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Datasheet for the decision of 25 May 2021

Case Number: T 0933/17 - 3.3.01

Application Number: 00950339.2

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IPC: G01N33/574, C12N15/10, G01N33/543

Language of the proceedings: EN

Title of invention:
INCREASED SEPARATION EFFICIENCY VIA CONTROLLED AGGREGATION OF MAGNETIC NANOPARTICLES

Patent Proprietor:
Janssen Diagnostics, LLC

Opponent:
Adams, Harvey Vaughan John

Headword:
Colloidal magnetic particles/JANSSEN

Relevant legal provisions:
EPC Art. 56
RPBA Art. 12(4)

Keyword:
Inventive step - (no)

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Case Number: T 0933/17 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 25 May 2021

Respondent: (Patent Proprietor)	Janssen Diagnostics, LLC 700 US Highway Route 202 Raritan, NJ 08869 (US)
Representative:	Mewburn Ellis LLP Aurora Building Counterslip Bristol BS1 6BX (GB)
Appellant: (Opponent)	Adams, Harvey Vaughan John Mathys & Squire LLP The Shard 32 London Bridge Street London SE1 9SG (GB)
Representative:	Miller, David James Mathys & Squire The Shard 32 London Bridge Street London SE1 9SG (GB)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 6 February 2017 concerning maintenance of the European Patent No. 1311820 in amended form**

Composition of the Board:

Chairwoman	M. Pregetter
Members:	J. Molina de Alba
	M. Blasi

Summary of Facts and Submissions

I. The decision under appeal is the interlocutory decision of the opposition division finding that European patent No. 1 311 820 as amended according to auxiliary request 2, and the invention to which it relates, met the requirements of the EPC.

II. The following documents are referred to in the present decision:

D2 WO 96/18731
D10 M.A. Gordon et al., A.J.C.P., 1974, 61, 488-94
D11 EP 0 038 181
D17 E. Racila et al., Proc. Natl. Acad. Sci., 1998, 95, 4589-94

III. The patent had been opposed on the grounds of Article 100(a) for lack of novelty and inventive step, 100(b) and 100(c) EPC.

In the appealed decision, the opposition division concluded, among other things, that the subject-matter of auxiliary request 2 was sufficiently disclosed and inventive starting from any of the documents proposed as the closest prior art, including D2 and D17.

IV. The opponent (appellant) filed an appeal against the opposition division's decision. The patent proprietor (respondent) also filed an appeal but subsequently withdrew it by letter dated 23 April 2021.

V. In its statement of grounds of appeal, the appellant raised objections under Articles 54, 56, 83 and 84 EPC and requested that the decision be set aside and that the patent be revoked in its entirety.

VI. With its reply to the appellant's statement of grounds of appeal, the respondent filed the claims of a main request and 18 auxiliary requests. The main request and auxiliary requests 1 to 16 were subsequently withdrawn (see letter dated 24 May 2021).

The claims of auxiliary request 17 are identical to those of the request held allowable by the opposition division. Claims 1 and 27 read as follows:

"*1. A method for isolating a target bioentity from a biological sample by means of colloidal magnetic particles with reduced aggregation of said magnetic particles, comprising:*

a) obtaining a biological specimen suspected of containing said target bioentity together with non-target bioentities and endogenous aggregating factors;

b) contacting said biological specimen with an aggregation inhibiting agent capable of inactivating any endogenous aggregating factors present in said specimen;

c) preparing an immunomagnetic suspension comprising a mixture of said specimen and colloidal, magnetic particles coupled to a biospecific ligand having binding affinity for at least one characteristic determinant present on said target bioentity; and

d) subjecting said immunomagnetic suspension to a magnetic field to obtain a target bioentity-enriched fraction; wherein said aggregation

inhibiting agent is selected from the group consisting of an immune-complex, an unconjugated ferrofluid, and diamino butane."

"*27. Use of a reducing agent or a chelating agent as an aggregation inhibiting agent for inactivating endogenous aggregation factors in a method for isolating a target bioentity from a biological sample by means of colloidal magnetic particles with reduced aggregation of said magnetic particles, said method comprising:*

a) obtaining a biological specimen suspected of containing said target bioentity together with non-target bioentities and endogenous aggregating factors;

b) contacting said biological specimen with said aggregation inhibiting agent being capable of inactivating any endogenous aggregating factors present in said specimen;

c) preparing an immunomagnetic suspension comprising a mixture of said specimen and colloidal, magnetic particles coupled to a biospecific ligand having binding affinity for at least one characteristic determinant present on said target bioentity; and

d) subjecting said immunomagnetic suspension to a magnetic field to obtain a target bioentity-enriched fraction."

