phosphoric acid, and mixtures of these components,

wherein the buffer substance has a concentration range between 5 mM and 100 mM."

Claim 1 of auxiliary request 1 differs from claim 1 of the main request in that step c) includes the additional text at the end: "such that the monomeric monoclonal antibody is separated from aggregates".

Claim 1 of auxiliary request 2 reads:

"1. The use of a carboxy-methyl weak cation exchange material for purifying a monoclonal antibody from aggregates thereof in a method which comprises

a) providing a solution comprising a monoclonal antibody, a buffer substance;

b) bringing the solution and said weak cation exchange material in contact under conditions whereby the monoclonal antibody binds to said weak cation exchange material;

c) recovering the monomeric monoclonal antibody from said weak cation exchange material in a single step by using a solution comprising a buffer substance and a salt,

wherein the method comprises purification of the monoclonal antibody by a protein A affinity chromatography before step a);

wherein the monoclonal antibody is a member of the immunoglobulin class G, wherein the solution in the recovering step c) has a pH value of from pH 3 .0 to pH 7.0,

wherein the salt in step c) is selected from the group consisting of sodium chloride, sodium sulphate, potassium chloride, potassium sulfate, salts of citric acid, salts of phosphoric acid, and mixtures of these components,

wherein the buffer substance has a concentration range between 5 mM and 100 mM."

Claim 1 of auxiliary request 3 reads:

"1. Method for purifying a monoclonal antibody from aggregates thereof, wherein the method comprises

a) providing a solution comprising a monoclonal antibody, a buffer substance;

b) bringing the solution and a weak cation exchange material in contact under conditions whereby the monoclonal antibody binds to the weak cation exchange material;

c) recovering the monomeric monoclonal antibody from the weak cation exchange material in a single step by using a solution comprising a buffer substance and a salt, wherein the conductivity of said solution is increased by changing one condition all at once from a starting value to a final value so as to obtain said monoclonal antibody purified from aggregates thereof;

wherein the method comprises purification of the monoclonal antibody by a protein A affinity chromatography before step a);

wherein the weak cation exchange material is a carboxy-methyl weak cation exchange material,

wherein the monoclonal antibody is a member of the immunoglobulin class G, wherein the solution in the recovering step c) has a pH value of from pH 3.0 to pH 7.0,

wherein the salt in step c) is selected from the group consisting of sodium chloride, sodium sulphate, potassium chloride, potassium sulfate, salts of citric acid, salts of phosphoric acid, and mixtures of these components,

wherein the buffer substance has a concentration range between 5 mM and 100 mM."

Claim 1 of auxiliary request 4 is the same as of claim 1 of auxiliary request 2 except that it has been adapted to include the additional features of claim 1 of auxiliary request 3.

Claim 1 of auxiliary request 5 reads:

"1. Method for purifying a monoclonal antibody from aggregates thereof, wherein the method consists of the steps of

a) providing a solution comprising a monoclonal antibody, a buffer substance;

b) bringing the solution and a weak cation exchange material in contact under conditions whereby the monoclonal antibody binds to the weak cation exchange material;

c) recovering the monomeric monoclonal antibody from the weak cation exchange material in a single step by

using a solution comprising a buffer substance and a salt,

with the additional step of a purification of the monoclonal antibody by a protein A affinity chromatography before step a);

wherein the weak cation exchange material is a carboxy-methyl weak cation exchange material,

wherein the monoclonal antibody is a member of the immunoglobulin class G, wherein the solution in the recovering step c) has a pH value of from pH 3.0 to pH 7.0,

wherein the salt in step c) is selected from the group consisting of sodium chloride, sodium sulphate, potassium chloride, potassium sulfate, salts of citric acid, salts of phosphoric acid, and mixtures of these components,

wherein the buffer substance has a concentration range between 5 mM and 100 mM."

Claim 1 of auxiliary request 6 is the same as claim 1 of auxiliary request 5, except that part c) is the same as part c) of claim 1 of auxiliary request 3.

Claim 1 of auxiliary request 7, filed as auxiliary request 11 with the statement of grounds of appeal, differs from claim 1 of the main request in that the pH value of the solution used in the recovering step c) is 4.5 to 5.5.

VI. The following documents are mentioned in this decision.

D1: WO 95/22389

D4: EP 0 085 747

D9: Amersham Biosciences 2004, "Ion Exchange Chromatography and Chromatofocusing", 1-82.

D12: WO 99/62936

D17: US 5 164 487

D56: Roque A.C.A. *et al.*, Biotechnol. Prog. 2004, 20, 639-654.

VII. The relevant arguments of the appellant, submitted in writing and at the oral proceedings, can be summarised as follows:

Main and auxiliary request 1 - Claim 1
Novelty - Article 54 EPC

Claim 1 of these requests related to a method for purifying a monoclonal antibody from aggregates thereof. The method comprised two mandatory purification steps, namely a protein A chromatography step followed by a weak carboxy-methyl (CM) ion-exchange chromatography step.

Due to the "comprising" language the method did not exclude further steps. However, carrying out the claimed method had to achieve the purpose mentioned in the preamble, i.e. "purifying monoclonal antibody from aggregates thereof".

Since protein A chromatography was not able to separate monomeric monoclonal antibodies from aggregates, it was mandatory in the method according to claim 1 that this separation was achieved by the weak CM cation-exchange step.

In claim 1 of auxiliary request 1 this was further clarified by the inclusion of the phrase "such that the monomeric monoclonal antibody is separated from aggregates".

Thus, any method where no separation occurred in the CM cation-exchange step was not novelty-destroying.

Document D1 disclosed a method for the purification of monomeric antibodies from a mixture. The method comprised a protein A chromatography step, a cation-exchange chromatography step and a hydrophobic interaction chromatography (HIC) step.

