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Datasheet for the decision of 9 May 2022

Case Number: T 1558/19 - 3.3.01

Application Number: 15767581.0

Publication Number: 3092497

IPC: G01N33/68, G01N33/543

Language of the proceedings: EN

Title of invention:
LATERAL FLOW IMMUNOASSAYS FOR THE DETECTION OF ANTIBODIES AGAINST BIOLOGICAL DRUGS

Patent Proprietor:
Progenika Biopharma, S.A.

Opponent:
BÜHLMANN Laboratories AG

Headword:
LFIA/Progenika

Relevant legal provisions:
EPC Art. 56
RPBA 2020 Art. 13(2)
RPBA Art. 12(4)
EPC R. 106

Keyword:

Evidence filed after summons - taken into account (no)
Main request and auxiliary requests 1-4, 6 and 7 - inventive step (no)
Auxiliary requests 5 and 8 - admitted (no)
Objection under Rule 106 EPC - dismissed

Decisions cited:

G 0007/93, T 1742/12

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Case Number: T 1558/19 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 9 May 2022

Appellant: (Patent Proprietor)	Progenika Biopharma, S.A. Parque Tecnológico de Vizcaya Edificio 504 48160 Derio, Bizkaia (ES)
Representative:	Durán-Corretjer, S.L.P. Còrsega, 329 (Paseo de Gracia/Diagonal) 08037 Barcelona (ES)
Respondent: (Opponent)	BÜHLMANN Laboratories AG Baselstrasse 55 4124 Schönenbuch (CH)
Representative:	Stolmár & Partner Patentanwälte PartG mbB Blumenstraße 17 80331 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 4 April 2019 revoking European patent No. 3092497 pursuant to Article 101(3)(b) EPC**

Composition of the Board:

Chairwoman	T. Sommerfeld
Members:	J. Molina de Alba
	P. de Heij

Summary of Facts and Submissions

I. The decision under appeal is the opposition division's decision revoking European patent No. 3 092 497.

II. The decision was based on the patent as granted and the claims of seven auxiliary requests.

Claim 1 as granted reads as follows (emphasis in the original):

"*Lateral flow immunoassay for the detection of anti-drug antibodies against a biological drug comprising: a membrane comprising:*

- *a capture area;*
- *a sample application area;*
- *a flow path from the sample application area to the capture area; and*
- *a conjugate area located in the flow path,* ***characterized in that*** *the conjugate area comprises said biological drug detectably labeled and the capture area comprises said biological drug immobilized thereto.*"

III. In this decision, "lateral flow immunoassay" and "anti-drug antibody" are referred to as "LFIA" and "ADA", respectively.

IV. The following documents are cited in this decision:

D1 WO 2011/005357

D2 J. Pan et al., J Pharmacol Toxicol Methods, 63, 2011, 150-9

D3 O'Farrel, "Evolution in Lateral Flow-Based Immunoassays Systems", in Lateral Flow Immunoassays, R. Wong and H. Tse, 2009

D6 R.E. Biagini et al., Clinical and Vaccine Immunology, 13(5), 2006, 541-6

D24 Experimental report filed by the appellant on 16 March 2021

V. An opposition had been filed against the patent on the grounds that the claimed subject-matter lacked novelty and inventive step and was not disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art (Article 100(a) and (b) EPC).

In the decision under appeal, the opposition division concluded, among other things, that:

- the subject-matter of the main request and auxiliary requests 1 to 3 and 6 was not novel over D1
- the subject-matter of auxiliary request 5 did not involve an inventive step starting from D1 as the closest prior art
- auxiliary requests 4 and 7 were not admitted into the proceedings

VI. The patent proprietor (appellant) filed an appeal requesting that the opposition division's decision be set aside and that the patent be maintained as granted (main request).

With its statement of grounds of appeal, the appellant filed eight sets of claims as auxiliary requests 1 to 8. Auxiliary requests 1, 2 and 4 to 8 are identical to auxiliary requests 1 to 7 on which the decision under

appeal is based. Auxiliary request 3 is a new claim request.

Claim 1 of auxiliary request 1 differs from claim 1 as granted in that it specifies that "*the detectable label is covalently or non-covalently bound/coupled to the biological drug*".

Claim 1 of auxiliary request 2 differs from claim 1 as granted in that it specifies that the conjugate area comprises the biological drug detectably labelled "*with a moiety or a reagent that allows direct detection*".

Claim 1 of auxiliary request 3 differs from claim 1 as granted in that it specifies that the conjugate area comprises the biological drug detectably labelled "*with a moiety or a reagent that is directly detectable*".

Claim 1 of auxiliary request 4 differs from claim 1 of auxiliary request 2 in that it further specifies that "*the biological drug comprised in the conjugate area is detectably labelled with gold colloidal particles*".

Claim 1 of auxiliary request 5 differs from claim 1 of auxiliary request 4 in that the biological drug is limited to "*a monoclonal antibody or fragment thereof*".

Claim 1 of auxiliary request 6 differs from claim 1 of auxiliary request 4 in that the biological drug is limited to "*infliximab*".

Claim 1 of auxiliary request 7 reads as follows (emphasis in the original):

"*Use of a lateral flow immunoassay for the detection of antidrug antibodies against a biological drug comprising:*
a membrane comprising:
- *a capture area;*
- *a sample application area;*
- *a flow path from the sample application area to the capture area;*
- *a conjugate area located in the flow path,* ***characterized in that*** *the conjugate area comprises said biological drug detectably labeled with a moiety or a reagent that allows direct detection and the capture area comprises said biological drug immobilized thereto,*

wherein the biological drug comprised in the conjugate area is detectably labeled with gold colloidal particles
to detect anti-drug antibodies against a biological drug in a biological sample from a patient, wherein a sample is applied to the sample application area and the detectably labeled biological drug recognizes, reacts and binds the antidrug antibodies in the sample, if present, thereby forming biological drug-antidrug antibodies immunocomplexes conjugated with gold colloidal particles, which flow through the flow path to the capture area where the biological drug-antidrug antibodies immunocomplexes conjugated with gold colloidal particles bind to the immobilized biological drug, allowing detection of the antidrug antibodies."

Claim 1 of auxiliary request 8 differs from claim 1 of auxiliary request 6 in that it specifies that the sample application area "*comprises a blood separation pad*" and that "*the sample to be analysed is whole blood*".