Claim 1 of auxiliary request 18 differs from claim 1 of auxiliary 17 in that the aggregation inhibiting agent is mercapto ethane sulfonic acid (MES) and in that the endogenous aggregating factor and the biological specimen are specified to be IgM and peripheral blood, respectively.

VII. The board scheduled oral proceedings in line with the parties' requests. In a communication annexed to the summons to oral proceedings, the board gave its preliminary opinion.

VIII. On 25 May 2021, oral proceedings were held by videoconference as requested by the parties. The respondent did not attend as previously communicated to the board by letter dated 20 May 2021.

IX. The appellant's arguments, where relevant to the present decision, can be summarised as follows.

The subject-matter of claims 1 and 27 of auxiliary request 17 was not inventive. It differed from the closest prior art disclosed in document D17 in that it involved the use of an aggregation inhibiting agent (AIA). Although an AIA could reduce uncontrolled, natural aggregation of colloidal magnetic particles, such an aggregation did not happen in D17 because the ferrofluid had been chosen to not react with blood components (see D17, page 4589, right-hand column, last paragraph). The authors of D17 did not need to add an AIA to quantitatively isolate the target cells and visualise them with a digital camera (see D17, page 4590, left-hand column, paragraph 2). This was consistent with the teaching in the patent in paragraphs [0024], [0039] and [0040] that aggregation could be avoided by selecting the appropriate ferrofluid. Hence, the AIA in claims 1 and 27 did not provide any technical effect: its addition was arbitrary. The objective technical problem was the provision of an arbitrary alternative method for isolating a target bioentity from a biological sample. The addition of an arbitrary component with no associated effect could not involve an inventive step.

The method in claim 1 of auxiliary request 18 also lacked an inventive step. The additional differences in relation to D17 were the use of mercapto ethane sulfonic acid (MES) as the AIA and the specification that the endogenous factor causing ferrofluid aggregation was IgM. Like in the case of auxiliary request 17, these differences did not produce any technical effect: they were arbitrary and therefore obvious.

X. The respondent's arguments, where relevant to the present decision, can be summarised as follows.

The closest prior art was document D2. The inventive step of the subject-matter of auxiliary request 17 resided on the finding that endogenous aggregation factors in a biological sample caused uncontrolled aggregation of ferrofluids. This negatively affected quantitation and visualisation of isolated target cells and increased the number of false positives. These problems were solved by the solution proposed in claims 1 and 27, namely inactivating the endogenous aggregation factors in the sample by contacting them with an AIA prior to the addition of the magnetic colloidal particles. The claimed subject-matter solved the objective technical problem of providing an improved method for isolating a target bioentity from a biological sample by means of colloidal magnetic particles. This subject-matter would not have been obvious because the skilled person would not have been aware of the presence of endogenous aggregating factors in biological samples and because the prior art did not teach the use of an immune-complex, an unconjugated ferrofluid, diamino butane, a reducing agent or a chelating agent as an AIA to reduce uncontrolled,

natural aggregation. Regarding the additional documents cited by the appellant, including D10 and D11, the skilled person would not have considered them because they related to a different technical field.

The claims of auxiliary request 18 contained additional limitations in relation to the AIA, the biological specimen and the endogenous aggregation factor. They were narrower and closer to the patent examples. Therefore, their subject-matter was inventive too.

XI. The parties' final requests, as far as relevant to the present decision, were as follows.

The appellant requested that the decision be set aside and that the patent be revoked in its entirety.

The respondent requested that the appeal be dismissed, implying that the patent be maintained in the version held allowable by the opposition division, i.e. on the basis of auxiliary request 17, the claims of which were filed with the letter dated 2 November 2017. Alternatively, the respondent requested that the patent be maintained in amended form on the basis of the claims of auxiliary request 18 filed with the letter dated 2 November 2017.

The respondent also requested that 25% of the appeal fee be reimbursed under Rule 103(4)(a) EPC.

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

Reasons for the Decision

1. The appeal is admissible. It meets the requirements of Articles 106 to 108 and Rule 99(2) EPC.

2. The oral proceedings before the board took place in the absence of the respondent, which was duly summoned but chose not to attend (see the letter of 20 May 2021). In accordance with Rule 115(2) EPC, the board decided to continue the proceedings in the respondent's absence. Under Article 15(3) RPBA, the board was not obliged to delay any step in the proceedings, including its decision, by reason only of the respondent's absence from the oral proceedings. In line with this provision, the respondent was treated as relying on its written case. Hence, the board was in a position to announce a decision at the conclusion of the oral proceedings, in accordance with Article 15(6) RPBA.

