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**Datasheet for the decision
of 19 September 2018**

Case Number: T 1394/13 - 3.3.01

Application Number: 04793357.7

Publication Number: 1691198

IPC: G01N33/576, G01N33/531,
C12N7/00, C12N5/18, C07K16/10,
G01N33/53

Language of the proceedings: EN

Title of invention:
METHOD OF DETECTING HEPATITIS C VIRUS

Patent Proprietor:
Advanced Life Science Institute, Inc.

Opponent:
Roche Diagnostics GmbH

Headword:
Pre-treatment of HCV samples/ADVANCED LIFE SCIENCE INSTITUTE

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step - (no)

Decisions cited:

Catchword:



Beschwerdekammern

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Chambres de recours

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Case Number: T 1394/13 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 19 September 2018

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Decision under appeal: **Decision of the Opposition Division of the
European Patent Office posted on 18 April 2013
rejecting the opposition filed against European
patent No. 1691198 pursuant to Article 101(2)
EPC.**

Composition of the Board:

Chairman A. Lindner
Members: T. Sommerfeld
P. de Heij

Summary of Facts and Submissions

- I. European patent 1691198 is based on application 04793357.7, which was filed as an international application published as WO 2005/040815. The patent is entitled "Method of detecting hepatitis C virus" and was granted with 6 claims.

Claim 1 as granted reads as follows:

"1. A method of treating hepatitis C virus (HCV)-containing samples which method comprises treating HCV-containing samples with a treating agent containing:

(1) an acidifying agent selected from the group consisting of hydrochloric acid, sulfuric acid, acetic acid, trichloroacetic acid and trifluoroacetic acid, and

(2) a cationic surfactant which has both a straight chain alkyl group of 10 or more carbon atoms and a tertiary amine or a quaternary ammonium salt in the same molecule;

to effect the release of the HCV antigen and the inactivation of antibodies that bind to the HCV antigen."

- II. Opposition was filed against the granted patent, the opponent requesting revocation of the patent in its entirety on the grounds of lack of inventive step (Articles 56 EPC and 100(a) EPC), insufficiency of disclosure (Article 100(b) EPC) and added subject-matter (Article 100(c) EPC).

- III. In its decision announced at the oral proceedings, the opposition division rejected the opposition under Article 101(2) EPC.

IV. The opponent (appellant) lodged an appeal against that decision. In its statement of the grounds of appeal, the appellant requested that the decision of the opposition division be set aside and the patent be revoked in its entirety.

V. The patent proprietor (respondent) replied by letter dated 15 January 2014 requesting that the appeal be dismissed and that the patent be maintained as granted (**main request**) or alternatively according to auxiliary requests 1 to 6, all filed with the said letter.

Claim 1 of **auxiliary requests 1 to 4** is identical to claim 1 of the main request.

Claim 1 of **auxiliary requests 5 and 6** differs from claim 1 of the main request in that it is restricted to HCV core antigen: "... to effect the release of the HCV core antigen and the inactivation of antibodies that bind to the HCV core antigen."

VI. The oral proceedings before the board took place on 19 September 2018. At the end of the oral proceedings the chairman announced the board's decision.

VII. The documents cited during the proceedings before the opposition division and the board of appeal include the following:

D1 US 4703001
D4 EP 967484

VIII. The appellant's submissions, in so far as they are relevant to the present decision, may be summarised as follows:

The goal of the patent was to make D4's method faster (patent, paragraphs [0010] to [0012], [0013], [0015], [0019] and [0020]), hence the technical problem could be formulated as the improvement of D4's method, and the solution was to combine an acidifying agent with a cationic surfactant. However, the problem could not be considered solved, because the results in the tables on pages 10 to 12 raised doubts about the clinical suitability of the claimed method, since it could not detect HCV in a number of samples that were known to be HCV-positive. A less ambitious technical problem was the provision of an alternative method to that of D4. Example 15 of D4 tested a number of different surfactants, and while many of them were also not able to detect HCV in all tested samples, cetyltrimethylammonium bromide, a cationic surfactant, allowed the detection of HCV in all samples. It was well-known to use acid treatment where antibodies were present: D1, abstract, column 4, lines 29 to 32, column 3, line 59 ff. The present claim was directed to the situation where it was not known whether antibodies were present. Therefore, pre-treatment was required to inactivate antibodies in case they were present. D4 taught that anionic or cationic surfactants could be used to release the antigens, and, since it was known that anionic surfactants should not be combined with acids due to the consequent formation of precipitates (as described in the patent on page 9, line 37), the skilled person would choose cationic surfactants. There was no incompatibility between the two embodiments of D4 since the acid used in the pre-treatment was of course neutralised before detection: this was taught in D1 (bottom of column 5) and was also what the patent had done. The alternative method provided by the patent was therefore an obvious combination of well-known measures.

IX. The respondent's arguments, in so far as they are relevant to the present decision, may be summarised as follows:

Example 15 of D4 related to the so-called second embodiment, which did not involve acid treatment because it used samples containing no antibodies. This embodiment was not directed to the same purpose as the claimed method and was not a proper starting point; rather, the first embodiment, disclosed in paragraphs [0015], [0022] and [0023], represented the closest prior art. According to paragraphs [0023] and [0024], the method of the first embodiment included acid treatment and a chaotropic ion, and, optionally, a nonionic surfactant. Paragraphs [0080] and [0081] of D4 also taught that the contemplated surfactants were amphoteric and nonionic. The difference with the claimed method was that this one involved use of a cationic surfactant in addition to acidifying agent, and the objective technical problem was the provision of an alternative method to treat HCV-containing samples with the aim of releasing the HCV antigens and inactivating antibodies. The claimed method solved this problem. The technical problem as formulated by the appellant was not correct, because the claimed method did not impose any speed or sensitivity requirements, the only requirements being that the antigen be released and the antibodies inactivated. The solution was not obvious, because D4 did not suggest providing such a treating agent: it only suggested the use of amphoteric and nonionic surfactants, the latter ones being preferred, as was apparent from examples 10 to 13. The only reference to a cationic surfactant was in the context of the second embodiment, where it was made clear that the purpose of using surfactant was to

expose viral particles. The skilled person would not consider employing such surfactant conditions to the first embodiment, as it would not expect any additional effects, such as advantages or improvements. In fact, the conditions of the two embodiments were incompatible because detection could not take place in the presence of acid, which would inactivate the detection antibodies. Paragraph [0087] taught against using acid treatment, and detection was performed in the presence of the surfactant (paragraph [0088]). Treatment of samples containing antibodies was far more complex than treating antibody-free samples: patent, paragraphs [0037], [0038] and [0042]. D4 did not teach cationic surfactants as preferred; the exemplary surfactants of paragraphs [0028], [0090] and [0091] included some cationic surfactants but did not suggest that cationic surfactants were preferred. The data in Tables 10 and 11 instead showed the best results for the anionic surfactant sodium dodecyl-N-sarcosinate; this, however, did not work in the method of the patent (D4, paragraph [0075]). The selection of cationic surfactants as a mere alternative possibility was only possible with *ex post facto* analysis.

- X. The appellant requested that the decision of the opposition division be set aside and the patent be revoked in its entirety.

The respondent requested that the appeal be dismissed and that the patent be maintained as granted (main request) or alternatively be maintained according to auxiliary requests 1 to 6, all filed with letter dated 15 January 2014.

Reasons for the Decision

1. The appeal is admissible.

2. Main request - inventive step

2.1 The present patent is directed "to a method for detecting or quantifying hepatitis C virus (HCV)-related antigen in the serum as well as a very simple and reliable method of treating samples for use in such detection and quantification of HCV antigen" (paragraph [0001]). It discusses a number of available methods and the problems associated therewith and concludes that "there are needs for the development of methods of obtaining HCV particles in particular HCV antigen in the serum in a simple manner and at a high yield, and of highly sensitive methods of detecting and quantifying them" (paragraph [0018]). It then explains, in paragraph [0024], that, since test samples containing the HCV antigen may contain virus particles and immune complexes formed by the HCV antigen and the antibody, "in order to detect the HCV core antigen, it is necessary to: I) destroy HCV particles so as to release the core antigen from the HCV particle as well as to convert the core antigen into monomers as much as possible, II) inactivate or remove the host-derived antibodies against the HCV antigen, and III) dissociate the core antigen from the interaction with blood components other than the antibody against the HCV antigen". The patent goes on to teach that "release as much as possible into monomer form of the core antigen contained in the limited amount of samples in a given detection system from the HCV particle, antibodies against the HCV antigen, other blood components etc. increases the number of antigen molecules that can