VII. In its reply to the statement of grounds of appeal, the opponent (respondent) requested, among other things, that the appeal be dismissed and that auxiliary requests 5 and 8 not be admitted into the appeal proceedings.

VIII. At the respondent's request, based on the appellant's intention to institute infringement proceedings against the respondent in Switzerland, the board accelerated the appeal proceedings.

IX. Oral proceedings were scheduled in line with the parties' requests. In a communication sent in preparation for the oral proceedings, the board gave its preliminary opinion.

X. In reply to the board's preliminary opinion, the appellant filed the experimental report D24.

XI. In subsequent letters, the parties disputed the admittance of D24.

XII. Oral proceedings were held before the board. During the oral proceedings, the appellant raised an objection under Rule 106 EPC which was dismissed by the board. At the end of the oral proceedings, the board announced its decision.

XIII. The appellant's arguments relevant to this decision can be summarised as follows.

Admittance of D24

D24 was filed in response to the board's preliminary opinion that there was no evidence on file that the LFIA of claim 1 of the main request was advantageous

over the one in Figure 2 of D1. This issue had never been raised for the main request. The decision referred to this issue in the context of then auxiliary request 5, which had distinguishing features other than those of the main request. Moreover, D24 did not change the appellant's case: the appellant had always defended that the claimed LFIA was advantageous. D24 merely confirmed a fact on which the appellant had always relied. Furthermore, before the board's preliminary opinion, the appellant had no need to carry out comparative tests with the LFIA in Figure 2 of D1 because it had always maintained that the closest prior art was D2.

Main request

The LFIA of claim 1 was inventive. The closest prior art was D2. If, nevertheless, D1 had to be regarded as the closest prior art, the skilled person would focus on the embodiment in Figure 1 rather than Figure 2.

Starting from the LFIA in Figure 2 of D1, the LFIA of claim 1 differed in that the biological drug in the conjugate area was detectably labelled. This difference made the claimed LFIA simpler because it required only two binding steps to work: binding the ADA first to the detectably labelled drug in the conjugate area and subsequently to the immobilised drug in the capture area. In contrast, the LFIA in Figure 2 of D1 required three binding steps: the biotin-labelled drug had to bind both the ADA and the gold-streptavidin particle to build a conjugate that should subsequently bind the immobilised drug in the capture area. Reducing the number of binding steps also reduced the chances of giving a false negative. So the LFIA of claim 1 was more reliable and accurate than the one in Figure 2 of

D1. This effect was confirmed by the high sensitivity (low detection limits) observed in Examples 2 and 3 of the patent. The sensitivity in these examples could not be compared with that reported for the LFIA in Figure 2 of D1 (paragraph [0188]) because the test conditions in D1 were not specified. Additional advantages of the LFIA of claim 1 were cited in paragraphs [0015], [0100] and [0101] of the patent: the LFIA was small, portable, simple, fast, easy to use, cost-effective and did not require a qualified operator, additional equipment or sample manipulation.

The objective technical problem was providing an improved LFIA for the detection of ADA.

The skilled person would not have reduced the number of binding steps in D1. First, D1 did not suggest such a modification. To the contrary, it taught that the three binding steps were essential. Second, a reduction of the number of binding steps could be expected to reduce the reliability of the assay. The claimed solution was not obvious in view of document D3 or D6 either, not even if the objective technical problem was formulated as the provision of an alternative LFIA. D3 was too general and did not refer to detecting ADAs. D6 taught away from the invention because its LFIA did not contain the drug to which the ADA binds in nature but a recombinant antigen.

Auxiliary requests 1 to 4

For the same reasons, the skilled person confronted with the task of providing an improved method of detecting ADA had neither motivation nor expectation of success to modify the LFIA of the closest prior art to

arrive at the LFIAs of any of auxiliary requests 1 to 4.

Auxiliary request 5

Auxiliary request 5 had been filed as auxiliary request 4 during the oral proceedings before the opposition division. It responded to objections raised for the first time at those oral proceedings. The auxiliary request had not been admitted because it contained features taken from the description and new objections under Article 123(2) EPC were allegedly expected.

There was no rule prohibiting to amend an auxiliary request with a feature taken from the description. The amendment should have been expected by the respondent because it related to the core of the invention and it was covered by claim 1 of the main request. Moreover, the amendment had literal support in the application as filed. By not admitting the request, the opposition division had exercised its discretion incorrectly.

Auxiliary request 6

The LFIA of claim 1 of auxiliary request 6 was inventive. D1 did not mention infliximab. Therefore, the skilled person had no reason to modify the design in Figure 2 of D1 for detecting anti-infliximab antibodies. Neither would the skilled person have expectations of success since the reliability of LFIAs depended very much on the analyte for which they were intended. The statement in paragraph [0188] of D1 that "*the assay design can be used to detect ADA's to any type of therapeutic antibody*" was a blunt statement on which the skilled person would not rely. Although D2 mentioned infliximab (Remicade®) as a biological drug,

the design of the LFIA in D2 was different from the one claimed. So D2 led away from the invention. The fact that three documents (D3, D6 and D2) had to be combined with D1 to arrive at the LFIA of claim 1 was an indicator of hindsight.

Auxiliary request 7

Auxiliary request 7 was auxiliary request 6 on which the decision under appeal was based. The opposition division had held that the subject-matter of this request lacked novelty over D1. The appellant re-filed the request with its statement of grounds of appeal. It explained why the opposition division had erred in considering that the claimed subject-matter lacked novelty and why the claimed subject-matter was inventive. The respondent never rebutted the appellant's arguments; in its reply to the appeal, the respondent just filed a new novelty objection based on D6. The board's preliminary opinion did not contain details on inventive step for auxiliary request 7 either; it did not indicate that D1 was the closest prior art. At the oral proceedings before the board, the respondent substantiated an inventive step objection against auxiliary request 7 for the first time. The appellant was taken by surprise. Therefore, the objection should not be admitted.

By admitting the respondent's inventive-step objection against auxiliary request 7, the board violated the appellant's right to be heard. So an objection under Rule 106 EPC was raised. If the respondent's objection was taken into consideration, the board should admit D24 into the proceedings and postpone the oral proceedings to give the appellant a fair opportunity to

demonstrate that the subject-matter of auxiliary request 7 produced an effect over D1.

