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Datasheet for the decision of 11 March 2022

Case Number: T 2171/19 - 3.3.01

Application Number: 09835643.9

Publication Number: 2381947

IPC: A61K31/568, C12Q1/68, G01N33/68

Language of the proceedings: EN

Title of invention:
MASS SPECTROMETRY ASSAY FOR ESTROGENIC COMPOUNDS

Applicant:
Quest Diagnostics Investments Incorporated

Headword:
Estrogen assay/QUEST

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step - (no)

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Case Number: T 2171/19 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 11 March 2022

Appellant: (Applicant)	Quest Diagnostics Investments Incorporated 300 Delaware Avenue Wilmington, DE 19899 (US)
Representative:	Harrison IP Limited 3 Ebor House Millfield Lane Nether Poppleton, York YO26 6QY (GB)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 21 January 2019 refusing European patent application No. 09835643.9 pursuant to Article 97(2) EPC**

Composition of the Board:

Chairman	A. Lindner
Members:	J. Molina de Alba
	R. Romandini

Summary of Facts and Submissions

I. The decision under appeal is the examining division's decision refusing European patent application No. 09835643.9.

The decision was based on a sole claim request consisting of 12 claims. Claim 1 reads as follows.

"*1. A method for determining the level of circulating estrogenic compounds in an individual undergoing hormone replacement therapy (HRT), wherein said compounds comprise three or more estrogenic compounds selected from the group consisting of estrone (E1), estrone sulfate (E1s), 17α-estradiol (E2a), 17β-estradiol (E2b), estradiol sulfate (E2s), estriol (E3), equilin (EQ), 17α-dihydroequilin (EQa), 17β-dihydroequilin (EQb), equilenin (EN), 17α-dihydroequilenin (ENa), 17β-dihydroequilenin (ENb), and Δ8,9-dehydroestrone (dE1), the method comprising:*

(a) ionizing a sample comprising three or more estrogenic compounds from the body fluid of an individual undergoing HRT as a single sample injection to ionize each of the three or more analytes to produce one or more ions detectable by mass spectrometry from each of three or more estrogenic compounds, wherein said ionizing comprises ionization by atmospheric pressure chemical ionization (APCI) or electrospray ionization (ESI), wherein if 17α-estradiol (E2a) or 17β-estradiol (E2b) is selected, then the precursor has a mass-to-charge (m/z) ratio of 271.12 ±0.50;

(b) determining the amounts of one or more ions from each of the three or more estrogenic compounds by tandem mass spectrometry; and

(c) *using the amounts of one or more ions from each of the three or more estrogenic compounds to determine the amounts of each of the three or more estrogenic compounds in the body fluid sample of the individual.*"

II. The decision cited, *inter alia,* the following prior-art documents.

D1 WO 2004/090525

D2 B.R. Bhavnani et al., J Soc Gynecol Investig, 7(3), 2000, 175-83

D3 E. Arteaga et al., Climateric, 1(4), 1998, 284-9

D4 S.M. Troy et al., Current Therapeutic Research, 55(4), 1994, 359-72

III. In the decision, the examining division concluded that the method of claim 1 was not inventive. Starting from Dl, the claimed method differed in that the sample was taken from individuals undergoing hormone replacement therapy (HRT). It solved the objective technical problem of providing an alternative method for analysing multiple estrogenic compounds by tandem mass spectrometry (MS/MS) in a specific sample type. The solution proposed in claim 1 was obvious from Dl alone or in combination with the teaching of D2 to D4. The latter related to the analysis by MS/MS of at least two estrogenic compounds in a sample from a patient who had received HRT.

IV. The applicant (appellant) filed an appeal requesting that the decision be set aside and that a patent be granted on the basis of the claims on which the

decision was based. Oral proceedings were requested as a precautionary measure.

V. The board scheduled oral proceedings in line with the appellant's request. In a communication accompanying the summons to oral proceedings, the board gave its preliminary opinion that the method of claim 1 was not inventive starting from either D1 or any of D2 to D4.

VI. By letter dated 3 March 2022, the appellant withdrew its request for oral proceedings.

VII. The board cancelled the oral proceedings and continued the proceedings in writing.

VIII. The appellant's arguments, where relevant to the present decision, can be summarised as follows.

The method of claim 1 differed from the one in Dl not only in the individuals from which the sample was collected (undergoing HRT) but also in that it simultaneously analysed three or more estrogenic compounds from the list in claim 1 and in that ionisation was carried out by APCI or ESI. The objective technical problem was the provision of a method for simultaneously analysing three or more estrogenic compounds in the body fluid of an individual undergoing HRT. The solution proposed in claim 1 was not obvious because the three estrogenic compounds disclosed in Dl (paragraph [0044]) could not be analysed simultaneously: estradiol was typically analysed in positive mode, while estrone and estriol in negative mode. In addition, the skilled person would not have ionised the sample by APCI or ESI but by atmospheric pressure photoionisation (APPI), which was the preferred method in D1 (paragraph [0042]).