3. Auxiliary request 17 - inventive step (Article 56 EPC)

3.1 The patent relates to the isolation of target bioentities from biological samples using colloidal magnetic particles (ferrofluids). The colloidal magnetic particles of the invention are coupled to a biospecific ligand which binds the target bioentity to form a complex which is separated from the sample by the application of a magnetic field. The patent focuses on the isolation of circulating rare cells in peripheral blood, such as tumour cells (see paragraphs [0014], [0038], [0042], [0045] and the examples).

3.2 The claims of auxiliary request 17 are identical to those held allowable by the opposition division. In the appealed decision (sections 5.2 and 7), the opposition division considered four documents as the closest prior art in relation to claims 1 and 27. They included documents D2 and D17.

The appellant provided inventive step arguments starting from each of the four documents (see appellant's statement of grounds of appeal, section 6.3) but concentrated on D17 (see letter dated 23 April 2021, section 4). In its preliminary opinion (section 10.1.1), the board had considered that D17 was indeed a suitable starting point for the assessment of inventive step.

The respondent regarded D2 as the closest prior art in relation to claims 1 and 27. In its inventive step arguments (see the respondent's reply dated 2 November 2017, section 2.3.1), it made general considerations on the effects and advantages provided by the addition of an AIA in the claimed methods and developed the problem-solution approach starting from D2. It did not address the issue of inventive step starting from D17.

3.3 D17 concerns (see the abstract) the detection, quantification and characterisation of tumour cells in peripheral blood using colloidal magnetic particles which specifically bind the target cells and are subsequently separated by a magnetic field. Hence, D17 belongs to the technical field of the patent and is a suitable starting point for the assessment of inventive step.

D17 discloses the results of an assay for detecting epithelial cells in peripheral blood of 30 patients with carcinoma of the breast, 3 patients with prostate cancer and 13 controls. In the assay, a ferrofluid was coupled to an antibody that specifically binds to epithelial cells (EPCAM). The characteristics of the EPCAM-ferrofluid were chosen such that the ferrofluid "*maintained colloidal properties, did not react with blood components, and still could be separated in an open field magnetic configuration*" (see D17, page 4589, right-hand column, last full sentence). The method achieved a recovery of carcinoma cells of between 75 and 100% (page 4590, right-hand column, paragraph 1), and no false positives were observed (page 4592, left-hand column, paragraph 1). The isolated epithelial cells were studied using a digital camera attached to a light microscope (page 4590, left-hand column, paragraph 2), and their architecture was not distorted (page 4592, left-hand column, paragraph 2).

3.4 It was undisputed that the subject-matter of claims 1 and 27 differs from the method of D17 in that the biological sample is treated with an AIA before the colloidal magnetic particles are added.

3.5 In its general considerations on inventive step, the respondent submitted that the effect brought about by treating the biological sample with an AIA was a reduction of uncontrolled, natural aggregation of the ferrofluid produced by endogenous aggregation agents in the sample. This provided two advantages: i) the samples had uniform levels of aggregation, this allowing quantification and comparison between samples, and ii) the isolated target cells could be better visualised under the microscope. On the basis of these effects, the respondent formulated the objective

technical problem as the provision of an improved method for isolating a target bioentity from a biological sample by means of colloidal magnetic particles.

The board disagrees with that formulation of the problem. As noted by the appellant, the ferrofluid used in D17 (see page 4589, right-hand column, last full sentence) was chosen to maintain colloidal properties and not react with blood components. Thus, the ferrofluid was not affected by the endogenous aggregation factors in the sample. This is corroborated by the fact that the advantages of reducing natural, uncontrolled aggregation mentioned in the patent were also found in D17. Although no AIA had been added, i) epithelial cells could be isolated at high rates and quantified, allowing for comparison between samples, and ii) no problems were reported in relation to the study of the isolated cells under the microscope. The patent also acknowledges that natural, uncontrolled aggregation can be avoided by selecting a ferrofluid which does not react with endogenous aggregation factors such as IgM. This is directly derivable from the following statements (emphasis added by the board):

> "*In the case where the endogenous aggregation factor is of the IgM class and reactive with ferrofluids*" (paragraph [0024]). From this sentence, it can be clearly taken that endogenous aggregation factors, in particular IgM, are not always reactive with ferrofluids.
>
> "*The endogenous ferrofluid aggregating substance found in blood has the following characteristics ... it reacts with 'bare' crystalline regions on direct coated*

ferrofluid" (paragraph [0039]). It follows that fully coated ferrofluids may not react with the endogenous aggregating substance.