Document D1 disclosed that only the final HIC step separated the monomeric antibodies from aggregates and protein A contaminants, see page 4, lines 16 to 27 and page 16, lines 18 and 19. It did not disclose that monomeric monoclonal antibody was separated from aggregates by virtue of the weak CM cation-exchange step.

It could be seen from Table 9 on page 32, which showed a summary of the results of Example ID, that no separation of aggregates occurred as a result of the CM step. It was apparent that the content of aggregates before and after the CM step was identical (0.4 %).

Any assumption that minor reductions in aggregate content might have taken place was mere speculation and

completely unfounded. Furthermore, there was no indication in Examples IA, IB, IC of document D1 that any aggregates were removed by the CM step.

The claim should be construed according the principles set out in decision T 1931/14. These were that if a claimed method stated a purpose which defined a specific application of the method, here "purifying a monoclonal antibody from aggregates thereof", then "*in fact it requires certain additional steps which are not implicit in the remaining features, and without which the claimed process would not achieve the stated purpose*" (see catchword). Such additional steps were not disclosed in document D1, which did not explicitly state that the cation-exchange step separated IgG monomers from aggregates, but did explicitly state that the HIC step separated monomers from IgG aggregates.

The claimed subject-matter was limited to those methods in which the cation-exchange step provided effective separation of aggregates for monomers.

Auxiliary requests 2, 4, 5 and 6
Admission - Article 12(4) RPBA

Auxiliary requests 2, 4, 5 and 6 should not be excluded from the proceedings pursuant to Article 12(4) RPBA since each of these requests addressed and overcame points raised in the decision under appeal as follows.

The subject-matter of auxiliary requests 2 and 4 clearly addressed the opposition division's concerns regarding novelty over document D1. The claims were based on those of the main request and auxiliary request 3, respectively, but were reworded as use claims. This rewording excluded the possibility that

the separation did not take place in the CM chromatography step therefore avoided the subject matter disclosed in document D1.

The subject-matter of auxiliary requests 5 and 6 corresponded to the subject-matter of the main request and auxiliary request 3, respectively, but with the claims reworded into a "consisting" language which limited the subject-matter to methods in which the separation of monomeric monoclonal antibody was performed by using the CM cation-exchange step. Once again this amendment clearly addressed the concerns of the opposition division in relation to lack of novelty over document D1.

Auxiliary Requests 2, 4, 5 and 6 were filed on 28 February 2014, i.e. four days before the oral proceedings before the opposition division on 4 March 2014. The amendments were very straight-forward and focused on the separation of the monoclonal antibody from its aggregates in the CM cation-exchange step. This was in line with all previous lines of argument made before the opposition division, thus the requests were convergent with the other pending requests. They did not "*create a new case to examine*" as implied by respondent II and did not require any new search for prior art. In fact, both changing a method into a use claim as in auxiliary requests 2 and 4 and replacing the word "comprising" by "consisting" as in claim 1 of auxiliary requests 5 and 6 was so trivial that a request specifying these amendments would normally be allowed, even during oral proceedings before an opposition division.

According to the Guidelines for Examination in the EPO (see H-V, 7.4) and the established case law of the

boards of appeal (see decision T 332/94 and Case Law of the Boards of Appeal, 7th edition 2013, page 426 citing decision T 420/86) the "*change in a claim from a method in which a certain product* [here: CM weak cation-exchange material] *is used to a claim to the use of that product in performing that same method is allowable*".

Auxiliary request 3 - Claim 1
Clarity - Article 84 EPC

The claim was clear for the reasons set out by the opposition division in its decision at point 13. The term "condition" was part of the feature "wherein the conductivity of said solution is increased by changing one condition all at once from a starting value to a final value so as to obtain said monoclonal antibody purified from aggregates thereof" and as such defined how the conductivity of the solution was changed during the single step elution in step c) of the claimed method.

It would be immediately apparent to the skilled person how the conductivity of an aqueous buffer could be increased. Even if there was any doubt, the patent provided exemplary ways in paragraph [0039] (pH, the ionic strength, salt concentration). The skilled person would understand how the terms conductivity, pH, ionic strength and salt concentration were interrelated and would only change one condition (e.g. the concentration of the elution salt OR the concentration of the buffer salt OR the pH) to achieve the increased conductivity and ultimately the elution of the monoclonal antibody.

Auxiliary request 7 (filed as auxiliary request 11 with statement of grounds of appeal)

Admission - Article 12(4) RPBA

The respondents' request to exclude auxiliary request 7 from the appeal proceedings had no legal basis. This claim request had not been discussed at the oral proceedings before the opposition division because of the allowance of a higher ranking request. It had been on file during the proceedings before the opposition division and it addressed a ground for opposition. The fact that a lower ranking request was not discussed at the oral proceedings before the opposition division was not a reason why it should be excluded from the appeal proceedings. At most, the board could remit the case to the opposition division to decide on this request.

Auxiliary request 7

Amendments - Article 123(2) EPC

Claim 1 was based on the main request but with a limitation to pH ranges of the recovering solution of 4.5 to 7.0. This pH range found its basis on page 8 line 29 of the application as filed.

Clarity - Article 84 EPC

The amendment of the pH range was clear and did not introduce any unclarity over claim 1 of the main request.

Novelty - Article 54 EPC

The claim differed from claim 1 of the main request which had been found to lack novelty in view of document D1 in that the pH value of the solution used in the recovering step c) fell outside of the range mentioned in that document.

Inventive step - Article 56 EPC

The claimed method differed from that disclosed in document D1 only in the pH used in the recovering step, making it a good candidate to represent the closest prior art. However, for the sake of argument it could be accepted that document D12 represented the closest prior art.

The differences between the claimed method and that disclosed in document D12 were threefold.

The first was that the authors of document D12 deliberately did not use a protein A chromatography step for the removal of impurities. Instead they used an anti-IgE antibody affinity column. The starting material used in document D12 did not have contaminants that necessitated using a protein A chromatography step since it was derived from a human myeloma cell line culture. Secondly, the methods disclosed for separating monomers from aggregates in document D12 used strong cation exchangers rather than weak cation exchangers. Thirdly, elution was always done as a linear gradient, not in a single step.

