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D E C I S I O N
of 1 April 2003

Case Number: T 0310/99 - 3.3.8

Application Number: 90903086.8

Publication Number: 0409956

IPC: G01N 33/76

Language of the proceedings: EN

Title of invention:
Down Syndrome Screening Method

Patentee:
MACRI, James N.

Opponent:
CIS Bio International

Headword:
Down Syndrome/MACRI

Relevant legal provisions:
EPC Art. 52(1), 52(4), 54, 56, 83, 123(2)

Keyword:
"Main request: allowability of an amendment (no)"
"First auxiliary request: invention technical in character (yes)"
"Excluded diagnostic method (no)"
"Sufficiency of disclosure (yes)"
"Novelty (yes)"
"Inventive step (yes)"

Decisions cited:
T 0385/86, T 0775/92, T 0931/95, T 0964/99

Catchword:
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Case Number: T 0310/99 - 3.3.8

D E C I S I O N
of the Technical Board of Appeal 3.3.8
of 1 April 2003

Appellant I: (Proprietor of the patent)
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Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted 22 January 1999 concerning maintenance of European patent No. 0 409 956 in amended form.**

Composition of the Board:

Chairman: L. Galligani
Members: T. J. H. Mennessier
C. Rennie-Smith

Summary of Facts and Submissions

I. The patent proprietor (appellant I) and the opponent (appellant II) both lodged appeals against the interlocutory decision of the opposition division posted on 22 January 1999, whereby the European patent No. 0 409 956 was maintained on the basis of the second auxiliary request as filed at the oral proceedings on 23 November 1998.

II. The patent had been opposed under Article 100(a) EPC, on the grounds that (i) the invention was not a patentable invention (Article 52(1) and (2) EPC), (ii) it related to diagnostic methods practised on the human body (Article 52(4) EPC), (iii) it lacked novelty (Article 56 EPC) and (iv) it did not involve an inventive step (Article 56 EPC) as well as under Article 100(b) EPC on the ground that the invention was not sufficiently disclosed (Article 83 EPC).

The opposition division decided that, while the main and first auxiliary requests on file lacked novelty in view of product claim 10, the second auxiliary request, wherein claim 10 was formulated as a use claim, met all the requirements of the EPC.

III. Both appellants filed a statement of grounds of appeal requesting that the decision of the opposition division be set aside, appellant I requesting the maintenance of the patent on the basis of a new main request.

IV. Each appellant filed additional observations in reply to the statement of grounds of appeal of the other appellant.

V. On 27 December 2002, the board issued a communication pursuant to Article 11(2) of the Rules of Procedure of the Boards of Appeal indicating its preliminary views.

VI. In reply thereto, appellant I filed with a letter dated 28 February 2003 a new main and two auxiliary requests.

The main request consisted of 17 claims, of which independent claims 1, 4, 9, 10, 11, 13, 14 and 17 read as follows:

"1. An in vitro screening method for determining if a pregnant woman is carrying a fetus with Down syndrome comprising: assaying a pregnant woman's blood for free beta human chorionic gonadotropin (hCG), the results of the assay being indicative of increased risk of fetal Down syndrome."

"4. An in vitro screening method for determining a pregnant woman's risk of carrying a fetus with Down syndrome comprising: measuring said pregnant woman's maternal blood for the free beta (hCG) level during a time period selected from the group consisting of: the first trimester of pregnancy, the second trimester of pregnancy and the third trimester of pregnancy, and comparing said level of free beta (hCG) to reference values of the level for free beta (hCG) during the time period in: (1) pregnant women carrying Down syndrome fetuses and (2) pregnant women carrying normal fetuses, said comparison being indicative of said pregnant woman's risk of carrying a fetus with Down syndrome, wherein a higher level of free beta (hCG) is indicative of a higher probability of carrying a fetus with Down syndrome."