The subject-matter of claim 1 of auxiliary request 7 was inventive. Claim 1 had been limited to a use explaining the functioning of the LFIA and specifying that the sample was a biological sample from a patient. D1 did not indicate that the sample applied on the LFIA in Figure 2 was from a patient. Although patient samples were particularly complex, the patent showed in Examples 2 and 3 that the LFIA of the invention provided very accurate results. The objective technical problem was providing an improved, ease-to-use and reliable assay for detecting ADAs in patient samples. The skilled person had no incentive to modify the assay in Figure 2 of D1 to arrive at the use of claim 1 with expectation of success.

Auxiliary request 8

Auxiliary request 8 corresponded to auxiliary request 7 filed at the oral proceedings before the opposition division. By not admitting the request, the opposition division had exercised its discretion incorrectly. The request was a legitimate attempt to overcome the inventive step objection starting from D1. The opposition division had surprisingly considered D1 as the closest prior art and had also expressed a surprising view on claim construction. The amendment in claim 1 did not add subject-matter. It was based on dependent claims 6 and 14 as granted. Although the claims belonged to different categories, it was apparent that they could be combined. In addition, contrary to the opposition division's allegation, the auxiliary request did not require a completely new problem solution approach.

If the opposition division's decision was not reversed, the request should at least be admitted by the board for being part of the appellant's case as put forward with the statement of grounds of appeal.

XIV. The respondent's arguments relevant to this decision can be summarised as follows.

Admittance of D24

D24 should not be admitted into the proceedings. It changed the appellant's case at a late stage of the proceedings for no exceptional reasons and required a complex and time consuming analysis. The report was intended to remedy the lack of evidence of a technical effect associated with the distinguishing feature between the claimed LFIA and the LFIA in Figure 2 of D1. However, this lack of evidence had already been referred to in the notice of opposition, the decision under appeal and the respondent's reply to the appeal. The appellant's contention that the board's preliminary opinion raised this issue for the first time for the main request could not hold. In the decision under appeal, the issue was dealt for then auxiliary request 5 merely because the subject-matter of the higher-ranking requests lacked novelty. So there was no need to discuss inventive step for the main request. Furthermore, if a technical effect had not been shown for the narrower claim, this was even more the case for the broader one. In any case, the issue was raised for the main request in the reply to the statement of grounds of appeal (page 11).

Main request

The LFIA of claim 1 was not inventive starting from the LFIA in Figure 2 of D1. Assuming that the claimed LFIA differed in that the biological drug in the conjugate area was detectably labelled, this difference did not have any technical effect. The general advantages recited in the patent were also disclosed in D1 (paragraphs [0006], [0007] and [0009]). Moreover, the LFIA of claim 1 was not simpler. It was used in the same way as the one in Figure 2 of D1; the user was not aware of the number of binding steps on which the assay relies. There was also no proof that the LFIA of claim 1 was more accurate, sensitive or reliable. In fact, the detection limit of the LFIA in Figure 2 of D1 (paragraph [0188]) was lower than those reported in Examples 2 and 3 of the patent. So the claimed LFIA was not more reliable, and it even had reduced sensitivity.

The objective technical problem was providing an alternative LFIA.

The solution proposed in claim 1 was obvious. It merely reflected the standard design of the LFIAs used for detecting ADAs, as shown in D3 (page 3) and D6 (Figure 2). The teaching of D3 was general and applicable to any LFIA. Moreover, D3 referred explicitly to the detection of antibodies. D6 taught that the drug in the conjugate area could be labelled with gold colloidal particles for direct detection. Whether the drug was natural or recombinant made no difference for the functioning of the assay. So the skilled person knew that the assay with fewer binding steps was a workable alternative.

Auxiliary requests 1 to 4

For the reasons put forward for the main request, the subject-matter of auxiliary requests 1 to 4 did not involve an inventive step either.

Auxiliary request 5

Auxiliary request 5 should not be admitted into the proceedings. The opposition division exercised its discretion not to admit the request in a correct manner. The request had been filed late and contained an amendment that could not have been expected because it was based on a single passage of the description. Furthermore, on its face, the amendment raised issues of added subject-matter, lack of novelty and lack of inventive step.

Auxiliary request 6

The combination of D1 with D2 and D3 or D6 rendered the LFIA of auxiliary request 4 obvious.

Claim 1 of auxiliary request 6 contained the additional limitation that the biological drug was infliximab. This limitation was an arbitrary selection that could not contribute to inventive step. The objective technical problem was the provision of a LFIA for detecting an anti-infliximab antibody. On the priority date, infliximab was a well-known therapeutic antibody to TNF commercialised as Remicade® (see patent, paragraph [0025]). D1 stated (paragraph [0188]) that the design of the LFIA in Figure 2 could be used to detect ADAs to any therapeutic antibody. It also referred explicitly to biological drugs that are antibodies to TNF (paragraph [0078]). Furthermore, D2,

which also dealt with the design of LFIAs for the detection of ADAs, disclosed an assay in which the biological drug was Remicade® (Figure 14). In that assay, infliximab could be marked and immobilised in the LFIA without difficulty. Therefore, the selection of infliximab as the biological drug was obvious. D3 and D6 taught the detectable labelling of the biological drug with gold colloidal particles.

The fact that D1 was combined with three documents did not render the claimed subject-matter inventive. The need for more combination documents was merely due to the limitation of claim 1 with additional features that did not interact with each other to produce a combined effect and therefore had to be regarded separately.

Auxiliary request 7

The reply to the statement of grounds of appeal (page 26, penultimate paragraph) indicated that the inventive-step objections raised against the main request and auxiliary request 4 were also applicable to auxiliary request 7. This was self-evident since, compared to the main request and auxiliary request 4, claim 1 of auxiliary request 7 did not contain any additional distinguishing feature or associated effect over D1. The board had also drawn attention to this fact in its preliminary opinion (point 19.1). Therefore, the respondent did not need to repeat its arguments on inventive step for auxiliary request 7. The appellant's right to be heard was not violated, and there was no reason for admitting D24 or postponing the oral proceedings.

