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Datasheet for the decision of 21 March 2017

Case Number: T 1119/12 - 3.3.08

Application Number: 06734145.3

Publication Number: 1844163

IPC: C12Q1/68

Language of the proceedings: EN

Title of invention:
HIGHLY ORTHOGONAL UNIVERSAL SEQUENCES FOR USE IN NUCLEIC ACID ASSAYS

Applicant:
Siemens Healthcare Diagnostics Inc.

Headword:
Orthogonal oligonucleotides/SIEMENS HEALTHCARE DIAGNOSTICS

Relevant legal provisions:
EPC Art. 54, 56, 84, 123(2)

Keyword:
Main Request and Auxiliary Request 1 - extension beyond the content of the application as filed (yes)
Auxiliary request 2 - inventive step (no)

Decisions cited:
T 0939/92

Catchword:

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Case Number: T 1119/12 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 21 March 2017

Appellant: (Applicant)	Siemens Healthcare Diagnostics Inc. 511 Benedict Avenue Tarrytown, NY 10591 (US)
Representative:	Schweitzer, Klaus Plate Schweitzer Zounek Industriepark Kalle-Albert Rheingaustrasse 196 65203 Wiesbaden (DE)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 30 December 2011 refusing European patent application No. 06734145.3 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairwoman	M. R. Vega Laso
Members:	B. Stolz
	R. Winkelhofer

Summary of Facts and Submissions

I. The applicant (appellant) filed an appeal against a decision of the examining division, dated 30 December 2011, refusing European patent application No. 06734145.3 with the title "Highly orthogonal universal sequences for use in nucleic acid assays".

II. In the decision under appeal, the examining division found that the claims of the sole request then on file lacked clarity and support (Article 84 EPC), were directed to non-patentable subject-matter (Article 52(2)(d) EPC), and lacked novelty in view of documents (1) and (2) (Article 54 EPC).

III. With the statement setting out the grounds of appeal, the appellant filed three sets of claims as a new main request and new auxiliary requests 1 and 2. As a subsidiary request, it requested oral proceedings.

IV. The examining division did not rectify its decision and the appeal was forwarded to the board (Article 109 EPC).

V. The appellant was summoned to oral proceedings. In a communication pursuant to Article 15(1) of the Rules of Procedure of the Boards of Appeal (RPBA) annexed to the summons, the board informed the appellant of its provisional non-binding opinion on some of the issues to be discussed at the oral proceedings. The board expressed its provisional view that the main request and auxiliary request 1 did not meet the requirements of Articles 84 and 54 EPC and contravened Article 123(2) EPC. Moreover, auxiliary request 2 seemed to lack inventive step (Article 56 EPC) in view

of document (1) in combination with document (3) introduced into the proceedings by the board.

VI. In reply to the board's communication, the appellant informed the board that it maintained the main request and both auxiliary requests, but was withdrawing its request for oral proceedings and would not be attending them. The reply did not include any substantive arguments.

VII. Oral proceedings were held on 21 March 2017 in the absence of the appellant.

VIII. The following documents are referred to in this decision:

(1): M.L. Collins et al., "A branched DNA signal amplification assay for quantification of nucleic acid targets below 100 molecules/ml", Nucleic Acids Research (1997), Vol. 25, no. 15, 2979—84;

(3): S. Bushnell et al., "ProbeDesigner: for the design of probesets for branched DNA (bDNA) signal amplification assays", Bioinformatics (1999), Vol. 15, no. 5, 1999, 348-55.

IX. Claim 1 of the main request reads:

"1. An oligonucleotide having a universal sequence, prepared from six nucleotide bases comprised of four natural bases selected from the group consisting of guanosine (G), cytosine (C), adenosine (A), and thymidine (T) or uracil (U) and two non-natural bases, wherein the two non-natural bases are selected from the group consisting of iso-guanosine (iso-G) and iso-

cytosine (iso-C) and wherein one to four nucleotides of the natural bases, arranged in no specific order, are selected from the group consisting of guanosine (G), cytosine (C), adenosine (A), and thymidine (T) or uracil (U) and are separated by one or both nucleotides of the non-natural bases such that approximately 65% or more of the sequence is comprised of G/C bases and the sequence has a melting temperature (Tm) of approximately 80-85°C, wherein the number of isoG and isoC bases in the sequence is balanced."