One of the technical effects of these differences was that using a weak cation exchanger was more effective than using a strong one. The technical problem to be

solved could be formulated as providing an alternative method for separating monomers of monoclonal antibodies from aggregates thereof.

The claimed solution was not obvious - the person skilled in the art would have known from document D12, in particular from the results summarised in Table I, that a good separation of monomers from aggregates was achieved either using an anion-exchange column or using a strong cation-exchange column. For instance, the strong cation-exchange material Resource S™, eluted using a linear gradient of NaCl, was reported to result in "*Equivalent to Q separation*", where "*Q separation*" referred to Resource Q™, an anion exchanger. There was therefore no pointer in document D12 or in any other cited document to change from using either anion chromatography or strong cation-exchange chromatography to weak cation-exchange chromatography as a solution to the technical problem.

It was irrelevant that weak cation-exchange chromatography was mentioned in general on page 5 of document D12 and it was not disputed that weak cation-exchange columns were known for protein separation in general.

Another consideration was that the skilled person starting from document D1 would have considered the use of HIC chromatography to achieve separation of aggregates from monomers.

Respondent II had suggested that the skilled person might have combined the disclosure in document D12 with a disclosure in document D17 of the use of weak cation exchangers for separating antibody aggregates from the monomers. However, document D17 concerned methods for

the purification of polyclonal antibodies, and thus the separation of hetero-aggregates, and not the separation of homo-aggregates which was the aim of the claimed method.

Moreover, document D17 suggested the use of various ion-exchange materials including strong ones, see column 3. In fact, document D17 focused on the use of octanoic acid to manufacture an intravenously tolerable IgG preparation, see column 2, lines 40 to 43.

Thus, the skilled person would not have combined the method disclosed in document D12 with the disclosure in document D17 to arrive at the method claimed.

Disclosure of the invention - Article 83 EPC

The respondents had merely alleged that the skilled person would be faced with an undue burden in carrying out the claimed invention with respect to the whole scope of the claim. However, they had not provided any evidence in support of this allegation. The case law of the boards of appeal had consistently held that to substantiate an objection that an invention was insufficiently disclosed it was necessary that there were serious doubts substantiated by verifiable facts, see "Case Law of the Boards of Appeal of the European Patent Office", 9th edition, 2019, page 373 and decision T 19/90.

Although the respondents had argued that the skilled person would have encountered difficulties in choosing suitable parameters that would allow the adaption of the claimed method to the physico-chemical properties of particular IgG monoclonal antibodies, this was contradicted by the submissions of respondent V on

inventive step. In this context they had argued that such optimisation was a matter of routine for the skilled person at the relevant date of the patent, as evidenced by e.g. document D9 (see page 47/188) which taught that "*when binding and elution conditions for a target protein(s) and contaminants have been determined, usually during preliminary gradient elution separations, conditions were chosen to maximise binding of the target protein and minimise binding contaminants during sample application the target protein(s) is then eluted by a single buffer change in an enriched, concentrated form*".

VIII. The relevant arguments of the respondents, submitted in writing and at the oral proceedings, can be summarised as follows:

Main and auxiliary request 1 - Claim 1
Novelty - Article 54 EPC

In view of the "comprising" language, the claimed method was not limited to steps recited in the claim. Other steps could be carried out before or after the two explicitly recited steps. It was also to be noted that claim 1 did not specify to which extent aggregates were removed. Thus, the wording of claim 1 encompassed for example the removal of only a small amount of aggregates as a result of the CM step.

Moreover, in the light of document D55, it was clear that antibody monomers and aggregates could be separated at least partially by protein A affinity chromatography.

Document D1 disclosed a method for purification of monomeric antibodies from a mixture which comprised,

inter alia, aggregates thereof. It did not disclose that aggregates were separated from the monomeric antibody only by the HIC step or that the cation-exchange step did not separate monomers from aggregates at all. In fact, it disclosed that the aggregates were separated from the monomers as a result of both steps - the cation-exchange chromatography step "*removes protein and [...] impurities*" (page 15, lines 18 to 19). The HIC step "*removes additional protein and [...] impurities*" (page 16, line 18).

Thus, it was clear that the HIC step in document D1 was an additional "polishing" step, following at least one step in which "*aggregates and misfolded species*" would already have been at least partially purified (page 10, lines 4 to 24).

The chromatography conditions disclosed in document D1 including the pH, salt, buffer and buffer concentration of the single step elution were in line with claim 1, see in Table 1 on page 18 the single "CM SEPHAROSE Elution Buffer".

Since the method disclosed in document D1 had all the features of the claimed method, it must be presumed that, if the invention of claim 1 of the main request worked, the same effect would have been achieved in document D1.

Table 9 of document D1 only disclosed the results of one specific working example. What had to be assessed was however, whether the whole disclosure of document D1 was detrimental to the novelty. Document D1 disclosed that in experiments IA, IB and IC aggregates were removed by weak cation exchange chromatography in a single step.

The percentages disclosed in Table 9 were imprecise because they provided only 1 decimal place. Since the error range was at least 10% it could not be deduced that aggregates were not removed to a certain extent in this step.

This was in line with common general knowledge. Aggregates were nothing but protein impurities, which could be separated by various chromatography processes because of different physical properties. Furthermore, aggregates were diverse. Any disclosure in document D1, that aggregates - in contrast to other protein impurities - could not be removed by cation-exchange chromatography, would be technically absurd.

