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**Datasheet for the decision
of 12 September 2019**

Case Number: T 2213/14 - 3.3.01

Application Number: 06805885.8

Publication Number: 1931999

IPC: G01N33/82

Language of the proceedings: EN

Title of invention:

RELEASE REAGENT FOR VITAMIN D COMPOUNDS

Patent Proprietor:

Roche Diagnostics GmbH
F. Hoffmann-La Roche AG

Opponent:

Immundiagnostik AG

Headword:

Release agent for vitamin D/ROCHE

Relevant legal provisions:

EPC Art. 108, 100(a), 100(c), 54

Keyword:

Admissibility of appeal - appeal sufficiently substantiated
(yes)

Added subject-matter (no)

Novelty - (yes)

Inventive step - (yes)



Beschwerdekammern

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Case Number: T 2213/14 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 12 September 2019

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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted on 1 October 2014 rejecting the opposition filed against European patent No. 1931999 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairwoman T. Sommerfeld
Members: M. Pregetter
 L. Bühler

Summary of Facts and Submissions

- I. European patent No. 1 931 999 is based on European patent application No. 06805885.8, filed as an international application published as WO2007/039194 (hereinafter "application as filed").

Claim 1 of the patent as granted (main request) reads as follows:

"1. Reagent composition for the release of vitamin D from vitamin D-binding protein which has a pH value of 3.8 to 4.8 and contains 5 to 30 volume percent of one or more amphiphilic reagents selected from the group consisting of dimethyl sulfoxide (DMSO), dimethylformamide (DMF), N,N-dimethylacetamide, tetramethylurea (TMU), N-methylpyrrolidone (N-MP), 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidone (DMPU) and hexamethylphosphoric acid triamide (HMPT), and 0.7 to 8 volume percent of a short-chain (C1 to C3) alcohol selected from methanol, ethanol, propanol and isopropanol."

- II. The following documents, cited during the opposition and appeal proceedings, are referred to below:

(4) US 5,714,586

(6) WO02/46746

(9) WO2004/063704

(10) Takagai et al., Chem. Pharm. Bull., 2003, 51(4), 373-377

(11) Wikipedia, catchword "Acetonitrile", 2 pages

(12) Wikipedia, catchword "Solvent", 5 pages

Annex A: Römpp-Chemie-Lexikon, 9., erweiterte und neu-bearbeitete Auflage (1995), pages 26, 983 and 987

Annex B: A. Streitwieser, Jr., C.H. Heathcock, "Organische Chemie", VCH Verlagsgesellschaft mbH, Weinheim, 1990, page 172

III. The patent was opposed under Article 100(a) and (c) EPC on the grounds that the claimed subject-matter lacked novelty and inventive step and extended beyond the content of the application as filed.

The opposition division rejected the opposition.

IV. The opponent (hereinafter "appellant") appealed this decision. Together with its statement setting out the grounds of appeal, it submitted documents (11) and (12).

V. In their reply to the grounds of appeal, the patent proprietors (hereinafter "respondents") requested that the appeal be rejected as inadmissible or, alternatively, that the appeal be dismissed, or that the patent be maintained according to the claims of auxiliary request 1 filed with the letter of reply. They furthermore requested that documents (11) and (12) not be admitted into the proceedings.

VI. In a communication pursuant to Article 15(1) RPBA, the board indicated certain points to be discussed. A positive preliminary opinion was given as to the admissibility of the appeal.

- VII. The appellant submitted Annex A and Annex B with a letter dated 22 May 2019.
- VIII. The respondents requested that Annex A and Annex B not be admitted into the proceedings.
- IX. Oral proceedings before the board took place on 12 September 2019.
- X. The appellant's arguments, insofar as they are relevant to the present decision, may be summarised as follows:

Admission of documents

Documents (11) and (12) represented common general knowledge as proven by the contents of Annex A and Annex B, being an encyclopaedia and a textbook, respectively. These documents had merely been submitted in support of common general knowledge. Consequently, they should be admitted into the proceedings.

Amendments

Claim 1 as filed, and the corresponding passages of the description, related to a composition comprising, at most, 30 percent by volume of an organic solvent (amphiphilic reagent), considering usual drafting praxis when defining Markush groups. Short-chain alcohols, in a certain amount, could optionally form part of the organic solvent. The addition of alcohols was not linked to a certain functionality in the application as filed.

