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Datasheet for the decision of 7 September 2020

Case Number: T 2721/16 - 3.3.08

Application Number: 04077617.1

Publication Number: 1568787

IPC: C12Q1/70

Language of the proceedings: EN

Title of invention:
Method for using nucleic acid sequences as primers and probes in the amplification and detection of all subtypes of HIV-1

Patent Proprietor:
bioMérieux BV

Opponent:
Hologic, Inc.

Headword:
HIV-1 primers/BIOMERIEUX

Relevant legal provisions:
EPC Art. 76(1), 123(2)

Keyword:
Auxiliary request 1 upheld at first instance (sole request) - added subject-matter (yes)

Decisions cited:

Catchword:

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

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Case Number: T 2721/16 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 7 September 2020

Appellant: (Opponent)	Hologic, Inc. 35 Crosby Drive Bedford, MA 01730 (US)
Representative:	Marshall, Cameron John Carpmaels & Ransford LLP One Southampton Row London WC1B 5HA (GB)
Respondent: (Patent Proprietor)	bioMérieux BV Boseind 15 5281 RM Boxtel (NL)
Representative:	van Someren, Petronella F. H. M. Arnold & Siedsma Bezuidenhoutseweg 57 2594 AC The Hague (NL)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 10 October 2016 concerning maintenance of the European Patent No. 1568787 in amended form.**

Composition of the Board:

Chairman	B. Stolz
Members:	P. Julià
	R. Winkelhofer

Summary of Facts and Submissions

I. European patent no. 1 568 787 was granted with 3 claims. It is based on European patent application no. 04 077 617.1 (hereinafter, "the patent application"), a divisional application of the European patent application no. 98 943 872.6 (published as EP 1 002 138), filed under the PCT as international patent application PCT/EP98/04945 and published as WO 99/07898 (hereinafter, "the earlier patent application").

II. An opposition was filed on the grounds set forth in Articles 100(a), (b) and (c) EPC. The opposition division considered the main request (claims as granted) to contravene Articles 76(1) and 123(2) EPC. Auxiliary request 1 was considered to fulfil the requirements of the EPC and, accordingly, the patent was maintained in amended form on the basis of this auxiliary request.

III. The opponent (appellant) lodged an appeal maintaining the objections raised under Articles 76(1), 123(2), 83 and 56 EPC at first instance.

IV. The patent proprietor (respondent) refuted these objections.

V. Both parties requested oral proceedings as an auxiliary measure.

VI. The parties were summoned to oral proceedings and, in a communication pursuant to Article 17 Rules of Procedure of the Boards of Appeal (RPBA 2020), they were informed of the board's provisional opinion on the issues of the

case. In particular, the board stated, *inter alia*, that auxiliary request 1 as upheld by the opposition division contravened Articles 76(1) and 123(2) EPC.

VII. Without making any substantive submissions, the respondent informed the board that they would not attend the oral proceedings.

VIII. In reply thereto, the appellant informed the board that their request for oral proceedings was "conditional on the Board not being able to reach a decision on the basis of the written procedure".

IX. The oral proceedings were cancelled.

X. The description, figure and claims of the patent application and the earlier patent application are literally identical. References given in the parties' submissions are only to the earlier patent application, i.e. the international patent application WO 99/07898.

XI. Claims 4, 6 and 9 of the earlier patent application read as follows:

"4. Pair of oligonucleotides, for use as a set in the amplification of a target sequence located within the LTR region of the genome of HIV-1, said pair consisting of a first oligonucleotide being 10-50 nucleotides in length and comprising, at least a fragment of 10 nucleotides, of a sequence selected from the group consisting of:

SEQ ID 1: G GGC GCC ACT GCT AGA GA
SEQ ID 2: G TTC GGG CGC CAC TGC TAG A
SEQ ID 3: CGGGCGCCACTGCTA

and a second oligonucleotide being 10-50 nucleotides in length and comprising, at least a fragment of 10 nucleotides, of a sequence selected from the group consisting of:

SEQ ID 4: CTG CTT AAA GCC TCA ATA AA
SEQ ID 5: CTC AAT AAA GCT TGC CTT GA
SEQ ID 12: GAT GCA TGC TCA ATA AAG CTT GCC TTG AGT.