Claim 1 of auxiliary request 7 was merely a reformulation of the LFIA of auxiliary request 4 as a

use with an explanation of how the LFIA works. There was no technical effect and the problem was still the provision of an alternative assay. At the oral proceedings before the board, the appellant argued for the first time that the feature in claim 1 that the sample is a patient sample contributed to inventive step. This argument was flawed since the LFIA in Figure 2 of D1 was also aimed for testing patient samples, including serum and blood (see paragraphs [0088], [0089] and [0188]). The feature was also obvious from D6 (page 541, right-hand column, paragraph 3; Figures 3 and 4), which disclosed LFIAs for measuring an ADA in serum or whole blood samples.

Auxiliary request 8

The opposition division's decision not to admit current auxiliary request 8 was correct and should not be overruled. The request should not be admitted by the board either.

The new combination of features in claim 1 was not supported by claims 6 and 14 as granted. A feature disclosed in a method claim could not simply be added to a product claim. The combination also raised clarity concerns and changed the appellant's case in relation to inventive step. Moreover, the request could and should have been filed earlier in the opposition proceedings. D1 had always been considered novelty destroying for claim 1, and inventive-step arguments starting from D1 had been put forward in the notice of opposition (point 8.2, in relation to claims 2, 7 and 9), the opposition division's communication of 13 June 2018 and the respondent's letter of 20 December 2018.

XV. The parties' final requests relevant to the present decision were the following.

The appellant requested that:

- the decision under appeal be set aside and the patent be maintained as granted
- alternatively, the patent be maintained in amended form on the basis of the claims of any of auxiliary requests 1 to 8, all filed with the statement of grounds of appeal
- auxiliary requests 5 and 8 and the experimental report D24 be admitted into the appeal proceedings

The respondent requested that:

- the appeal be dismissed, implying that the opposition division's decision revoking the patent be upheld
- auxiliary requests 5 and 8 and the experimental report D24 not be admitted into the appeal proceedings

Reasons for the Decision

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

2. Admittance of D24

2.1 D24 is an experimental report filed by the appellant after notification of the summons to oral proceedings before the board. Its admittance is to be assessed

under Article 13(2) RPBA 2020. In accordance with this provision, any amendment to a party's appeal case made after notification of the summons to oral proceedings is, in principle, not to be taken into account unless there are exceptional circumstances, which have been justified with cogent reasons by the party concerned.

2.2 For the following reasons, the filing of D24 constituted an amendment to the appellant's case for which there were no exceptional circumstances.

During the opposition and subsequent appeal proceedings, the appellant relied on the patent disclosure and related arguments for defending that the claimed LFIA was advantageous over the one in Figure 2 of D1. This strategy failed because the advantageous effects alleged by the appellant were not supported by experimental evidence (decision under appeal, point 23.9 and board's preliminary opinion, point 15.1). The appellant tried to fill this probative gap by filing D24. This constitutes an amendment of the appellant's case.

On whether there were exceptional circumstances for filing D24 at such a late stage of the proceedings, the appellant argued that before the board's preliminary opinion (point 15.1), the lack of comparative data had never been raised for the main request. In the decision under appeal (point 23.9), this consideration had been made only for then auxiliary request 5, which contained distinguishing features other than those in the main request.

This argument must fail. The lack of comparative data showing a technical effect for the distinguishing feature between the LFIA of the invention and that of

D1 had been raised by the opposition division in its communication dated 13 June 2018 (points 10.2.1 and 10.2.2.1) and in the decision under appeal (point 23.9). The appellant is right that in the communication the issue had not been raised for claim 1 of the main request but for claim 2, and during the oral proceedings for then auxiliary request 5. However, as noted by the respondent, the opposition division did not discuss inventive step for the higher-ranking requests because their subject-matter had been considered not novel. It is nevertheless apparent that if evidence was required for a claim resulting from the limitation of claim 1 of the main request, as is the case of claim 1 of auxiliary request 5 before the opposition division, this was even more the case for claim 1 of the main request. Moreover, auxiliary request 5 on which the decision under appeal is based is auxiliary request 6 in these appeal proceedings. So the comparative examples should at least have been filed with the statement of grounds of appeal for defending auxiliary request 6. On top of that, the respondent reiterated this lack of comparative examples in its reply to the statement of grounds of appeal referring to claim 1 of the main request (page 11).

It is therefore apparent that D24 could and should have been filed on several occasions and, at the latest, well before the summons to oral proceedings in response to the reply to the statement of grounds of appeal. The board's preliminary opinion agreeing with the respondent's view on the lack of comparative examples did not create exceptional circumstances justifying the filing of D24.

2.3 Therefore, D24 was not admitted into the appeal proceedings.

Main request (patent as granted)

3. Inventive step

3.1 The patent concerns (paragraph [0001]) the design of a LFIA for the detection of antibodies against biological drugs, also called "anti-drug antibodies" or "ADAs". A schematic representation of the LFIA of claim 1 is depicted in Figure 1 of the patent, reproduced here below. The figure is explained in paragraph [0030] of the patent: No.1 represents the sample application area, where the sample potentially containing the ADA is applied; No.2 is the conjugate area, which contains the biological drug in detectably labelled form; No.3 is the capture area, where the immobilised drug binds the complex ADA-labelled drug.

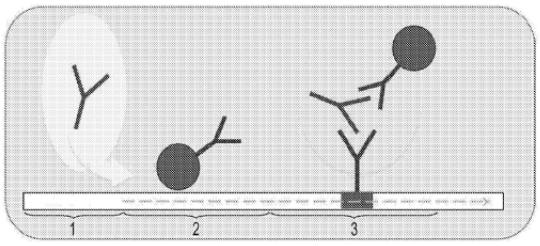

FIG. 1

Like the patent, D1 (paragraph [0007]) concerns the design of a LFIA for the detection of ADAs. Example 4 (paragraph [0188]) discloses a LFIA for detecting the ADA produced by a goat exposed to mouse IgG. The LFIA is depicted in Figure 2 of D1, which is reproduced here below. Its functioning is described in paragraphs [0088] to [0090] of D1.