Auxiliary requests 2, 4, 5 and 6
Admission - Article 12(4) RPBA

Auxiliary request 2 was identical to auxiliary request 10 filed on 28 February 2014 before the opposition division. This request was late filed during opposition proceedings and not admitted into the proceedings by the opposition division. The opposition division's view that the subject-matter of the claims as granted and that of various auxiliary requests lacked novelty had already been stated in the communication accompanying the summons to oral proceedings. It was only a few days before the oral proceedings in opposition that this request was filed. Admitting it at the appeal stage would also create a new case to examine by the board. The change of category from a 'method' to a 'use' was not trivial, raising a number of additional issues. These included the question of whether or not the subject-matter of the claim was actually different from that of claim 1 of higher ranking requests. In particular, it appeared

that the claimed subject-matter remained a method for the production of a purified monoclonal antibody and lacked novelty for the same reason as claim 1 of the main request. Hence the new request did nothing to overcome the lack of novelty of the method of claim 1 of the main request.

Auxiliary requests 4 to 6 had not been admitted into the proceedings by the opposition division. They should be excluded from the appeal proceedings for the same reasons as auxiliary request 2.

Auxiliary request 3 - claim 1
Clarity - Article 84 EPC

The term "condition" was not defined in the patent. It was not clear how conductivity was increased by changing "a" condition since there was no disclosure about how to select this one condition, or how to select and adjust the difference between starting value and the final value. It was not clear what was meant by "all at once", particularly since paragraph [0039] (which defined "single step") stated that the condition was changed "incrementally, i.e. stepwise". "Incrementally" meant small steps.

In addition it was not clear whether the limitation to changing one condition meant that only one condition was changed or whether the only one condition was changed "all at once", while other conditions could be changed in several steps.

Moreover, it was not clear what was meant by "condition". Paragraph [0039] set out some non-limiting examples of conditions but there was no definition of the term. In the submissions concerning novelty in the

appellant's grounds of appeal it was considered that changing the buffer strength and adding salt amounted to changing condition**s**. However, increasing the buffer strength and adding salt both changed the ionic strength - indeed, the buffer was itself a salt - so that no distinction could be drawn between a buffer and a salt in terms of change of ionic strength. Hence, a change in one "condition", ionic strength, could be achieved by changing either or both the buffer or salt concentration.

Auxiliary request 7 (filed as auxiliary request 11 with the statement of grounds of appeal)
Admission - Article 12(4) RPBA

This claim request had not been dealt with by the opposition division, being lower ranking than the claim request considered allowable. However, its claimed scope was broader than that of then pending auxiliary requests 7 to 9. It should not be admitted because it was not convergent with the preceding claim requests. Admitting a claim request with broader claims was unfair to the respondents. The board had discretion not to admit non-converging requests, as evidenced in decision T 1903/13.

Furthermore, this request should not be admitted into the proceedings because it was late filed in the proceedings before the opposition division and also because it had been filed to improve the appellant's position with respect to meeting the requirements of Article 83 EPC. It did not improve the appellant's position in relation to novelty or inventive step or cure any defects noted under Article 123(2) EPC or Article 84 EPC.

Article 84 and Article 123(2) EPC

There were no objections pursuant to Article 84 EPC or Article 123(2) EPC.

Claim 1

Respondent IV considered that the subject-matter of claim 1 of this request was not directly and unambiguously disclosed in the application as filed in relation to the limitation of the pH to 4.5 to 5.5. The disclosure on pages 30 to 32 of the application as filed did not disclose that this pH range was for the elution buffer in step c). This was especially true in view of the pH values used in the working examples which were 4.0, 5.5 and 6.0.

Claim 6

Respondent V maintained the objection according to Article 123(2) EPC raised against the main request that the subject-matter of claim 6 had no basis in the application as filed. The feature that "the elution in step c) is at the same time the buffer substance" was said to derive from page 9, lines 20 to 22 of the application as filed. This read "[a]*nother preferred embodiment of the invention is the use of the salt, causing the elution, at the same time as buffer substance*". The opposition division had been wrong to consider that this provided a basis for the subject-matter of the claim because the wording of the passage on page 9 was ambiguous.

Novelty - Article 54 EPC
Disclosure of the invention - Article 83 EPC

The amendments made in this request did not improve the appellant's position. The request was objected to under Articles 54 and 83 EPC for the same reasons as the main request.

Inventive step - Article 56 EPC
Claim 1

According to the claimed invention, monoclonal antibodies were separated from aggregates thereof by means of a CM ion-exchange chromatography step. Both documents D1 and D12 also dealt with the purification of monoclonal antibodies. However, document D1 mentioned that aggregates were removed in the HIC step whereas the invention disclosed in document D12 was concerned with the separation of monomers from aggregates using ion-exchange chromatography. Document D12 was therefore a better document to represent closest prior art for the claimed invention than document D1.

The term "*aggregates*" used in the patent included all forms of antibody apart from the monomeric form. This interpretation was supported by figure 3 of the patent in which the fraction called "*aggregated immunoglobulin*" had two peaks and was distinguished from the single peak of "*monomeric immunoglobulin, free of aggregates*". Thus the invention in document D12 concerned the separation of monomeric antibody from aggregated forms of antibody and had the same purpose as the present invention. In contrast to the claimed method, document D12 did not disclose the use of a pre-purification step using protein A chromatography. The

technical effect of this difference was the removal of impurities.

The problem to be solved by the claimed method was therefore the provision of an improved method for the separation of monomers from aggregates of monoclonal antibodies. However, the claimed solution, i.e. the use of a protein A chromatography step, was essentially common general knowledge. That this was so was evidenced in the disclosure, for instance, of document D56 at page 646.

Moreover, document D12 at page 5, second full paragraph, made it clear that the skilled person would have chosen a cation-exchange resin suited to the particular impurity to be separated. The optimisation of the ion-exchange step was entirely routine. It was also clear from document D12 (*ibid*) that choosing a weak cation-exchange resin was entirely routine since examples of weak cation exchangers CM52 Cellulose™, CM Spherodex™, and CM Sepharose™ were all listed as useful matrix materials. A similar disclosure was to be found in document D17, see column 3 and document D4, see page 11, lines 22 to 27.