6. Pair of oligonucleotides according to any of claims 4-5 wherein the first oligonucleotide is provided with a promoter sequence recognized by a DNA dependent RNA polymerase.

9. Method for the detection of HIV-1 nucleic acid in a sample wherein the sample is subjected to a nucleic acid amplification reaction using a pair of oligonucleotides according to claim 4 and suitable amplification reagents and the presence of any amplified nucleic acid is detected."

XII. Claim 1 of auxiliary request 1 as upheld by the opposition division reads as follows:

"1. Method for the detection of HIV-1 nucleic acid in a sample wherein the sample is subjected to a transcription based nucleic acid amplification reaction using a pair of oligonucleotides as primers and suitable amplification reagents, and the presence of any amplified nucleic acid is detected, wherein the pair of oligonucleotides consists of a first oligonucleotide being 26 nucleotides in length and comprising SEQ ID: 1 :

G GGC GCC ACT GCT AGA GA

and a second oligonucleotide being 15-26 nucleotides in length and comprising at least a fragment of 10 nucleotides of SEQ ID: 5 :

CTC AAT AAA GCT TGC CTT GA,

wherein the first oligonucleotide is operably linked to a promoter sequence for use as promoter primer."

XIII. The appellant argues that several features of claim 1 of the auxiliary request 1 as upheld by the opposition division had no basis in the (earlier) patent application (Articles 76(1) and 123(2) EPC), *inter alia*: i) the length (26 nt) of the first oligonucleotide not including a promoter; and ii) the difference in the length of the first and second oligonucleotides (26 nt and 15-26 nt, respectively) as well as in the definition of the first (specific sequence length) and the second (permitting fragments) oligonucleotides.

XIV. In reply thereto, the respondent argues that most amendments were simply linguistic amendments arising from claiming a sequence no longer as a member of a group of sequences. The amendments to the claims as upheld by the opposition division as compared to the claims of the (earlier) patent application were: i) the amendment that the first oligonucleotide was provided with a promoter sequence; ii) the range "10-50 nucleotides" for the first oligonucleotide was amended to "26 nucleotides", and the range "10-50 nucleotides" for the second oligonucleotide was amended to "15-26 nucleotides"; and iii) the deletion of SEQ ID 2, 3, 4 and 12 leaving the combination between SEQ ID 1 and 5.

As regards the first oligonucleotide being provided with a promoter, there was abundant basis in the earlier patent application for the combination of the first oligonucleotide with an additional promoter sequence, such as on page 5, line 28; page 6, lines 28 and 29, and claim 6 of the earlier patent application.

As regards the value "26 nucleotides" for the first oligonucleotide, this value was disclosed as the endpoint of the range 15-26 on page 5, lines 26 to 28 of the earlier patent application. It was established practice that the endpoints of a range were also disclosed in isolation. This disclosure made also clear that primers could be longer than 15-26, and thus longer than 26 nucleotides, because they could contain additional sequences such as promoter sequences. The term "additional" made it clear that the promoter sequence could be linked to the 15-26 nucleotides that were "substantially complementary or homologous to the target sequence", providing thereby sufficient disclosure to support the claims. The description on page 5 of the earlier patent application defined primers with and without a promoter sequence. Primers without promoter sequence were said to be 15-26 nucleotides long, primers with a promoter were longer. The promoter was extra and thus, came in addition to the 26 nucleotides. Nothing in this definition suggested that primers were claimed in which the promoter overlapped with the 26 nucleotides of the first oligonucleotide. From SEQ ID 9, disclosed on page 7, lines 9 and 13 to 15 of the earlier patent application, it followed that a promoter, such as the T7 promoter, could be 25 nucleotides long. When this promoter was part of the 26 nucleotides then only one nucleotide remained for hybridization. It was clear that such a definition was nonsensical.