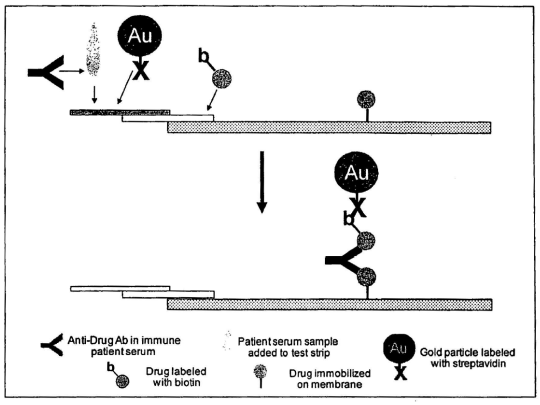

Figure 2

3.2 The board agrees with the respondent that D1, in particular the LFIA used in Example 4 and illustrated in Figure 2, is a suitable starting point for the assessment of inventive step.

The appellant contended that the teaching of D2 was closer to the invention than that of D1 (statement of grounds of appeal, section 5.1). Furthermore, if D1 had to be taken as the closest prior art, the skilled person would choose the embodiment in Figure 1 rather than the one in Figure 2.

In accordance with the established case law of the boards of appeal, when two or more pieces of prior art are suitable as the starting point for the assessment of inventive step, a conclusion that the subject-matter claimed is inventive can only be reached after assessing this requirement starting from all the possible pieces of closest prior art (see, for instance, T 1742/12, Reasons 6). Therefore, the appellant cannot argue against assessing inventive step starting from the LFIA in Figure 2 of D1.

3.3 The next step of the problem and solution approach requires identifying the feature distinguishing the LFIA of claim 1 from the one in Figure 2 of D1.

In the written proceedings, the parties disputed whether the feature in claim 1 that the conjugate area comprises the biological drug in a detectably labelled form was a distinguishing feature. They made abundant submissions on their interpretations of this feature and put forward the consequences that these interpretations had for novelty. At oral proceedings, the board proposed that the parties present their arguments on inventive step assuming that this controversial feature indeed distinguished the LFIA of claim 1 from the LFIA in Figure 2 of D1. To the appellant's benefit, the following assessment of inventive step is based on this assumption. In view of the outcome of the assessment, the assumption has no negative consequences for the respondent.

Thus, the LFIA of claim 1 is assumed to differ from the LFIA in Figure 2 of D1 in that the drug in the conjugate area is detectably labelled.

3.4 The parties disputed the effect brought about by this difference.

3.4.1 The appellant referred to the advantages recited in the patent in paragraphs [0015], [0100] and [0101], namely that the LFIA of the invention is small, portable, fast, easy to use, cost-effective and does not need a qualified operator, additional equipment or sample manipulation. However, these appear to be typical advantages of LFIAs, and most of them are also mentioned in D1 (paragraphs [0006], [0007] and [0009]). So these general advantages do not constitute any technical effect of the LFIA of claim 1 over the one in Figure 2 of D1.

3.4.2 The appellant also argued that the LFIA of claim 1 was simpler, more reliable and more accurate. It pointed to the high sensitivity (low detection limit) shown in Examples 2 and 3 of the patent for the detection of ADAs in serum and blood samples. Allegedly, the effect resulted from the lower number of binding steps involved in the LFIA of claim 1.

The respondent replied that the appellant's submissions were mere allegations. The LFIA in Figure 2 of D1 was as simple to use as the one in claim 1. Moreover, the reduced number of binding steps in the LFIA of claim 1 was detrimental to sensitivity. This was apparent when comparing the detection limits reported in D1 (paragraph [0188]) and Examples 2 and 3 of the patent (25 ng/mL in D1 vs 160 and 120 ng/mL in the patent).

The board agrees with the respondent that fewer binding steps do not necessarily make the LFIA of claim 1 simpler. For users, the number of binding steps does not make any difference; they just have to apply the sample, let it flow to the capture area and read the result. It is also not apparent that the production of the claimed LFIA would be less complex.

Neither can the board recognise an effect on reliability, accuracy or sensitivity. The parties' allegations on these properties were unsupported or referred to experimental data that cannot be compared. On the one hand, no common general knowledge or evidence on file supports that a LFIA requiring fewer binding steps is generally more reliable or more accurate or that it is less sensitive. On the other hand, the detection limits reported in Examples 2 and 3 of the patent and in Example 4 of D1 (paragraph [0188])

cannot be compared because the assays were not carried out under the same conditions.

Therefore, the LFIA of claim 1 does not bring about any technical effect over the one in Figure 2 of D1.

3.5 It follows that the objective technical problem to be solved is providing an alternative LFIA for the detection of an ADA to a biological drug.

The board is satisfied that the solution proposed in claim 1 solves the problem posed. This was undisputed.

3.6 On obviousness, the respondent referred to the common general knowledge disclosed on page 3 of D3 and the LFIA illustrated in Figure 2 of D6.

D3 is an extract from a textbook on the historic evolution of LFIA systems. On page 3, it shows the typical configuration of a LFIA (Figure 1.1 reproduced below) and explains how it works.

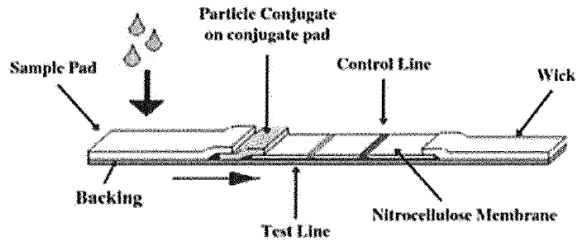

Fig. 1.1 Typical configuration of a lateral flow immunoassay test strip

In relation to the conjugate pad, D3 (page 3) explains that it contains a particle conjugate composed of a particle and one of the biological components of the assay, either an antigen or an antibody. The particle can typically be colloidal gold or a coloured,

fluorescent or paramagnetic monodisperse latex particle.

D6 (abstract) is a scientific publication dealing with the development of a rapid LFIA for measuring a specific ADA in serum or whole-blood samples. It uses colloidal gold nanoparticles as the detection reagent. An example is depicted in Figure 2, reproduced here below.