The appellant's main comment in relation to document D12 was that it only disclosed linear or multistep gradients for elution rather than single step. However, it was routine to use single step elution as evidenced by the disclosure in document D9 (see the page labelled 47/118).

The fact that the antibodies separated in documents D17 and D4 were polyclonal would not have dissuaded the skilled person from employing the ion exchange methods disclosed therein because the problem of separating

monomers from aggregates was common to purifying both monoclonal and polyclonal antibodies.

It followed from the above arguments that the claimed solution to the technical problem lacked an inventive step being obvious in the light of the disclosure of document D12 alone or in the light of the disclosure of documents D12 when combined with the disclosures in, document D17 or document D4.

Disclosure of the invention - Article 83 EPC
Claim 1

The claimed method was for the purification of any monoclonal antibody and specified no defined buffers for use in any of the steps and allowed the use of a number of different salts in step c). Moreover, the range of buffer concentrations allowed was very large.

In contrast, the twelve examples of the patent concerned only two specific monoclonal antibodies and in all of them only a single buffer, sodium citrate, and only a single salt, NaCl, was used. Given the discrepancy between the broad range claimed and the small number of exemplified embodiments, it was an undue burden for the skilled person to determine which conditions to use over the whole range claimed, aside from those exemplified.

Respondent IV's request for a different apportionment of costs - Article 104 EPC, Article 16 RPBA

The appellant had incurred unnecessary costs for respondent IV by filing auxiliary requests 10 to 13 late in the proceedings before the opposition division. Respondent IV incurred additional unnecessary costs by

introducing these requests again in the appeal proceedings. As a result, the respondent again had to deal with these requests in the written and oral proceedings. Overall, this was unfair and delayed the proceedings.

IX. In a communication pursuant to Article 15(1) RPBA, the board informed the parties of its provisional and non-binding preliminary appreciation of the substantive and legal matters concerning the appeal.

In relation to respondent IV's request for a different apportionment of costs it was stated that the board "*could see no persuasive reason to allow this request in so far as it is based on respondent IV's submission that auxiliary requests 2, 4, 5 and 6 were re-filed by appellant I with the statement of grounds of appeal. In particular, it is not apparent to the board why appellant I's actions should be considered as unfair or lead to a delay of the appeal proceedings. In relation to costs which might have occurred during the proceedings before the opposition division, the board is of the opinion that it cannot decide on a different apportionment of costs in relation to such costs, since the opposition division took no decision on the matter, either on request of respondent IV or its own motion (see also decision T 1059/98, point 2.2 of the reasons)*".

X. Respondents I and III to VII informed the board in writing that they would not attend the oral proceedings.

XI. Oral proceedings before the board took place on 29 and 30 November 2019. During these proceedings the appellant reordered the auxiliary requests, such that

auxiliary request 11 filed with the statement of grounds of appeal became auxiliary request 7 and auxiliary requests 7 to 9 filed with the statement of grounds of appeal became auxiliary requests 8 to 10. At the end of the proceedings, the Chair announced the decision of the board.

XII. The appellant requested that the decision under appeal be set aside and that the patent be maintained in amended form on the basis of one of the sets of claims

- of the main request, or alternatively, of auxiliary requests 1 to 6, all filed with the statement of grounds of appeal,
- or further alternatively, of auxiliary request 7, filed as auxiliary request 11 with the statement of grounds of appeal,
- or further alternatively, of auxiliary requests 8 to 10, filed as auxiliary requests 7 to 9 with the statement of grounds of appeal.

Furthermore, the appellant requested that respondent IV's request for a different apportionment of costs be rejected.

XIII. All respondents requested that the appeal be dismissed. Respondent IV requested a different apportionment of costs.

Reasons for the Decision

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

2. Respondents I and III to VII although duly summoned, did not attend the oral proceedings. The board decided

to continue the proceedings in their absence in accordance with Rule 115(2) EPC and to treat them as relying on their respective written cases in accordance with Article 15(3) RPBA.

Novelty - Article 54 EPC

Main request - Claim 1

Claim construction

3. The claim is for a method for purifying an IgG monoclonal antibody from aggregates thereof. The method comprises an initial protein A chromatography step and a subsequent weak carboxy-methyl cation-exchange step, in which the elution is carried out "in a single step by using a solution comprising a buffer substance and a salt" (see claim 1(c)).

4. The appellant argued in writing that the claim was only for methods in which the separation of monomeric antibodies from aggregates is achieved by the weak CM cation-exchange step. At the oral proceedings before the board, the appellant further argued that the claim should be construed according to the principles set out in decision T 1931/14 (see Catchword). In the appellant's view, the purpose stated in the claim, i.e. "purifying a monoclonal antibody from aggregates thereof" defined the claimed method's application or use (as opposed to its effect; see point 2.2.4 of decision T 1931/14). In line with decision T 1931/14, this purpose had to be considered as a functional technical feature of the claim, i.e. it represented a limitation of the process (see point 2.2.2 of the decision).

5. Furthermore, the appellant relied on point 2.2.4 of decision T 1931/14 according to which in cases where the stated purpose of the claimed method "*defines the specific application of the method, in fact it requires certain additional steps which are not implied by or inherent in the other remaining steps defined in the claim, and without which the claimed process would not achieve the stated purpose ... In this manner the stated application represents a genuine technical limitation of the method and the claimed method must be applied in that manner.*"

6. In summary, it was the appellant's view that claim 1, should be construed such that the claimed method requires the selection of conditions that allow the purification of a monoclonal antibody from aggregates thereof in the CM weak cation-exchange step, for each particular monoclonal antibody.

7. The present board considers that the finding in decision T 1931/14 (see reasons, 2.2.4) that - "*[w]here the stated purpose defines the specific application of the method, in fact it requires certain additional steps which are not implied by or inherent in the other remaining steps defined in the claim, and without which the claimed process would not achieve the stated purpose*" - can only hold in cases where it is unambiguously clear that the purpose implies such steps and where it is also unambiguously clear what those steps in fact are.