Claim 1 of the main request had been amended to define a composition that mandatorily comprised certain short-

chain alcohols within a range of 0.7 to 8 percent by volume. The volume of the short-chain alcohols was in addition to the volume of the amphiphilic reagents. The maximum amount of organic solvents had thus been raised to 38 percent by volume. Moreover, the wrong designation of dimethyl sulfoxide, dimethylformamide and the further solvents in the list as "amphiphilic reagents" in claim 1, in combination with making the short-chain alcohols an obligatory element of claim 1, changed the total technical teaching of the application. Consequently, the subject-matter of claim 1 of the main request extended beyond the content of the application as filed.

Novelty

Documents (4) and (10) took away the novelty of claim 1 of the main request.

Document (4) disclosed a solution comprising ethanol, dimethyl sulfoxide and a buffer, and having a pH in the range of 4 to 8.5 (claim 1). The percentages by volume of the solvents were not explicitly disclosed. However, it was inherent that ingredients that were disclosed as being present were contained in a composition in reasonable amounts. The purpose of document (4) was the same as the purpose of the composition of the patent in suit, i.e. to dissolve proteins. The functionality of the ingredients thus required certain amounts, these amounts being well known to the skilled person. This was supported by document (6), which, on page 8, lines 18 to 24, pointed to the fact that the skilled person knew which ranges of solvents to choose. Claim 1 of document (4) explicitly disclosed combinations of the solvents. Furthermore, in column 8, lines 14 to 18, substituting a composition comprising less than 10% of

co-solvent by ethanol or dimethyl sulfoxide (DMSO) was described. The subject-matter of claim 1 of the main request was thus anticipated by document (4), when read in its entirety.

Document (10), in Figure 3, disclosed a buffered composition comprising 30% DMSO. Ethanol was disclosed as one of three water-miscible organic solvents to be added (page 374, left column, penultimate line) and was in fact usually present in such compositions, since it allowed for improved handling due to lowering of the surface tension of the composition.

Inventive step

The closest prior art was document (9). It disclosed the release of vitamin D from vitamin D-binding protein by lowering the pH using a composition including 10% acetonitrile, a polar aprotic solvent.

The examples of the patent in suit did not provide any useful information, since they did not constitute evidence for a correct measurement of vitamin D. Due to the fact that they gave a merely statistical evaluation and did not consider the influence of the varying amounts of vitamin D-binding protein, due to, for example, pregnancy or stay in intensive care, the data resulting from these examples were meaningless. In addition, there was no comparison with the closest prior art. The technical problem was thus the provision of an alternative co-solvent. The function of an organic solvent such as acetonitrile was obviously to keep certain components dissolved. The replacement of acetonitrile by an equivalent polar aprotic solvent, i.e. a solvent from the row of aprotic polar solvents as depicted in the table on page 11, point 6.2.2 of the

statement of grounds, involved no inventive skill. This was all the more so as the ranges for the solvents in claim 1 of the main request were extremely broad. Furthermore, document (6) explicitly mentioned dimethyl sulfoxide for vitamin D release (page 8, lines 21 to 24). As to ethanol, this had always been disclosed in the application as filed as a merely optional component.

XI. The respondents' arguments, insofar as they are relevant to the present decision, may be summarised as follows:

Admissibility of appeal

From the statement setting out the grounds of appeal it was impossible to understand immediately why the impugned decision was alleged to be incorrect. The appeal was therefore inadmissible, as it was not sufficiently substantiated.

Admission of documents

Documents (11) and (12) were first filed in the appeal proceedings, without any explanation concerning their introduction. Furthermore, they were not prima facie relevant. Also, no reasons for the introduction of Annex A and Annex B were given. These documents were not used to substantiate any of the grounds for opposition. They should therefore not be admitted into the proceedings.

Amendments

The addition of short-chain alcohols was an optional element in the application as filed. However, as could

be seen from the terms "as well as" and "additionally" which preceded the definition of the volume percent of short-chain alcohol to be added, adding the alcohol in addition to the solvents making up the amphiphilic reagents had always been foreseen. Furthermore, it was clear from the definition of the groups "amphiphilic reagents" in claim 2 as filed and "short-chain alcohols" in page 5, line 26 to 28, that there was no overlap of the groups. Therefore, it was not possible that the range defined for the amphiphilic reagents included the short-chain alcohols. A possible lack of clarity linked to the term "amphiphilic" fell under Article 84 EPC, which was not a ground for opposition.

Novelty

Neither document (4) nor document (10) disclosed the technical features of claim 1 of the main request in combination.