As regards the range "15-26 nucleotides" for the second oligonucleotide, the disclosure on page 5, line 26 related to all primers and thus, it was also a basis for the length of the second primer.

XV. The appellant (opponent) requests that the decision under appeal be set aside and that the patent be revoked.

XVI. The respondent (patent proprietor) requests that the appeal be dismissed.

Reasons for the Decision

1. The present decision is based on the same grounds, arguments and evidence on which the board's provisional opinion was based. It was neither questioned by any of the parties, nor did other aspects come up that would require its reconsideration.

Auxiliary request 1 as upheld by the opposition division (the sole request in appeal proceedings)

Articles 76(1) and 123(2) EPC

2. As outlined above, the description, figure and claims of the patent application and the earlier patent application are literally identical. Thus, when assessing whether there is a direct and unambiguous disclosure of the claimed subject-matter in the patent application and in the earlier patent application, reference is only made to the description of the international patent application WO 99/07898. Any deficiency identified in the earlier patent application

(Article 76(1) EPC) is also relevant for the patent application (Article 123(2) EPC).

3. The earlier patent application is concerned with test kits and methods for detecting HIV-1 nucleic acid in a sample (claims 9 to 13), a product used in said method, namely a pair of oligonucleotides or a combination of two oligonucleotides (claims 4 to 7), the components of said product and test kits, namely oligonucleotide sequences that are located in the LTR part of the HIV-1 genome (claims 1, 2 and 8), and the use of these oligonucleotide sequences in said method and test kit (claim 3). In the earlier patent application, test kits, methods, products and components are all disclosed at different levels of generalisation, in particular the product (pair of oligonucleotides or combination of two oligonucleotides) used in the method for HIV-1 detection and the components of this product (oligonucleotides).

4. "Oligonucleotides" are broadly defined on page 6, lines 8 to 34, by a length range of 10-50 nucleotides comprising at least a fragment of 10 nucleotides of a sequence selected from a group of nine specific nucleotide sequences (SEQ ID 1 to 8, and SEQ ID 12) or the complementary sequences thereof. There is also a reference to "minor deletions, additions and/or substitutions of nucleic acid bases, to the extent that such alterations do not negatively affect the yield or product to a significant degree" (cf. page 6, lines 22 to 25; see also page 5, lines 11 to 16 for "analogues of oligonucleotides"). More specific disclosures are the "preferred oligonucleotides" which are oligonucleotides "consisting essentially of a sequence selected from" twelve specific nucleotide sequences (SEQ ID 1 to 12) (cf. page 6, line 35 to page 7,

line 12). Claims 1 and 2 correspond to these broad and more specific disclosures.

5. In the earlier patent application, two different uses are contemplated for these "oligonucleotides", namely in a nucleic acid amplification reaction (in the HIV detection method) and as a probe (in the HIV test kit) for the detection of HIV in a sample (cf. page 5, lines 9 and 10; page 8, lines 5 to 19; claim 3). When used in an amplification reaction, these oligonucleotides are used as "primers". A broad definition of the term "primer" is found on page 5, lines 17 to 28, where a typical primer is defined as containing "at least about 10 nucleotides in length of a sequence substantially complementary or homologous to the target sequence, but somewhat longer primers are preferred". And, immediately thereafter, it is stated that "[u]sually primers contain about 15-26 nucleotides but longer primers may also be employed, especially when the primers contain additional sequences such as a promoter sequence for a particular polymerase".

6. This definition of the term "primer" is ambiguous. According thereto, a primer contains an oligonucleotide of a specific length (at least 10 nucleotides) with a particular property (substantially complementary or homologous to the target sequence). However, this property is not clearly required over the whole sequence (length) of the preferred "somewhat longer primers". It may be so, but it is not necessarily the case. The same ambiguity is present in the definition of the usual primers which are defined as containing "about 15-26 nucleotides", but which may also be longer "especially when the primers contain additional sequences". This wording does not clearly exclude the presence of such "additional sequences" in primers of a

length falling within the range of "about 15-26 nucleotides" and containing "at least about 10 nucleotides in length of a sequence substantially complementary or homologous to the target sequence". It may be so, but it is not necessarily the case.