8. It is also noted that in the case underlying decision T 1931/14, where the claim related to a process for producing oxygen, the purpose stated in the claim was "*to fuel an integrated gasifier combined cycle power generation system*". This purpose indicates to the

skilled person in which context the process is to be used and thus, at least, a step that has to be taken, namely the use in the context of an integrated gasifier combined cycle power generation system. In that particular case, the further steps needed to make the method work in that particular system were even stated in the claim (see decision T 1931/14, reasons 2.3).

9. In the present case, the board can identify no indication, either in the claim itself or in the description, that would lead the skilled person to understand that the stated purpose "for purifying a monoclonal antibody from aggregates thereof", implies that the claimed method contains additional steps. It is the board's view that the skilled person would consider that the claim specifies all the essential features of the invention in line with Rule 43 EPC and hence would consider that carrying out the process steps set out in the claim, necessarily achieves the stated purpose, i.e. the separation of monomers from aggregates of IgG monoclonal antibodies.

10. It is noted that, according to established jurisprudence, if the wording of a claim is in itself clear and unambiguous, it does not need interpretation in the light of the description and that restrictive definitions contained in the description of a term present in the claim must be disregarded (see e.g. decisions T 197/10, point 2.3 and T 2221/10, point 33).

Document D1

11. Document D1 discloses a method for the purification of monomeric antibodies from a mixture which *inter alia* comprises aggregated antibodies. The method includes a protein A chromatography step, a cation-exchange

chromatography step with the carboxy-methyl (CM) cation-exchange material and a hydrophobic interaction chromatography (HIC) step.

12. It was common ground between the parties that document D1 discloses a process for purifying a monoclonal antibody from aggregates thereof comprising the steps a) and b) of claim 1. It was further common ground that document D1 discloses a process for the same purpose as the claimed process, namely the purification of a monoclonal IgG antibody from aggregates thereof. There was disagreement about which of the process steps disclosed in document D1 served to achieve this purpose, see point 13., below. Thus, the question of whether or not the purpose-related feature was disclosed in document D1 did not arise - in contrast to the case underlying decision T 1931/14 where the purpose-feature of the claim under consideration "*to fuel an integrated gasifier combined cycle power generation system*" was held not to be disclosed in the relevant document.

13. The appellant argued that document D1 discloses that only the final HIC step separates the monomeric antibodies from aggregates and protein A contaminants and that the claimed method differed from the one disclosed in document D1 in that it achieved this separation by means of a CM weak cation-exchange step.

14. However, in view of the board's construction of the claim under consideration as achieving the purpose of separation by following the steps set out therein, and in view of the fact that the method disclosed in document D1 has these same steps, the only conclusion that can be drawn is that the method disclosed in document D1 must also achieve the separation of

aggregates from the monomeric forms of antibody by means of the cation chromatography step alone.

15. As set out in points 3. to 10. above, the claimed method does not contain any implicit additional steps by virtue of its purpose. Thus, contrary to the appellant's view, there are no steps, allegedly implied by the purpose, that serve to differentiate the claimed method from that disclosed in document D1.

16. It follows from the above considerations that the method disclosed in document D1 falls within the ambit of the claim simply because it discloses a method having all the steps and meeting the all the conditions specified in the claim. It thus anticipates its subject-matter. Claim 1 does therefore not meet the requirements of Article 54 EPC.

Auxiliary request 1 - Claim 1

17. This claim differs from claim 1 of the main request in that it includes in step c) the additional phrase "such that the monomeric monoclonal antibody is separated from aggregates".

18. Since the board decided on the novelty of claim 1 of the main request based on the consideration that the separation of monomeric monoclonal antibody from aggregates was due to the steps set out in the claim and not due to additional steps, for instance the hydrophobic interaction chromatography (HIC) step disclosed document D1, the conclusion reached for claim 1 of the main request applies equally.

Auxiliary requests 2, 4, 5 and 6

Admission - Article 12(4) RPBA

19. Auxiliary request 2 is identical to auxiliary request 10 which was filed on 28 February 2014, i.e. shortly before the oral proceedings of 4 March 2014 before the opposition division, and was renumbered as auxiliary request 2 during those oral proceedings. The request was not admitted by the opposition division due to its late filing and complexity (see decision under appeal, points 9 and 10).

20. Pursuant to Article 12(4) RPBA, everything presented by a party, in particular with the statement of grounds of appeal, is to be taken into account by the board if and to the extent it relates to the case under appeal and meets the requirements in Article 12(2) RPBA. This is, however, subject to the power of the board, to hold inadmissible *inter alia* requests which had not been admitted into the proceedings by the opposition division.

21. In line with the established case law (see e.g. decision T 229/08, reasons 3.1), the boards of appeal are in the first place charged with reviewing the opposition division's exercise of discretion. Such a review is limited to assessing whether or not the opposition division exercised its discretion in accordance with the right principles or whether it exercised its discretion in an unreasonable way, and thus exceeded the proper limits of its discretion (cf. decision G 7/93, OJ EPO 1994, 775, reasons 2.6).

22. In the present case, the opposition division considered the timing the auxiliary request's filing, which was just about one working day before the oral proceedings,

the fact that the position of the division had already been explained in the communication accompanying the summons to oral proceedings - meaning that the request could have been filed earlier, its complexity and its *prima facie* allowability. These were the proper considerations to be made by the opposition division when considering admitting a late filed claim request into the proceedings. Thus, the board is satisfied that the opposition division exercised its discretion according to the right principles. In view of the reasons given for its decision, the board is also satisfied that the opposition division, in applying these principles, did not exercise its discretion in an unreasonable way.