X. Claim 1 of auxiliary request 1 reads as follows (amendments to claim 1 of the main request shown in bold):

"1. An oligonucleotide having a universal sequence, prepared from six nucleotide bases comprised of four natural bases selected from the group consisting of guanosine (G), cytosine (C), adenosine (A), and thymidine (T) or uracil (U) and two non-natural bases , wherein the two non-natural bases are selected from the group consisting of iso-guanosine (iso-G) and iso-cytosine (iso-C) and wherein one to **five** nucleotides of the natural bases, arranged in no specific order, are selected from the group consisting of guanosine (G), cytosine (C), adenosine (A), and thymidine (T) or uracil (U) and are separated by one or both nucleotides of the non-natural bases such that approximately 65% or more of the sequence is comprised of G/C bases and the sequence has a melting temperature (Tm) of approximately 80-85°C, wherein the number of isoG and isoC bases in the sequence is balanced **and the sequence has at least one incidence of five natural bases separated by isoC or isoG**".

XI. Claim 1 of auxiliary request 2 reads as follows:

> "1. An oligonucleotide having a universal sequence, wherein said universal sequence is selected from the group consisting of the sequences SEQ ID NO: 1 to SEQ ID NO: 66."

XII. The appellant's sole arguments submitted with the statement of grounds of appeal are:

Amendments and their basis (Article 123(2) EPC)

In all requests, the wording "*oligo nucleotide having a universal sequence*" had been added, and the term "*bDNA assay*" had been amended to "*branched DNA assay*" for clarification. An implicit basis for this could be found in the complete description (e.g. paragraphs [0002]-[0012], [0036]-[0046]) and in the examples.

In the main request, the features "*such that approximately 65% or more of the sequence is comprised of G/C bases*", and "*wherein the number of isoG and isoC bases in the sequence is balanced*" had been added. Support for the changes to claim 1 could be found in the specification at, *inter alia*, paragraphs [0064], [0090] and [0092].

In auxiliary request 1, the features "*wherein the number of isoG and isoC bases in the sequence is balanced*", and "*the sequence has at least one incidence of five natural bases separated by isoC or isoG*" had been added. Support for the changes to claim 1 could be found in the specification at, *inter alia*, paragraphs [0064], [0090], [0092] and in the examples.

As regards auxiliary request 2, the sequences with SEQ ID NO 1 to 66 were supported by the sequence protocol and Table 1.

Novelty and inventive step (Articles 54 and 56 EPC)

Regarding the claims of the main request and auxiliary request 1, the prior art did not disclose or suggest the claimed invention. In document (1), the LE tail of Table 1 had 4 iso-G bases and 1 iso-C base; accordingly, the number of iso-G and iso-C bases in the LE tail of Table 1 was not balanced. The Preamplifier repeat of Table 1 had 2 iso-G bases and 4 iso-C bases; accordingly, the number of iso-G and iso-C bases in the Preamplifier repeat of Table 1 was not balanced. The Amplifier repeat of Table 1 had a G/C content (including iso-G and iso-C) of 61.9%; accordingly, the G/C content of the Amplifier repeat was not at least 65%.

Further, the prior art did not disclose or suggest the oligonucleotides of auxiliary request 2.

XIII. The appellant requests that the decision under appeal be set aside and a patent be granted on the basis of the claims of any of the main request and auxiliary requests 1 and 2, all filed together with the statement of grounds of appeal.

Reasons for the Decision

Main request

Article 123(2) EPC

1. Claim 1 specifies that "*approximately 65% or more of the sequence is comprised of G/C bases*". The appellant referred to paragraphs [0064], [0090] and [0092] of the application as filed (published international patent application WO 2006/083925) as the basis for this feature, without however explaining why it considered these paragraphs to directly and unambiguously disclose the subject-matter of claim 1.

2. With respect to the G/C concentration, it is stated in paragraph [0064] of the application as filed, which is part of the general description of the invention, that: "[...] *under certain circumstances it may be preferred to have [...] G/C concentrations in the range of 51% through 75% or greater*". This passage does not however disclose a G/C content of "*approximately 65% or more*".

3. Paragraph [0090] discloses the generation of one hundred 20mer sequences of which 36 were selected for further analysis "*based on a 65% to 70% G/C content (including iso-G and iso-C)*". This is the sole mention of the figure "65%" in the entire patent application, but only as the lower limit of a range of 65% **to 70%** G/C content.

4. Paragraph [0092] does not mention any percentage for the G/C content at all.

5. Hence, none of the passages of the application as filed on which the appellant relied discloses, explicitly or implicitly, oligonucleotides according to claim 1 which comprise a G/C content of "***approximately*** *65%* ***or more***" (emphasis added).

6. Claim 1 has been further amended to specify that "*the number of isoG and isoC bases in the sequence is balanced*". The appellant referred to the same paragraphs as the basis for this amendment.