7. Whilst, based on this ambiguity, the appellant interprets these paragraphs as allowing the presence of non-complementary or non-homologous nucleotides in primers with a length falling within the range of "about 15-26 nucleotides", the respondent interprets them as requiring all primers with a length falling within the range of "about 15-26 nucleotides" not to have any such "additional sequences".

8. In any case, the same ambiguity is also inherent in the wording of claim 1 of auxiliary request 1 as upheld by the opposition division, since the "first oligonucleotide" used as a primer is defined as "being 26 nucleotides in length" and comprising the sequence of SEQ ID 1 with a length of 18 nucleotides. The claim does not define the properties of the remaining 8 nucleotides (26 minus 18) which may thus be either "substantially complementary or homologous to the target sequence" or not. Likewise, the second oligonucleotide used as a primer is defined as "being 15-26 nucleotides in length and comprising at least a fragment of 10 nucleotides of the sequence SEQ ID 4", and thus, allows the presence of as many as 16 nucleotides (26 minus 10) or as little as 5 nucleotides (15 minus 10) which may be either "substantially complementary or homologous to the target sequence" or not.

9. As regards the appellant's objection that the first oligonucleotide of 26 nucleotides in length as defined

in claim 1 of the request upheld at first instance does not include a promoter sequence, the following has to be stated:

9.1 In the broad definition of a primer on page 5 of the earlier patent application discussed above, reference is made to the presence of "a promoter sequence for a particular polymerase" as an example of "additional sequences" present in the primer (cf. page 5, line 28). According to this definition, a primer may be longer than "about 15-26 nucleotides", but the total length of the primer is not defined.

9.2 Oligonucleotides with combinations of sequences of specific SEQ IDs and the T7 promoter sequence are disclosed on page 7, lines 9 to 16 of the earlier patent application. These oligonucleotides are described as being "especially suitable for use as upstream primer in a transcription based amplification technique". The total length of the specific oligonucleotides used as upstream primers is 47, 49 and 40 nucleotides (SEQ ID 9, 10 and 11, respectively), all shorter than 50 nucleotides. The "upstream" and "downstream" primers are described in the (earlier) patent application (cf. page 5, lines 29 and 31; page 7, line 31 to page 8, line 4) and referred to also as "first" and "second" primers, respectively, such as when the "most preferred pair of oligonucleotides" - used in all the Examples of the earlier patent application - is described (cf. page 8, lines 5 to 9).

9.3 The combination of claims 4 and 6 of the earlier patent application defines the first oligonucleotide as "being 10-50 nucleotides in length and comprising at least a fragment of 10 nucleotides of a sequence selected from the group consisting of SEQ ID 1 to 3 .... , wherein

the first oligonucleotide is provided with a promoter sequence". In light of the specific combinations disclosed in the description of the earlier patent application, the length range (10-50 nucleotides) is understood as defining the length of the first oligonucleotide/upstream primer, regardless of whether or not it comprises a promoter sequence. In fact, when it is provided with the specific T7 promoter sequence, the first oligonucleotide is ("consisting essentially of") the SEQ ID 9 sequence of 47 nucleotides in length (claim 7 of the earlier patent application); if the complete length of the first oligonucleotide is 50 nucleotides, the additional three nucleotides may be "substantially complementary or homologous to the target sequence" or completely different therefrom (*supra*).

9.4 In claim 1 of auxiliary request 1 as upheld at first instance, the first oligonucleotide is defined as "being 26 nucleotides in length and comprising the sequence SEQ ID 1 [of 18 nucleotides] ..., wherein the first oligonucleotide is operably linked to a promoter sequence for use as promoter primer". This definition appears to exclude the presence of (a part of) the promoter sequence within the 26 nucleotides. It combines a feature of a generic disclosure, namely the specific "26 nucleotides in length" - disclosed on page 5 of the earlier patent application as the upper-end of a (sub)range of lengths, where neither a specific sequence (SEQ ID) nor the complete length of the sequence substantially complementary or homologous to the target sequence (except for being "at least about 10 nucleotides in length") were defined - with other features disclosed at a different level of generalisation, and which included *inter alia* the specific oligonucleotide sequences of SEQ ID 1 and 5 of

both, the first and second oligonucleotides/primers. Combinations of disclosures of different levels of generalisation usually result in new intermediate generalisations that are neither directly nor unambiguously derived from the earlier patent application (cf. "Case Law of the Boards of Appeal of the EPO", 9th edition 2019, II.E.1.9, 482).