23. The appellant's arguments that the amendments made were straightforward, consisting of a change in category from a method to a use, which was easy to understand, were clearly allowable under Article 123(2) and (3) EPC and directly addressed the concerns of lack of novelty of the corresponding "method" claim did not persuade the board to admit auxiliary request 2 into the proceedings. The issues that the amended claim request were indented to overcome had been on the table at the oral proceedings before the opposition division, even at the time of issuing the summons to oral proceedings (cf. the annex to opposition division's summons to oral proceedings, point 3.4.3 and also point 10 of the decision under appeal). In the circumstances of the present case, the board saw nothing which would have justified auxiliary request 2 nevertheless being taken into consideration at the appeal stage in the form of a legitimate reaction to the decision under appeal.

Auxiliary requests 4 to 6

24. These requests were not admitted into the proceedings by the opposition division, see decision under appeal points 16 and 17. The board held them inadmissible in accordance with Article 12(4) RPBA for the same reasons as given above for auxiliary request 2.

Auxiliary request 3 - Claim 1

Clarity - Article 84 EPC

25. Claim 1 differs from claim 1 of the main request *inter alia* in that step c) contains the feature "wherein the conductivity of said solution is changed by increasing one condition all at once from starting value to a final value so as to obtain said monoclonal antibody purified from aggregates thereof."

26. "*In considering whether, for the purposes of Article 101(3) EPC, a patent as amended meets the requirements of the EPC, the claims of the 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 Article 84 EPC*", see decision G 3/14 (see OJ EPO 2015, A102, reasons 81).

27. In the present case, the granted claims do not contain the feature mentioned in point 25. above. Thus, a lack of clarity introduced by the amendment may be examined for compliance with Article 84 EPC.

28. The appellant considered that the skilled person would have no difficulty understanding what was meant by the term 'condition'. It was defined in the claim as being

a feature able to change the conductivity of the solution. An example of such a 'condition' was the salt concentration. Paragraph [0039] provided some examples of conditions that could be changed. The claim was limited to changing just one of these conditions, for example changing the concentration of a single salt.

29. The board considers that, on the one hand, in the context of the claim, 'one condition' may be interpreted as changing only 'one condition'. Alternatively, it could mean changing at least 'one condition'. Both of these interpretations are technically sensible to the skilled person, however, they do not have the same technical meaning.

30. Furthermore, changing 'one condition' could refer to a change in concentration of a single salt, but it could equally refer to changing the composition and/or the concentration of a mixture of salts (cf. penultimate line of the claim). Similarly, if 'one condition' were to include ionic strength, then changing this 'one condition' could be achieved by changing the concentration of a single salt or by changing the concentration of multiple salts, which might otherwise be regarded as separate conditions.

31. In view of the above considerations, claim 1 is considered to lack clarity and therefore does not fulfil the requirements of Article 84 EPC.

Auxiliary request 7

Admission - Article 12(4) RPBA

32. This claim request was filed as auxiliary request 11 with the statement of grounds of appeal. It is

identical to the claims of auxiliary request 2 filed on 10 April 2013, i.e. submitted with the reply to the notices of opposition, and was renumbered during the oral proceedings before the opposition division as auxiliary request 11.

33. Since the opposition division decided that auxiliary request 9 met the requirements of the EPC, it did not have to consider the lower ranking auxiliary request 11. In view of the fact that (current) auxiliary request 7 was filed with the appellant's statement of grounds of appeal, it is part of the appellant's case and is, as a general rule, to be taken into account by the board pursuant to Article 12(4) RPBA.

34. Convergence of claim requests is not referred to in Article 12(4) RPBA as a mandatory criterion for assessing holding a request inadmissible nor is the question of whether or not a request improves a parties' position with respect to objections under provisions of the EPC regarded by the board as a relevant criterion in this respect. Hence, the arguments supplied by the respondents for holding auxiliary request inadmissible according to Article 12(4) RPBA did not persuade the board. The board also saw no other reason to exclude the request from the appeal proceedings. In particular, the request was not regarded as creating a "fresh case", going beyond the legal and factual framework underlying the decision under appeal. It follows that auxiliary requests 7 was not held inadmissible under Article 12(4) RPBA.

Amendments - Article 123(2) EPC

Claim 1

35. The board considers that the passage at page 13, lines 30 to 32 of the application as filed discloses a method of claim 1 in which the pH value of the solution in the recovering step c) is from 4.5 to 5.5. A similar disclosure can be found on page 8, lines 27 to 29. Thus, the amendment meets the requirements of Article 123(2) EPC.

Claim 6

36. Claim 6 is for a method according to any one of claims 1 to 5 characterised in that the salt causing the elution is at the same time the buffer substance.

37. The basis for this subject-matter is to be found on page 9, lines 20 to 22 of the application as filed. This passage reads "[*A*]*nother preferred embodiment of the invention is the use of the salt, causing the elution, at the same time as buffer substance, especially with citric acid and salts thereof or phosphoric acid and salts thereof*". The board considers that this passage discloses that the elution salt can also be the buffering agent. Moreover, it is clear from this passage that citric acid and salts thereof or phosphoric acid and salts thereof may simultaneously act as buffering agent and elution salt.

Novelty - Article 54 EPC

Claims 1 to 6

38. The method of claim 1 differs from that disclosed document D1 *inter alia* in that the solution comprising a buffer and a salt (elution buffer) used in the recovering step c) has a pH value in the range from 4.5 to 5.5, while in document D1 the corresponding recovering step is done with an elution buffer having a pH of 6 (see page 15, second full paragraph and Table 1). Thus, the subject-matter of claim 1 is novel with respect to the disclosure in document D1.