Document (4) defined in claim 1 the addition of a co-solvent selected from propylene glycol, ethanol, dimethyl sulfoxide, or combinations. A combination of ethanol and dimethyl sulfoxide was not directly disclosed in claim 1 of document (4). Furthermore, no concentrations were given, neither for ethanol nor for dimethyl sulfoxide. The passage in column 8, lines 15 to 18, taught that some or all of the propylene glycol could be substituted by ethanol or by DMSO. No combination of ethanol and DMSO was disclosed.

Figure 3 of document (10) did not disclose the presence of ethanol. Furthermore, the composition of Figure 3 had a pH of 2.3, which was outside the claimed range.

The subject-matter of the claims of the main request was novel over documents (4) and (10).

Inventive step

The closest prior art, document (9), relied exclusively on the lowering of the pH for the release of vitamin D from vitamin D-binding protein. The problem to be solved was the provision of an alternative reagent for release of vitamin D from vitamin D-binding protein. The problem was solved by the claimed subject-matter. The attack by the appellant on the examples of the patent in suit was not backed up by any experimental evidence. This attack was late filed and based on mere allegations. The subject-matter of claim 1 of the main request differed in three aspects from document (9). Firstly, acetonitrile had to be left out. Secondly, a solvent leading to better results had to be added. Thirdly, a short-chain alcohol had to be added. It could be seen from the examples of the patent in suit that the addition of the amphiphilic reagents according to claim 1 of the main request led to better results. Document (9) was completely silent as to the function of acetonitrile. The skilled person thus had no guidance as to its potential replacement. Document (6) could not lead to the subject-matter claimed as it related to a completely different system which was incompatible with the teachings of document (9). Also, the pH to be used in document (6) was 7.4, which was not encompassed by the teachings of document (9). Furthermore, document (6) led away from the solution presented in claim 1 of the main request, since its preferred solvent was methanol, to be used in a concentration of 16 percent by volume. Replacing acetonitrile by a mixture of solvents as defined in claim 1 of the main request would have only been done

using hindsight. The subject-matter of the claims of the main request involved an inventive step.

XII. The final requests of the parties were as follows:

The appellant requested that the decision under appeal be set aside and that the European patent No. 1 931 999 be revoked.

The respondents requested to dismiss the appeal, or, alternatively, to maintain the patent according to the claims of auxiliary request 1 filed by letter dated 10 July 2019.

Reasons for the Decision

1. Admissibility of appeal

In accordance with Article 108, third sentence, and Rule 99(2) EPC, a statement setting out the grounds of appeal must be filed which indicates the reasons for setting aside the decision impugned, and the facts and evidence on which the appeal is based. The grounds of appeal should not be confined to an assertion that the contested decision is incorrect, but should state the legal and/or factual reasons which constitute the basis of its challenge to the validity of the decision. The grounds must address one or more of the reasons on which the contested decision was based. It is not a matter of whether the arguments put forward are actually effective, but rather that circumstances are demonstrated which by their nature may in principle challenge the reasons for the decision.

By discussing various points of the impugned decision, see e.g. paragraphs 5.2., 6.1.1. or 6.2.6 of the statement of grounds of appeal, the appellant has enabled the board to understand why the decision is alleged to be incorrect. Even if, as argued by the respondents, some of the appellant's arguments in the statement of grounds of appeal might be a repetition of the arguments which had been submitted before the opposition division, this is not per se detrimental to the appeal's admissibility as long as there are arguments addressing the reasons of the appealed decision. The requirements of Article 108, third sentence, and of Rule 99(2) EPC are thus fulfilled. The appeal is admissible.

2. Admission of documents

The board has decided to admit documents (11) and (12), Annex A and Annex B. These documents relate merely to common general knowledge and thus cannot provide any new or surprising information. These documents do not introduce complex matter into the proceedings and do not lead to a situation that could not be dealt with without adjournment of oral proceedings.

The board, exercising its discretion, has thus admitted documents (11) and (12) in accordance with Article 12(4) RPBA, and Annex A and Annex B in accordance with Article 13 RPBA.

3. *Main request - patent as granted*

3.1 *Amendments (Article 100(c) EPC)*

3.1.1 Claim 1 of the main request is based on a combination of claims 1 and 2 as filed, together with the

disclosure on page 5, lines 5 to 9. Furthermore, the addition of a short-chain (C1 to C3) alcohol has been made mandatory by replacing the term "as well as optionally" of claim 1 as filed with the term "and". A comma has been inserted before the "and". Also, the short-chain (C1 to C3) alcohol has been clarified to be a member of the list disclosed on page 5, lines 26 to 28, of the description as filed.

- 3.1.2 The appellant has argued that the introduction of a merely optional feature, which, furthermore, had not been linked to a functionality in the application as filed, changed the teaching of the patent and thus extended its subject-matter beyond the application as filed.