9.5 In the present case, the combination of 18 nucleotides of SEQ ID 1 with the T7 promoter sequence results in a sequence of 47 nucleotides (SEQ ID 9), longer than the 26 nucleotides of the first oligonucleotide as defined in claim 1. In fact, all first oligonucleotides disclosed in the (earlier) patent application comprising a promoter sequence are longer than 26 nucleotides, the specific length defined in claim 1 of the request upheld at first instance.

Closer inspection of SEQ ID 9 reveals a "non-promoter" sequence of 24 nucleotides operably linked to a T7 promoter. Indeed, there is no disclosure in the earlier patent application of any primer of 26 nucleotides not comprising parts of a promoter sequence. Thus, the definition of the first oligonucleotide as being 26 nucleotides in length and not including (parts of) a promoter sequence is not directly and unambiguously derivable from the earlier patent application (Articles 76(1) and 123(2) EPC).

10. As regards appellant's objection on the differences in the length and the definition of the first and second oligonucleotides:

10.1 In claim 1 of auxiliary request 1 as upheld at first instance, the first and second oligonucleotides are differently defined. Whilst the first oligonucleotide

is characterised by its length (26 nucleotides; no range) and the presence of the complete sequence SEQ ID 1 (18 nucleotides), the second oligonucleotide is defined by a range of lengths (15-26 nucleotides) and a fragment of at least 10 nucleotides of sequence SEQ ID 5.

10.2 In the earlier patent application, there is a generic disclosure of "a set of primers" on page 5, lines 29 to 31, with reference as well to a promoter sequence in general (cf. page 5, line 32 to page 6, line 7). The "pair of oligonucleotides" or "a combination of two oligonucleotides" is defined in more specific terms on page 7, line 19 to page 8, line 4; where the first and second oligonucleotides are both characterised by the same length range (10-50 nucleotides) and same minimal length (at least 10 nucleotides) of the fragment defined by a specific SEQ ID sequence (claims 4 and 5 of the earlier patent application). A disclosure in even more specific terms is the "most preferred pair of oligonucleotides" described on page 8, lines 5 to 9, which is used to exemplify the earlier patent application (cf. page 12, Example 2 to page 16, Example 6; SEQ ID 9/SEQ ID 5), i.e. the subject-matter of claim 7 of the earlier patent application.

10.3 The combination of the specific upper-end value of a (sub)range of a range of lengths of one (first) oligonucleotide with the broad (sub)range of lengths of the other (second) oligonucleotide in claim 1 has no basis in the earlier patent application because these (sub)ranges are disclosed in the earlier patent application only in the context of a generic disclosure and without any reference to either the first or the second oligonucleotide. Moreover, claim 1 not only combines particular lengths of the first (26 nt) and

second oligonucleotides (5 to 26 nt) but further requires the first oligonucleotide to comprise all of SEQ ID 1, i.e. 18 nucleotides of SEQ ID 1, and the second oligonucleotide to comprise "at least a fragment of 10 nucleotides" of SEQ ID 5.

10.4 The specific combination of features in claim 1 results in an intermediate generalisation which is not directly and unambiguously derivable from the earlier patent application, but goes beyond its disclosure.

11. It follows from all the considerations above that the auxiliary request 1 upheld by the opposition division contravenes Articles 76(1) and 123(2) EPC.

Conclusion

12. In the absence of any request fulfilling the requirements of the EPC, the patent has to be revoked.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairman:

I. Aperribay B. Stolz

Decision electronically authenticated