39. There were no other objections to the claims of this auxiliary request under any of Articles 84, 123(2) and (3) EPC.

Inventive step - Article 56 EPC

Claim 1

The closest prior art

40. Document D12 concerns a process for separating polypeptide monomers from dimers and/or other multimers using ion-exchange chromatography (see page 1 paragraph 1). Example 1 of document D12 discloses a process for separating humanised anti-IgE monoclonal antibodies (IgG) monomers from dimers and/or other multimers using ion-exchange chromatography (see page 6, "*Proteins*"). The example concerns experiments done to compare the efficacy of various different ion exchange materials, in particular anion-exchange columns are compared to cation-exchange columns. In as far as cation-exchange columns are tested, it is

disclosed that Resource S™ (a strong cation-exchanger) allows "*recovery and purity of Mab monomer [...] comparable to that of the anion-exchange resin*" (see page 9, penultimate paragraph). From Table 1 of document D12 it can be seen that the equilibration buffer used in these experiments was sodium phosphate at pH 6 and that the elution was carried out using a linear gradient of 0 to 0.5 M NaCl.

41. The board considers that the separation of IgG1 monomers from dimers and multimers using strong cation-exchange chromatography disclosed in example 1 of document D12 can be taken to represent the closest prior art for the claimed invention since it employs a method of cation-exchange chromatography for the same purpose as the currently claimed method, i.e. separation of monoclonal IgG monomers from aggregates thereof.

42. The method disclosed in document D12 differs from the claimed method in the following aspects:

43. Firstly, the claimed method uses weak as opposed to strong cation-exchange chromatography. Secondly, the pH of the equilibration and elution buffer for the successful separations disclosed in Table 1 of document D12 is 6 in the case of sodium phosphate buffer and 4.3 in the case of sodium acetate buffer. The claimed method employs a pH in the range of 4.5 to 5.5. Thirdly, the claimed method comprises the step of purification of the monoclonal antibody by protein A affinity chromatography before step a), whereas the antibodies to be purified in example 1 of document D12 are instead subjected to an antibody-based affinity chromatography. Finally, the claimed method employs single step elution while the methods disclosed in

example 1 of document D12 employ a linear gradient elution.

The technical problem

44. It was common ground amongst the parties present at the oral proceedings that the problem to be solved should be formulated as the provision of an improved method for purifying of monoclonal antibodies from aggregates thereof. There is nothing in the submissions of the other respondents that would persuade the board that this formulation of the problem should not be accepted.

Obviousness

45. In assessing the obviousness of the claimed subject-matter, the question to be answered is whether or not, starting from monomer-multimer separations using strong cation-exchange materials disclosed in Example 1 of document D12, it was obvious to the skilled person to modify these in such a way as to arrive at the presently claimed method.

46. Considering the change from strong to weak-cation-exchange chromatography materials - document D12 in the general section discloses the use of various different ion-exchange materials including weak cation-exchange materials such as CM52 Cellulose™, CM Spherodex™, and CM Sepharose™ (see page 5, lines 12 to 22). In any case, it was common ground that weak anion-exchange columns were known for use in the purification of proteins and antibodies. However, the exemplified successful methods presented in Table 1 of document D12 all employ either anion-exchange chromatography or strong cation-exchange chromatography for the purpose of separating monoclonal antibody monomers from dimers

and multimers (see Table 1 and page 9, lines 21 and 22). Consequently, the board cannot conclude that the disclosure of document D12 would have motivated the skilled person to employ a weak cation-exchange material to solve the above formulated technical problem.

47. Thus, the board considers that substituting a weak cation-exchange material for the strong cation-exchange material employed in the example of document D1 was not obvious to the person skilled in the art.

48. It is therefore not necessary to assess whether or not it would have been obvious for the skilled person to adapt the method disclosed in document D1 to include a protein A separation and a single step elution using a pH from within the range specified in the claim.

49. In view of the above considerations, the claimed subject-matter involves an inventive step. Claim 1 therefore meets the requirements of Article 56 EPC. This conclusion applies equally to the subject-matter of dependent claims 2 to 6.

Disclosure of the invention - Article 83 EPC

50. The requirements of Article 83 EPC are complied with if the application discloses the claimed invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.

51. In the present case this means that the skilled person at the relevant date of the patent should be able to employ the method as claimed to achieve the separation of a monoclonal antibody from aggregates thereof without undue burden.

52. The description provides guidance in the form of examples of how to determine the correct type and concentration of salt, see in particular examples 3 to 5 and examples 7 and 8. The pH specified in the claim is now limited to the "most" preferred range of 4.5 to 5.5 (see page 8, line 29 of the application as filed; paragraph [0028] of the patent).

53. Furthermore, the board has seen no evidence that the skilled person would have encountered any difficulty in choosing suitable parameters allowing the adaption of the claimed method to the physico-chemical properties of particular IgG monoclonal antibodies. Indeed, in their submissions on inventive step, respondent V argued that such optimisation was a matter of routine for the skilled person at the relevant date of the patent, as evidenced by e.g. document D9 on page 47/188 (see sections VII. and VIII.).

54. In view of the above considerations, the board concludes that the claimed invention is sufficiently disclosed for the skilled person to be able to carry it out. Claim 1 meets the requirements of Article 83 EPC. This reasoning applies equally to the subject-matter of the dependent claims 2 to 6.

55. There were no objections by the respondents to auxiliary request 7 under Article 123(3) EPC. The board sees no reason to raise any objections of its own motion to the claims of auxiliary request 7.

56. In view of the above considerations, the claims of auxiliary requests 7 and their subject-matter meet the requirements of the EPC.

Different apportionment of costs - Article 104(1) EPC and Article 16(1) RPBA

57. In its communication in preparation for the oral proceedings, the board gave a preliminary (negative) opinion on respondent IV's request for a different apportionment of costs (see section IX., above). There were no further submissions on this point from any of the parties. The board therefore had no reason to change its view. Thus, respondent IV's request for a different apportionment of costs was rejected.

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 in amended form on the basis of the claims of auxiliary request 7 filed as auxiliary request 11 with the statement of grounds of appeal dated 2 December 2014, and a description and drawings to be adapted thereto, as necessary.

3. Respondent IV's request for a different apportionment of costs is rejected.

The Registrar: The Chair:

I. Aperribay G. Alt

Decision electronically authenticated