A combination with the teaching of any of D2 to D4 did not lead to the method of claim 1 either; none of D2 to D4 disclosed the simultaneous detection of three or more estrogenic compounds in a single sample using ESI or APCI as the ionisation technique.

IX. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the claims on which the decision was based.

Reasons for the Decision

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

2. After having received a negative preliminary opinion from the board, the appellant withdrew its request for oral proceedings.

Having regard to the appellant's submissions in the statement of grounds of appeal and the board's preliminary opinion, the board is in a position to take a final decision without holding oral proceedings (Articles 113(1) and 116(1) EPC and Article 12(8) RPBA 2020).

3. Inventive step (Article 56 EPC)

3.1 The application (paragraphs [0002] and [0008]) concerns the use of MS/MS for assessing a panel of estrogenic compounds in a sample from a body fluid of an individual undergoing HRT.

3.2 Both the examining division and the appellant put forward their inventive step arguments starting from document D1. The board sees no reason to differ.

D1 (paragraphs [00017], [00037], [00043], [00052] and [00062]) deals with the rapid analysis and quantification of a plurality of steroid hormones in a body fluid sample using MS/MS. As examples of analysable hormones, D1 mentions (paragraph [00036]) estradiol, estrone and estriol.

The method proposed in D1 (claims 1 and 16 and paragraphs [00038] to [00040]) comprises the steps of deproteinating the sample, separating the hormones and analysing them by MS. The two latter steps are preferably carried out by liquid chromatography (LC) and MS/MS, respectively, i.e. by LC/MS/MS. D1 (paragraph [00042] and claim 18) proposes photoionisation, ESI, APCI and electron capture ionisation as the ionisation techniques. Photoionisation is preferred. In its example, D1 shows the simultaneous quantitation of nine steroid hormones in a plasma sample using LC/MS/MS.

3.3 The board agrees with the appellant that the method of claim 1 differs from the teaching of D1 in three respects.

(i) The sample is collected from individuals undergoing HRT.
(ii) Three or more estrogenic compounds from the list in claim 1 are analysed.
(iii) The ionisation technique is specifically APCI or ESI.

3.4 The board also agrees with the appellant that the objective technical problem is providing a method for simultaneously analysing three or more estrogenic compounds in a body fluid sample of an individual undergoing HRT.

3.5 However, the board sees no inventive step in the solution proposed in claim 1 for the following reasons.

3.5.1 Regarding difference (i), D1 suggests (paragraph [0006]) using its method for analysing estrogen levels in individuals undergoing HRT. It (page 4, lines 1 to 6) acknowledges the problem of low MS sensitivity when estrogens are ionised by ESI or APCI. Nevertheless, this drawback is overcome by the method of D1 (page 7, points 9 and 11), which is highly sensitive for estrogens and allows analysing a wide range of hormone concentrations.

3.5.2 Regarding difference (ii), the method of D1 was conceived for simultaneously assessing a plurality of steroid hormones. This was illustrated in its example, which shows the simultaneous quantitation of nine steroid hormones in a sample using LC/MS/MS. D1 referred explicitly to the analysis and quantitation of estrogens in the context of HRT (paragraph [0006]). As acknowledged in the application (paragraph [0005]) and confirmed by documents D2 to D4 (see abstracts), the most common and widely prescribed form of HRT on the filing date was Premarin®. Premarin® contains ten estrogens, all of which are recited in current claim 1: estrone, equilin, 17α-dihydroequilin, 17α-estradiol, 17β-dihydroequilin, 17α-dihydroequilenin, 17β-dihydroequilenin, equilenin, 17β-estradiol and Δ8,9-dehydroestrone.

Thus, it was apparent to the skilled person that the method of D1 was useful for simultaneously assessing several of the estrogens contained in Premarin® and, consequently, in claim 1. The fact that D1 does not illustrate an example in which at least three of those estrogens were simultaneously assessed does not render the suitability of the method less apparent.

3.5.3 As to difference (iii), despite photoionisation being the preferred ionisation method in D1, ESI and APCI are presented as suitable alternatives (paragraph [0042] and claim 18).

On this point, the appellant argued that the three estrogens explicitly cited in D1 (paragraphs [00031] and [00032]) could not be simultaneously assessed because estradiol had to be analysed in the positive ionisation mode while estriol and estrone required ionisation in the negative mode.

This argument must fail. Indeed, estradiol was analysed in D1 in the positive mode and estriol and estrone in the negative mode. However, Dl (paragraph [0044]) clearly states that "it is possible to analyse any of the hormones in either positive or negative mode". Moreover, claim 1 recites more than ten estrogens so that obviously more than three of them must be analysable in at least one of the two possible modes.

3.6 Thus, the board concludes that the modifications to the method of D1 proposed in claim 1 fall within the obvious measures that the skilled person would have taken for solving the objective technical problem. Therefore, the method of claim 1 does not meet the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

M. Schalow A. Lindner

Decision electronically authenticated