react with the probe. The present invention realizes higher reactivity with the probe by a brief and simple treatment of samples to liberate into the monomer form as much as possible" (paragraph [0025]). The method of the invention is then disclosed as being "a treatment method which comprises allowing the HCV core antigen in a test sample to be converted into a state suitable for detection using a probe by a brief and simple procedure" and as comprising "inactivating, simultaneously, host-derived antibodies against the HCV core antigen that compete with the capturing probe and the detecting probe" (paragraph [0026]).

- 2.2 Document D4, which is also directed to methods for detecting HCV virus, was considered by both parties and the opposition division as the closest prior art. In paragraph [0022], D4 discloses "means to detect or determine a virus by disrupting the virus particle, fully exposing the virus antigen, disrupting antibodies, if present, against the virus antigen". Hence, the means of viral detection disclosed in D4 encompass steps for disrupting the virus particle and antibodies if present, which is the purpose of the method claimed in granted claim 1, namely, "to effect the release of the HCV antigen and the inactivation of antibodies that bind to the HCV antigen". Said method according to D4 is "characterized by treatment of a virus-containing sample with a treatment solution containing (1) a chaotropic ion and (2) an acidifying agent" (paragraph [0023]). As to the acidifying agent, paragraph [0080] teaches that "hydrochloric acid, sulfuric acid, acetic acid, trifluoroacetic acid, trichloroacetic acid, and the like are preferred". Hence D4 discloses a sample pre-treatment method making use of acidifying agents (in order to inactivate interfering antibodies present in the sample: paragraph

[0079]), and chaotropic ions (added with the aim of solving the problems associated with acid treatment such as precipitate formation; paragraph [0080]). It then teaches that "it is further preferred to add a surfactant to the treatment agent" (paragraph [0080]), and lists a number of preferred surfactants, which include amphoteric and nonionic surfactants (paragraph [0081]).

2.3 While the methods according to D4 and to granted claim 1 both use an acidifying agent selected from the group listed above, the difference between the two methods is that a chaotropic ion is also used in D4, while the method of claim 1 uses a cationic surfactant. There is no evidence on file for a technical effect associated with this difference. Thus, the technical problem is to be formulated as the provision of an alternative method for treating HVC-containing samples in order to release virus antigens and inactivate antibodies to the virus antigen present in the samples. It was not disputed that this problem was solved by the claimed solution and the board is also satisfied that the claimed method plausibly solves the technical problem.

2.4 It remains to be examined whether the skilled person would arrive at the claimed solution in an obvious way. In paragraphs [0091], [0093], [0167] and [0168] and in table 10, D4 discloses the use of a cationic surfactant by itself, for extracting (i.e. releasing and exposing) the virus antigen from the virus particles (paragraph [0090]). The surfactants listed in paragraph [0091] include cationic surfactants, as listed in granted claim 4 and in Table 10 (page 24) of D4. Accordingly, it was known at least from D4 that cationic surfactants were useful to release, thereby exposing, HCV viral antigens in samples. On the other hand, it was also

known from the prior art that antibodies in the samples could be inactivated by acidification, i.e. by adding acidifying agents, as confirmed in D4 itself: paragraph [0079]. Hence, from D4 alone, the skilled person, seeking to provide alternative methods for treating HCV-containing samples so as to effect the release of the HCV antigen and the inactivation of antibodies that bind to the HCV antigen, would certainly contemplate combining acid treatment with any of the many surfactants, such as cationic surfactants, which were known to have an effect on viral antigen release. The skilled person would thus arrive at the claimed subject-matter without the need for inventive skill.