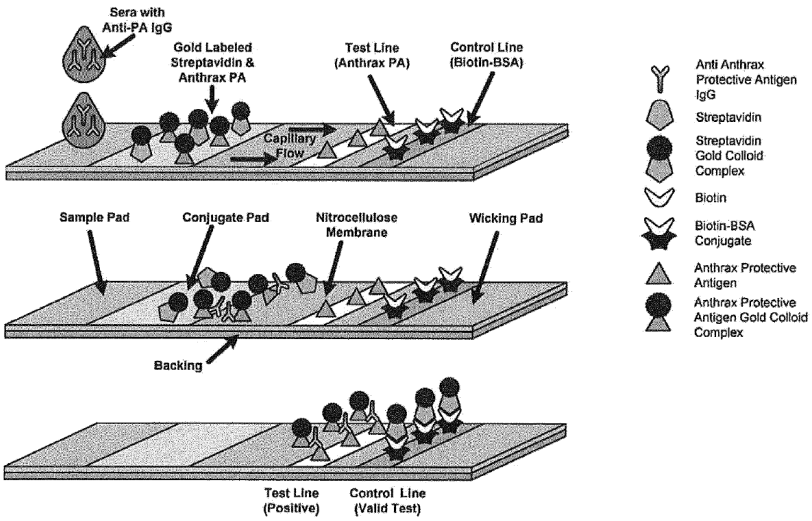

FIG. 2. Diagram of the mechanism of a direct sandwich assay.

Having regard to D3 and D6, the skilled person knew that in a typical design of a LFIA for detecting an ADA, the conjugate area contains the biological drug bound to a gold colloidal particle. When the ADA is present in the sample, it binds the gold-drug conjugate and migrates to the capture area (test line), where it is bound by the immobilised drug and can be directly detected. This is exactly the design defined in claim 1 of the main request. Therefore, the skilled person searching for a LFIA alternative to the one in Figure 2 of D1 would have arrived at the LFIA of claim 1 in an obvious manner.

3.7 The appellant maintained that the skilled person would not have reduced the number of binding steps of the LFIA in Figure 2 of D1 because they would have expected this to reduce the reliability of the assay. It also contended that the teaching of D3 was too general and did not refer specifically to the detection of ADAs. Regarding D6, the appellant argued that the biological drug in the conjugate and capture areas was not the drug to which the ADA binds in nature but a recombinant one. Therefore, the skilled person was led away from the invention.

These arguments are not convincing. No evidence on file supports that the skilled person had a prejudice against reducing the number of binding steps in LFIAs. On the contrary, D3 and D6 teach that the design in which the conjugate area contains the biological drug labelled with colloidal gold particles (i.e. detectably labelled) was a typical design for LFIAs that detect ADAs. In any case, the problem as formulated does not exclude an assay with reduced reliability. Maintained reliability is not part of the problem as it has not been demonstrated that the claimed assay has this effect. D3 contains general knowledge on the configuration of LFIAs. Obviously, this includes LFIAs for detecting ADAs. In fact, D3 explicitly refers to the detection of antibodies. As to D6, whether the biological drug in the conjugate area is recombinant or natural is immaterial. The skilled person would understand that the essential issue for the functioning of the assay is that the drug in the conjugate area is an antigen to the ADA, irrespective of its origin.

3.8 Therefore the ground for opposition of Article 100(a) EPC precludes the maintenance of the patent as granted for lack of inventive step (Article 56 EPC).

Auxiliary requests 1 to 4

4. Inventive step

4.1 In the written proceedings, the appellant did not submit detailed inventive-step arguments for auxiliary requests 1 to 4 starting from D1. It just stated in general terms that the skilled person had neither motivation nor expectation of success for modifying the closest prior art to arrive at the claimed LFIAs (statement of grounds of appeal, section 8). Also in this context the appellant formulated the objective technical problem as the provision of an improved method of detecting ADA.

In its preliminary opinion (point 16), the board noted that the outcome of the assessment of inventive step of the main request would also apply to auxiliary requests 1 to 4. The board confirmed this point at the oral proceedings after having announced its conclusion that the subject-matter of the main request did not involve an inventive step. The appellant nevertheless declined the board's invitation to discuss auxiliary requests 1 to 4.

4.2 Like for the main request, starting from the LFIA in Figure 2 of D1, it is assumed that the LFIA in claim 1 of each of auxiliary requests 1 to 3 differs in that the drug in the conjugate area is detectably labelled, possibly allowing direct detection. In the case of claim 1 of auxiliary request 4, it was undisputed that the difference was that the drug in the conjugate area was detectably labelled with gold colloidal particles. Therefore, it allowed direct detection.

For the reasons put forward for the main request, these differences do not have any technical effect. So the objective technical problem remains providing an alternative LFIA for the detection of an ADA to a biological drug.

Likewise, the common general knowledge on page 3 of D3 and the LFIA depicted in Figure 2 of D6 would have led the skilled person to the LFIA claimed in any of auxiliary requests 1 to 4 in an obvious manner.

4.3 Therefore, the subject-matter of auxiliary requests 1 to 4 does not involve an inventive step, contrary to Article 56 EPC.

Auxiliary request 5

5. Admittance

5.1 Auxiliary request 5 was filed as auxiliary request 4 at the oral proceedings before the opposition division. The opposition division assessed whether the request was clearly allowable and decided not to admit it into the proceedings at such a late stage for two reasons (decision under appeal, point 20.2): first, it had been amended with a feature taken from the description; second, it raised concerns of added subject-matter.

The appellant requested that the board reverts this aspect of the decision under appeal. In such a situation, it is not the function of the board to review all the facts and circumstances of the case as if it were in the place of the opposition division to decide whether it would have exercised the discretion in the same way. The board should only overrule the way in which the opposition division exercised its

discretion if it concludes that the division has not exercised its discretion in accordance with the right principles or that it has exercised its discretion in an unreasonable way and thus exceeded the proper limits of its discretion (similar, but in the context of *ex parte* proceedings, see G 7/93, Reasons 2.6).

The appellant considered (statement of grounds of appeal, section 9) that the opposition division had exercised its discretion incorrectly. The request was a legitimate intent to overcome objections raised for the first time during the oral proceedings before the opposition division. Although the request was amended with a feature taken from the description, it did not raise concerns of added subject-matter because it had a literal basis in the application as filed. Moreover, the amendment could have been expected because it related to the core of the invention.