The board cannot concur with this reasoning, since the addition of short-chain alcohols has explicitly been an option in the application as filed and this option has merely been turned into a mandatory presence. The addition of the short-chain alcohols was thus already envisaged at the filing date of the patent in suit. The lack of description of a possible function of the short-chain alcohols is irrelevant for the purposes of Article 100(c) EPC, since the claims of the main request are not restricted to any particular functionality of the short-chain alcohols.

- 3.1.3 Furthermore, the appellant has put forward that claim 1 as filed defined an amount of 5 to 30 percent by volume of one or more amphiphilic reagents. Since short-chain alcohols were also amphiphilic reagents, their presence in the claimed composition was also limited to an upper limit of 30 percent by volume of amphiphilic reagent. By changing the term "as well as optionally" to "and", preceded by a comma, the amount of alcohol was no

longer included in the 5 to 30 percent by volume of amphiphilic reagent(s), but in addition thereto. The maximum amount of amphiphilic reagent was thus raised from 30 to 38 percent by volume.

The board cannot adopt the way the appellant construes claim 1 as filed. Claim 1 as filed is, at most, ambiguous as to whether the specifically defined amounts of short-chain alcohol are to be taken as being within the amount of amphiphilic reagents (i.e. that 30 percent by volume is the maximum amount of amphiphilic reagent and within this total amount of amphiphilic reagent a certain concentration of alcohol may be present).

The description as filed renders it clear that the amphiphilic reagents do not include short-chain alcohols. Page 5, lines 5 to 14, relates to the amphiphilic (release) reagents and makes it clear that liquid organic amides and dimethyl sulfoxide are considered to form part of these reagents. No mention of any alcohols is made. The disclosure on page 5 goes on, starting from line 15, referring to the "amphiphilic reagents specified above", to state that several of these agents may be used. The section of the description relating to the amphiphilic (release) agents ends with the statement that preferably only one of the amphiphilic reagents mentioned above may be used (page 5, line 18). The next section concerns the preferred pH ranges of the composition (page 5, lines 19 to 21). This is then followed by a section relating to the short-chain alcohols (page 5, lines 22 to 28). Here, it is made clear that the short-chain alcohols are to be used in addition to the other components, i.e. the amphiphilic reagents, of the release reagent. It is thus apparent from the description as filed that

the amphiphilic reagents and the short-chain alcohols are separate, independent groups. Consequently, the amounts expressed by percent by volume are also to be seen as being independent.

3.1.4 The subject-matter of the main request does not extend beyond the application as filed.

3.2 *Novelty (Articles 100(a) and 54 EPC)*

The appellant has raised novelty objections against claim 1 of the main request based on documents (4) and (10).

3.2.1 Document (4) defines, in the context of a method claim, a buffered solution having a pH in the range of 4.0 to 8.5. The solution comprises a co-solvent selected from the group consisting of propylene glycol, ethanol, dimethyl sulfoxide (DMSO), and combinations thereof (claim 1). Column 8, lines 14 to 18, describes that when the propylene glycol (PG) co-solvent used amounts to 10% or less of the total volume, it can optionally be substituted by ethanol or dimethyl sulfoxide. Neither this passage nor claim 1 discloses amounts of ethanol or dimethyl sulfoxide. The passage in column 8 clearly states that ethanol and dimethyl sulfoxide are alternatives. A combination of these two solvents is not disclosed. Such a combination cannot be directly and unambiguously derived from claim 1 either. Document (4) thus fails to disclose a combination of dimethyl sulfoxide and ethanol in the required amounts.

3.2.2 Document (10) discloses in Figure 3 that a running buffer comprising 30% DMSO is used in a method of separating tryptophan derivatives. The pH of the running buffer used in the experiments depicted in

Figure 3 is 2.3 and thus outside the claimed range. Furthermore, there is no disclosure of ethanol being present. Ethanol is disclosed as one possible alternative water-miscible organic solvent in the passage on page 374, left column, last paragraph, but not in combination with DMSO.

- 3.2.3 The appellant has argued that these documents inherently disclose the subject-matter of claim 1 of the main request. It stated that compositions inevitably contain ingredients in certain amounts and that amounts of ethanol in the lower range claimed were always added to such compositions to improve handling by reduction of the surface tension of water.

The case law of the boards of appeal is based on a narrow concept of novelty. The question to be decided is what has been made available to the public, not what might have been inherent in what was made available to the public. The arguments of the appellant thus can not be adopted.