2.5 The respondent essentially argued that there was no suggestion in D4 to provide such a pre-treatment comprising acidifying agents and cationic surfactants. In the context of D4's first embodiment, which included acid treatment, only amphoteric and nonionic surfactants were envisaged; cationic surfactants were mentioned only in the context of the second embodiment, which did not include acid treatment. The skilled person would not expect any advantages from applying the surfactant conditions of the second embodiment to the first embodiment and in fact was taught away from doing so. Paragraph [0087], pertaining to the second embodiment, taught that the surfactant conditions should be mild enough to retain antibody function. Hence, the conditions of the two embodiments were incompatible.

2.6 The board notes that the cited paragraph of D4, which is in the context of the so-called second embodiment, does not relate to the pre-treatment of the samples but rather to the next stage, namely antigen detection: "A reaction system suitable for **antigen detection** in the

system provided by the present invention comprises a condition which is mild enough to retain the function of the antibody against the epitopes of the virus antigen (...)", D4, paragraph [0087], emphasis added by the board. Antigen detection methods are outside the ambit of the present claims, which are not directed at methods of detection but rather at methods for pre-treatment of samples in order to expose the antigens, which may also require destruction of antibodies present in the samples (D4's first embodiment) or not (D4's second embodiment "which relates to a method of detecting the virus antigen in a sample collected during the window period, antibody to the virus antigen has not been formed yet and so the disruption of the virus particle to expose the virus antigen is sufficient and there is no need to destroy antibodies present in the sample": paragraph [0084] of D4). Clearly, the conditions used for the detection immunoassay may be different to the conditions used in the pre-treatment of the viral samples. In the case of a pre-treatment involving acid treatment (D4's first embodiment), they certainly have to be different. However, the skilled person would know how to adapt the conditions accordingly, as is taught, for instance, in D1 (paragraph bridging columns 5 and 6).

2.7 It is true that there is no teaching in D4 to use cationic surfactants, in particular in the context of the first embodiment, i.e. together with acid treatment. However, as cationic surfactants are disclosed in D4 as also suitable - just like other surfactants - for exposing the virus antigen, the skilled person would be motivated to use them as an obvious alternative surfactant and thus one of several equally suitable alternative components of the treating agent in a pre-treatment method aimed at exposing the

virus antigen. The claimed pre-treatment method aims to destroy any antibodies present in the sample and release the virus antigen. In the prior art (e.g. D4 and D1), it was known that the first aim could be achieved by treatment with an acidifying agent, while the second aim could be achieved with many different types of surfactants, including cationic surfactants. In the absence of any teaching against combining cationic surfactants with acidifying agents, the skilled person would have no reason to doubt that such a combination would work just like any other possible combination.

2.8 Claim 1 of the main request thus lacks inventive step. The main request is not allowable for lack of compliance with Articles 56 and 100(a) EPC.

3. Auxiliary requests 1 to 4 - inventive step

3.1 Claim 1 of auxiliary requests 1 to 4 is identical to claim 1 of the main request. Hence, for the same reasons as discussed above in relation to the main request, auxiliary requests 1 to 4 are also not allowable for lack of compliance with Article 56 EPC.

4. Auxiliary requests 5 and 6 - inventive step

4.1 Claim 1 of auxiliary requests 5 and 6 differs from claim 1 of the main request in that it is restricted to "HCV core antigen".

4.2 The board notes that D4 repeatedly refers to the HCV core antigen as the viral antigen to be exposed for detection, and detection of the HCV core antigen after treatment of the samples with different surfactants is

in fact what is assessed in, for instance, example 15 of D4.

- 4.3 Accordingly, this further feature does not contribute to inventive step. Auxiliary requests 5 and 6 are thus also not allowable for lack of compliance with Article 56 EPC.

Order

For these reasons it is decided that:

1. The appealed decision is set aside.
2. The patent is revoked.

The Registrar:

The Chairman:



M. Schalow

A. Lindner

Decision electronically authenticated