In the board's view, the applied principle of clear allowability and the further reasons put forward by the opposition division, namely that the amendment had been taken from the description and that new objections under Article 123(2) EPC could be expected, are not incorrect. When a feature is taken from the description, questions indeed arise, namely whether the amendment could be expected, whether an additional search is necessary and whether the amendment adds subject-matter. Therefore, it cannot be concluded that the opposition division did not exercise its discretion in accordance with the right principles or that it exercised its discretion in an unreasonable way. As stated in its preliminary opinion (point 17), the board saw no reasons for overruling the opposition division's decision not to admit the request.

5.2 The board also considered whether auxiliary request 5 should be admitted as part of the appellant's case as filed with the statement of grounds of appeal. As the statement of grounds of appeal was filed on 6 August 2019, Article 12(4) RPBA 2007 applies. This provision gives the board the power to hold inadmissible requests that could have been presented or which were not admitted in the opposition proceedings.

According to the appellant's written submissions, the request was a response to objections raised for the first time during the oral proceedings before the opposition division (statement of grounds of appeal, paragraph 117). The board noted in its preliminary opinion (point 17) that the appellant had not mentioned what those new objections were. However, the appellant never reacted to this observation in the written proceedings and, at the oral proceedings before the board, it did not wish to comment on auxiliary request 5. So the appellant failed to justify why auxiliary request 5 could not have been filed during the opposition proceedings. Therefore, the board held auxiliary request 5 inadmissible pursuant to Article 12(4) RPBA 2007.

Auxiliary request 6

6. Inventive step

6.1 The LFIA in Figure 2 of D1 remains a suitable starting point for the assessment of inventive step.

Although in the written submissions the appellant had conceded that D1 disclosed infliximab in paragraph [0078], during the oral proceedings it was undisputed that claim 1 of auxiliary request 6 contains two

distinguishing features compared to that starting point:

(i) the biological drug in the conjugate area is labelled with gold colloidal particles

(ii) the biological drug is infliximab

As noted by the respondent, these two distinguishing features do not interact with each other to result in a combined or synergistic effect. Therefore, their contributions to inventive step need to be considered independently as solving two juxtaposed objective technical problems.

6.2 Regarding feature (i), it has been shown in the context of the main request and auxiliary request 4 (points 3.6 and 4.2) that labelling the biological drug in the conjugate area with gold colloidal particles is an obvious solution to the problem of providing an alternative LFIA for the detection of ADAs. This conclusion relies on the combination of D1 with D3 or D6.

6.3 As to feature (ii), the technical effect that it brings about is that the LFIA of claim 1 is suitable for detecting anti-infliximab antibodies. Therefore, the objective technical problem that it solves is providing an alternative ADA that can be detected with the LFIA.

6.4 On obviousness, the appellant did not contest that, at the priority date, infliximab was a known monoclonal antibody to TNF commercialised as, *inter alia*, Remicade® (see also patent, paragraph [0025]). D1 recited in paragraph [0078] a list of drugs that could be a target of its assay. This list included monoclonal

antibody-type drugs such as antibodies to TNF. Furthermore, D1 stated (paragraph [0188]) in relation to the LFIA in Figure 2 that "*the assay design can be used to detect ADA's to any type of therapeutic antibody*". From this teaching, the skilled person would have derived that the LFIA in Figure 2 of D1 was suitable for detecting anti-infliximab antibodies. The fact that D2 (Figure 14) disclosed a LFIA in which the biological drug was infliximab confirmed that a LFIA was a suitable option for detecting anti-infliximab antibodies. Therefore, contrary to the appellant's view, the skilled person had both the incentive to design a LFIA for the detection of anti-infliximab antibodies and the expectation that it would work. The appellant's allegation that the reliability of LFIAs depends very much on the analyte for which they are intended is not supported by evidence.

6.5 It follows that, starting from Figure 2 of D1, the solution of using infliximab as the biological drug was obvious from both D1 and D2. The other solution, namely labelling the biological drug in the conjugate area with gold particles was obvious from D3 and D6.

The appellant argued that combining the starting prior art with three additional documents indicated that the inventive-step objection was tainted with hindsight and that the claimed LFIA was inventive.

The board disagrees. The number of documents to be combined with Figure 2 of D1 is a direct consequence of limiting the claims with features that do not interact with each other to bring about a combined effect.

6.6 Therefore, the subject-matter of auxiliary request 6 does not involve an inventive step, contrary to Article 56 EPC.

Auxiliary request 7

7. Admittance of an inventive-step objection

At the oral proceedings before the board, the appellant submitted that, until then, no inventive-step objection had been substantiated against auxiliary request 7. Therefore, such an objection could not be raised at that stage of the proceedings.

The board disagrees. The objection had been raised and was sufficiently substantiated from the outset of the appeal proceedings. The respondent submitted in its reply to the statement of grounds of appeal (page 26, penultimate paragraph) that the inventive-step objections raised against the main request and auxiliary request 4 were also applicable to auxiliary request 7. Even though this submission is very succinct, in this case and for the reasons put forward below, it suffices for substantiating the objection.

Claim 1 of auxiliary request 7 is directed to the use of the LFIA of claim 1 of auxiliary request 4 for detecting an ADA against a biological drug in a sample from a patient. The claim also describes how the LFIA works. It is apparent from a comparison of claim 1 of auxiliary requests 4 and 7 that, for the assessment of inventive step, the circumstances of both claims are identical: inventive step hinges on the technical effects allegedly achieved when the LFIA of auxiliary request 4 is used for detecting an ADA in a patient sample. Therefore, it is clear that the inventive-step

objection against auxiliary request 4 applies equally to auxiliary request 7. The respondent is right that the inventive step arguments put forward against the main request and auxiliary request 4 did not need be repeated for auxiliary request 7. The appellant could perfectly identify the objection raised and understand the arguments that supported it. So did the board, which in its preliminary opinion (point 19.1) drew the parties' attention to this issue.

As there was no amendment to the respondent's case, the board saw no reason to exclude the inventive-step objection raised against auxiliary request 7 (Article 13(2) RPBA).

8. Objection under Rule 106 EPC

Following the non-exclusion of the inventive-step objection against auxiliary request 7, the appellant submitted in writing the following objection pursuant to Rule 106 EPC.