"*Based on the inability to inhibit aggregation by any component used in forming the ferrofluid except for magnetite crystals poorly coated with protein or magnetite crystals partially coated with detergent, it is believed that the epitope recognized by the IgM is present on the magnetite crystalline surface*" (paragraph [0040]). In other words, in general, the above findings regarding endogenous aggregating substances also apply to IgM.

Consequently, the addition of an AIA in a method as disclosed in D17 would not produce any technical effect. Therefore, in the board's view, the objective technical problem solved by the subject-matter of claims 1 and 27 is the provision of an alternative or further method for isolating a target bioentity from a biological sample by means of colloidal magnetic particles.

3.6 The board concurs with the appellant's argument that the provision of an alternative method by just adding a component which has no associated technical effect is arbitrary and can only be regarded as obvious. Indeed, the proposed arbitrary modification would have fallen within the routine measures the skilled person would have taken to solve the problem of providing a method which is merely different in some unspecified manner from those known. Hence, the solution proposed in claims 1 and 27 of auxiliary request 17 lacks an inventive step within the meaning of Article 56 EPC.

4. Auxiliary request 18 - admittance (Article 12(4) RPBA 2007)

Auxiliary request 18 was filed with the respondent's reply to the appellant's statement of grounds of appeal. In accordance with Article 12(4) RPBA 2007, the board decided to admit this request into the appeal proceedings. In view of the outcome of the examination of inventive step in relation to this claim request (see point 5), the board does not consider it necessary to give reasons for its decision concerning admittance.

5. Auxiliary request 18 - inventive step (Article 56 EPC)

5.1 Compared to the methods in claims 1 and 27 of auxiliary request 17, claim 1 of auxiliary request 18 is limited by the specification that the AIA is mercapto ethane sulfonic acid (MES), the endogenous aggregation factor is IgM, and the biological specimen is peripheral blood. The respondent did not provide additional inventive step arguments regarding auxiliary request 18; it merely stated (see the letter dated 30 December 2019, point 10) that the claims of auxiliary request 18 reflect the examples provided in the application as filed.

5.2 D17 remains a suitable starting point for the assessment of inventive step.

The limitation in claim 1 that the biological specimen is peripheral blood is not a distinguishing feature since the biological samples in D17 are also of peripheral blood (see the abstract).

However, D17 is silent on the presence of IgM as an endogenous aggregation factor and the addition of an AIA, namely MES.

As set out above (point 3.5), the ferrofluid in D17 was chosen to not be affected by blood components, in particular by the endogenous aggregation factors in the samples. As a result, the authors of D17 could isolate epithelial cells at high rates and quantify them and did not report any problem regarding the observation of isolated cells under the microscope. Such aggregation factors, albeit not mentioned in D17, certainly included IgM.

This derives from the fact that IgM is the predominant rheumatoid factor (see D10, page 488, right-hand column, paragraph 2) and, as stated in the patent (paragraph [0045]), rheumatoid factors are normally found in blood. This knowledge is corroborated by documents D10 (abstract) and D11 (page 2, lines 11-15) which teach that IgM or rheumatoid factors are normally found in serum, i.e. the fraction of blood remaining after the removal of clotting agents. Thus, although at least some, if not all, of the 46 peripheral blood samples analysed in D17 certainly contained IgM, the ferrofluid did not react with it, i.e. the ferrofluid was of the type suggested in the patent (paragraphs [0024], [0039] and [0040]) which does not react with IgM.

Hence, the addition of MES to the samples of D17 would not have provided any effect.

The board therefore concludes that the features in claim 1 not mentioned in D17 have no associated technical effect and that the objective technical

problem solved remains the provision an alternative or further method for isolating a target bioentity from a biological sample by means of colloidal magnetic particles.

5.3 For the reasons given in relation to auxiliary request 17, the solution proposed in claim 1 of auxiliary request 18 would have been obvious and lacks an inventive step within the meaning of Article 56 EPC.

6. *Reimbursement of the appeal fee paid by the respondent*

The respondent withdrew its appeal by letter dated 23 April 2021, i.e. more than one month after notification of the board's communication sent in preparation for the oral proceedings, dated 26 June 2020, but before the decision was announced at the oral proceedings. Therefore, 25% of the appeal fee is to be reimbursed under Rule 103(4)(a) EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

3. The patent proprietor's appeal fee is reimbursed at 25%.

The Registrar: The Chairwoman:

M. Schalow M. Pregetter

Decision electronically authenticated