- 3.2.4 The subject-matter of claim 1 of the main request is new with regard to the documents invoked by the appellant.

3.3 *Inventive step (Articles 100(a) and 56 EPC)*

- 3.3.1 Claim 1 of the main request is directed to a reagent composition for the release of vitamin D from vitamin D-binding protein. The release of vitamin D by the claimed composition will allow direct further analysis of the vitamin D compounds (see paragraphs [0001], [0014] and [0015] of the patent in suit).

3.3.2 The board considers, in agreement with the parties, that document (9) can be viewed as representing the closest state of the art.

Document (9) relates to a method of assaying a biological sample for the presence of vitamin D or vitamin D metabolites (page 1, lines 5 and 6). This method relies on lowering the pH of the sample to 5.5 or less to dissociate the 25-hydroxy-vitamin D from vitamin D-binding proteins (claim 1). A direct measurement of vitamin D is then possible (page 2, lines 19 to 23). Several possible pH ranges are identified. The lowering of the pH is effected by the addition of a buffer (page 3, lines 20 to 28). This buffer can be a phosphate-citrate buffer containing 10% organic solvents, surfactants, and preservatives at pH 4.3. The organic solvent is preferably acetonitrile (page 5, lines 21 to 31).

The difference between claim 1 and document (9) is the organic solvent(s) used.

No data comparing the use of the reagent composition according to the patent in suit to the assay buffer of document (9) are on file. Thus, it has not been shown that the change of organic solvents is linked to a technical effect.

3.3.3 Consequently, the technical problem is to be seen as the provision of an alternative composition suitable for the release of vitamin D from vitamin D-binding protein.

The patent in suit contains several examples showing that the problem has been solved for some of the solvents defined in claim 1.

Concerning the solvents which were not used in the examples of the patent in suit, no substantiated arguments have been provided as to why the use of these solvents would not lead to a composition suitable for the release of vitamin D from vitamin D-binding protein.

In a late-filed argument, the appellant has alleged that the problem has not been solved. During the oral proceedings, the appellant argued that the set-up of the experiments carried out in the examples of the patent in suit was not suitable for showing that accurate measurements of vitamin D could be obtained. However, no substantiation has been provided. In the end, the appellant restricted itself to pointing to the arguments provided under point 6 of the statement setting out the grounds of appeal (see also point 6 of the notice of opposition). Point 6 questions that there is an unexpected effect linked to the selection of the solvents. The suitability of the composition according to claim 1 to release vitamin D from vitamin D-binding protein is not questioned in this section.

The board is thus satisfied that the problem as formulated above has been solved.

- 3.3.4 It remains to investigate whether the proposed solution would have been obvious to the skilled person in light of the prior art.

As mentioned above, document (9) teaches the use of organic solvents in general and acetonitrile in particular, but it does not provide any pointer to the use of any of the amphiphilic reagents listed in the patent. The appellant has pointed to document (6) as

providing such a teaching. Document (6), in the context of a method for detection of vitamin D metabolites, discloses a composition comprising displacement agents, a buffer and a water-miscible solvent (page 8, lines 17 to 20). By using the term "displacement agent", the mechanistic principle underlying the method of document (6) becomes clear: the method is based on a non-competitive agent displacing vitamin D from the vitamin D-binding protein (page 8, lines 11 to 13). The composition of document (6) is thus geared to keeping the displacement agents in solution until they have been able to displace the vitamin D (or its metabolite) and to bind to the vitamin D-binding protein. The composition employed in document (6) is based on phosphate buffered saline which has a neutral pH. Due to the fact that document (6) relies on a different principle and the composition of document (6) fundamentally differs in pH from the composition of the closest prior art, the skilled person would not consider that the solvents listed in document (6) would be obvious alternative solvents when trying to replace the acetonitrile in document (9).

The board agrees with the appellant that lists of further polar aprotic solvents are part of the common general knowledge and well known to the skilled person. However, his knowledge is irrelevant in the present circumstances, since the closest prior art does not identify acetonitrile as a polar aprotic solvent nor points to the group of polar aprotic solvents as being suitable for use in the disclosed method. Indeed, there is no information at all in document (9) as to the properties or functionalities required of the organic solvent. Furthermore, it is noted that the list of solvents of document (6) includes solvents that are not

polar aprotic solvents.

3.3.5 Consequently, the solution presented in the claims of the main request represents a non-obvious alternative.

The subject-matter of the main request involves an inventive step.

4. None of the invoked grounds for opposition prejudices the maintenance of the European patent.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar:

The Chairwoman:



M. Schalow

T. Sommerfeld

Decision electronically authenticated