"*By admitting the opponent during the Oral Proceedings for the first time to contest the presence of a technical effect for AR7, the Patentee's right to be heard has been breached. The Patentee could not know the position of the Opponent about interpretation of AR7 and the contribution of the claimed features to a technical effect before the hearing. To give the Patentee a fair defense to this new objection D24 should be admitted into the proceedings. D24 demonstrate the technical effect of AR7 compared to D1 which the opponent contests for the first time during the oral proceedings.*"

As explained above (point 7), the inventive-step objection against auxiliary request 7 had been raised and sufficiently substantiated at the outset of the appeal proceedings. This objection was essentially the same as the one raised against the main request and auxiliary request 4. Its details were disclosed in sections 3.1 and 6 of the respondent's reply to the appeal: the starting point was the embodiment depicted in Figure 2 of D1, the distinguishing feature did not bring about any effect, and it was obvious in light of D3 (page 3) and D6 (Figure 2). In its preliminary opinion (point 15.1), the board was inclined to agree with the respondent's objection to the main request. Subsequently, it noted (points 16 and 19.1) that the outcome of the examination of inventive step for the main request would also apply to auxiliary request 1 to 4 and 7.

Therefore, at the oral proceedings, the appellant had no objective reasons to be surprised by the respondent's arguments that the subject-matter of claim 1 of auxiliary request 7 was not inventive starting from Figure 2 of D1 in combination with D3 (page 3) and D6 (Figure 2). The appellant could and should have been prepared to discuss this issue. So the board concluded that the appellant's right to be heard had not been violated and dismissed the objection under Rule 106 EPC.

9. Admittance of D24 and postponement of oral proceedings

The appellant requested that, in view of the unexpected turn of events at the oral proceedings before the board, D24 be admitted into the appeal proceedings and the oral proceedings be postponed. Both requests were rejected by the board.

As explained above (points 7 and 8), there was no surprising turn of events at the oral proceedings before the board, especially not on inventive step for auxiliary request 7. Therefore, the reasons for not admitting D24 for the discussion of inventive step for the main request also applied to auxiliary request 7. The appellant did not provide additional arguments. Furthermore, in the absence of a surprising turn of events, a postponement of the oral proceedings was unjustified.

10. Inventive step

10.1 Claim 1 of auxiliary request 7 claims the use of the LFIA of claim 1 of auxiliary request 4 for detecting an ADA against a biological drug in a sample from a patient. The claim includes a paragraph describing how the LFIA works.

At the oral proceedings before the board, the appellant argued for the first time that the feature of claim 1 that the sample was from a patient constituted an additional distinguishing feature. Furthermore, this feature rendered the claimed use inventive: even though samples from patients are highly complex, Examples 2 and 3 of the patent showed that they could be easily analysed with high sensitivity and accuracy using the LFIA of the invention.

10.2 However, it is clear that the assay depicted in Figure 2 of D1 is used to detect ADA in a sample from a patient by the indications "Anti-Drug Ab in immune patient serum" and "Patient serum sample added to test strip". The appellant has not argued that the term "patient" in claim 1 of auxiliary request 7 is neither

identical nor overlapping with the same term in D1. Therefore, starting from the assay depicted in Figure 2 of D1, claim 1 does not present any distinguishing feature that was not identified and assessed for claim 1 of auxiliary request 4 (see point 4.2 above).

Like the LFIA in claim 1 of auxiliary request 4, the LFIA in claim 1 of auxiliary request 7 contains the biological drug in the conjugate area labelled with gold colloidal particles. This results in a LFIA involving a lower number of binding steps. For the reasons put forward for the main request and auxiliary request 4, this difference does not bring about any technical effect. Therefore, the objective technical problem is providing an alternative LFIA for the detection of an ADA to a biological drug in a patient sample.

Like for auxiliary request 4, the solution proposed in claim 1 of auxiliary request 7 was obvious to the skilled person in light of D3 (page 3) and D6 (Figure 2).

10.3 Therefore, the subject-matter of claim 1 of auxiliary request 7 does not involve an inventive step (Article 56 EPC).

Auxiliary request 8

11. Admittance

11.1 The appellant filed current auxiliary request 8 (then auxiliary request 7) at the end of the oral proceedings before the opposition division. Claim 1 contained a new combination of features including that the biological drug was infliximab, the sample application area

comprised a blood separation pad, and the sample to be analysed was whole blood. According to the appellant, the basis for this combination of features in the application as filed was dependent claims 6 and 14.

The opposition division did not admit the request because it was not immediately apparent that it did not add subject-matter and because it changed the appellant's case in a way that a completely new problem and solution approach had to be discussed (decision under appeal, point 26). On the issue of added subject-matter, the opposition division noted that claim 14 was a method claim and that therefore it would be necessary to investigate whether these claims (of different category) could be combined without adding subject-matter.

In the board's view, the opposition division did not exceed the proper limits of its discretion. It considered whether the claim request was clearly allowable and came to the conclusion it was not, *inter alia* because the requirements of Article 123(2) EPC needed further investigation. It appears reasonable to consider that a claim based on the combination of dependent claims belonging to different categories may add subject-matter and that it requires investigation. Therefore, at least for that reason, the board saw no justification to overrule the way in which the opposition division exercised its discretion.

11.2 The appellant requested that if the board did not overrule the opposition division's decision not to admit auxiliary request 8, the request be admitted as part of the appellant's case as filed with the statement of grounds of appeal. The relevant provision

in this case is Article 12(4) RPBA 2007 (see above, point 5.2).

At the oral proceedings before the board, the appellant argued that the filing of auxiliary request 8 with the statement of grounds of appeal was justified by an unexpected turn of events at the oral proceedings before the opposition division, namely D1 was considered to be the closest prior art for the first time, giving rise to a new inventive-step objection.

This argument does not reflect reality. It is apparent from the notice of opposition (point 8.2), the opposition division's communication in preparation for the oral proceedings (point 10.2.1) and the respondent's letter of 20 December 2018 (point 4.2), that inventive step starting from D1 as the closest prior art had been discussed throughout the opposition proceedings. So auxiliary request 8 could and should have been filed in the opposition proceedings. Furthermore, the alleged surprising claim construction by the opposition division has not been substantiated. Therefore, the board held auxiliary request 8 inadmissible pursuant to Article 12(4) RPBA 2007.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairwoman:

B. Atienza Vivancos T. Sommerfeld

Decision electronically authenticated