7. This second amendment too results in an extension of the claimed subject-matter beyond the content of the application as filed. The only passage relating to a balance of the isobases is found in Example 1 (paragraph [0090]) and reads: "*An additional isobase (either iso-G or iso-C with an attempt to balance the two bases within the particular sequence) was then added to the 5' end of each of the 16 sequences ....*". **The addition of an isobase to the 5' end** to each of 16 sequences **in an attempt to balance** the ratio of iso-G to iso-C of specific oligonucleotides generated in a single example does not provide a basis for a generalisation like that in claim 1.

8. In view of the above, the amendments introduced into claim 1 contravene Article 123(2) EPC.

Auxiliary request 1

9. Apart from two further amendments, claim 1 of auxiliary request 1 includes the same amendments as claim 1 of the main request. For the same reasons as those given above for the main request, the amendments introduced into claim 1 of auxiliary request 1 contravene Article 123(2) EPC.

Auxiliary request 2

Articles 123(2), 84 and 54 EPC

10. Claim 1 is directed to an oligonucleotide having a sequence selected from the group of SEQ ID NO: 1 to SEQ ID NO: 66.

11. Oligonucleotides with SEQ ID NOs 1 to 66 are disclosed in Table 1 of the patent application. The wording of claim 1 is clear and the claimed oligonucleotides are not anticipated by any of the prior art documents on file. Claim 1 therefore meets the requirements of Articles 84 and 54 EPC and does not contravene Article 123(2) EPC.

Article 56 EPC

12. Document (1), which represents the closest state of the art, discloses improved oligonucleotides for use in branched DNA signal amplification assays (cf. abstract). Under the headings "*Oligonucleotide probe design*" and "*Universal sequence design*", it describes a set of oligonucleotides of 20 and 21 nucleotides in length which are designed to include iso-G and iso-C bases at approximately every fourth position (cf. page 2981, right column, first paragraph). The oligonucleotides have no secondary structure longer than a trimer, no interactions longer than a trimer, except with their complements, and a melting temperature in excess of 80^{o}C (cf. page 2980, right column, top paragraph). For the design of the improved oligonucleotides, a computer program was used that calculates various parameters and optimises and selects

probes with the lowest homologies (see page 2980, left hand column, lines 3 to 11).

13. Starting from this document, the problem to be solved can be defined as the provision of further oligonucleotides with the same properties.

14. As a solution to this problem, claim 1 proposes oligonucleotides having the SEQ ID NOs: 1 to 66.

15. It remains to be established whether or not the claimed subject-matter was obvious to a person skilled in the art at the relevant date.

16. Starting from document (1), a skilled person seeking to design further oligonucleotides with the same properties would have followed the teaching of this document. The computer program used by the authors of document (1) to optimise and select the probes with the lowest homologies was commercially available at the filing date of the present patent application (cf. the abstract of document (3)). Thus, based on the teachings of document (1) and using the program described in document (3), an average skilled person was able to solve the problem of providing further oligonucleotides with the required properties without any inventive skills and with a reasonable expectation of success.

17. Compared to the oligonucleotides disclosed in document (1), the oligonucleotides of claim 1 show no new or unexpected properties on the basis of which inventive step could be acknowledged. Although a remark to that effect was made in point 35 of the board's communication attached to the summons to oral proceedings, the appellant did not make any submission addressing this issue.

18. Every alternative oligonucleotide obtained by applying the methodology of document (1) is, in the absence of any new or unexpected properties, regarded as an equally suitable solution to the underlying technical problem. The selection of the oligonucleotides defined by SEQ ID NOs: 1 to 66 from the multitude of possible alternative oligonucleotides is nothing but an arbitrary selection which according to the jurisprudence of the Boards of Appeal does not involve an inventive step (cf. e.g. point 2.5.3 of decision T 939/92 of 12 September 1995).

19. Consequently, the subject-matter of claim 1 of auxiliary request 2 does not fulfil the requirement of Article 56 EPC.

Conclusion

20. In the absence of an allowable request, the appeal must be dismissed.

Article 113(1) EPC

21. According to Article 113(1) EPC, decisions of the European Patent Office may only be based on grounds or evidence on which the parties concerned have had an opportunity to present their comments.

22. In the communication attached to the summons to oral proceedings, the board indicated the reasons on which the present decision is based. The appellant thus had an opportunity to present its comments by submitting substantive arguments in writing and/or at the scheduled oral proceedings, but chose not to avail itself of it.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairwoman:

N. Schneider M. R. Vega Laso

Decision electronically authenticated