"9. An in vitro method for determining if a pregnant woman is at significant risk of carrying a fetus with Down syndrome comprising: measuring the pregnant woman's maternal blood level of an analyte selected from the group consisting of free beta (hCG), a variant (variants) of free beta (hCG), or an aberrant form (aberrant forms) of the free beta (hCG) and comparing the data of measurement of the analyte to a set of reference data to determine the pregnant woman's risk of carrying a fetus with Down syndrome."

"10. An assay kit adapted to carry out a method as claimed in claims 1, 2, 4 or 5 for determining if a pregnant woman is at significant risk of carrying a fetus with Down syndrome, comprising means for assaying a pregnant woman's blood for free beta hCG and means for comparing the measured level of the free beta hCG to a set of reference data."

"11. Use of an apparatus for the method of any of claims 1 to 9, said apparatus comprising: means adapted for receiving the data of measurement of a pregnant woman's maternal blood level of free beta (hCG) and computer means for comparing the data of measurement of the level of the free beta (hCG) to a set of reference data to determine fetal chromosomal trisomies."

"13. Use of an apparatus for the method of any of claims 1 to 9, said apparatus comprising:
means adapted for receiving the data of measurement of the pregnant woman's maternal blood level of free beta (hCG), means adapted for receiving the data of measurement of the pregnant woman's maternal blood level of alpha fetoprotein, and computer means for calculating a set of normative data from a set of

reference data containing reference values of the level of free beta (hCG) and the level of alpha fetoprotein at various gestational ages in: (1) pregnant women carrying Down syndrome fetuses and (2) pregnant women carrying normal fetuses, and for incorporating said data of measurements of said levels of said free beta (hCG) and alpha fetoprotein, and said pregnant woman's gestational age into a probability density function, thereby comparing said levels and said pregnant woman's gestational age to the set of normative data to determine said pregnant woman's risk of carrying a fetus with Down syndrome."

"14. Use of an apparatus for the method of any of claims 1 to 9, said apparatus comprising: means adapted for receiving the data of measurement of a pregnant woman's maternal blood level of free beta (hCG), and computer means for calculating a set of reference data and for incorporating said data of measurement of said levels of free beta (hCG) and said pregnant woman's gestational age into a probability density function, thereby comparing said pregnant woman's level of free beta (hCG) and said pregnant woman's gestational age to the set of normative data to determine said pregnant woman's risk of carrying a fetus with Down syndrome."

"17. Use of an apparatus for the method of any of claims 1 to 9, said apparatus comprising: means adapted for receiving the data of measurement of a pregnant woman's maternal blood level of an analyte selected from the group consisting of free beta (hCG), a variant (variants) of free beta (hCG), or an aberrant form (aberrant forms) of the free beta (hCG) and computer means for calculating a set of reference data and for incorporating said data of measurement of said level of

the analyte and said pregnant woman's gestational age into a probability density function, thereby comparing said pregnant woman's level of said analyte and said pregnant woman's gestational age to the set of normative data to determine said pregnant woman's risk of carrying a fetus with Down syndrome."

Claims 2, 3, 5 to 8, 12, 15 and 16 of the main request were dependent claims.

Auxiliary request 1 differed from the main request only in that claim 10 read:

10. "Use of an assay kit for carrying out the method claimed in claims 1, 2, 4 or 5 for determining if a pregnant woman is at significant risk of carrying a fetus with Down syndrome comprising: means for assaying a pregnant woman's blood for free beta hCG."

Each of the main and the first auxiliary requests differed from the claims as granted in that in claims 4 and 9 the terms "in vitro" had been added and claim 10 was formulated differently.

Claim 10 as granted read:

"10. An assay kit for carrying out the method claimed in claims 1, 2, 4 or 5 for determining if a pregnant woman is at significant risk of carrying a fetus with Down syndrome comprising: means for assaying a pregnant woman's blood for free beta (hCG)."

The first auxiliary request differed from the claims on the basis of which the patent was maintained (see section I, supra) only in that the terms "in vitro" had

been added in each of claims 4 and 9.

VII. Oral proceedings took place on 1 April 2003. They were attended only by appellant I, appellant II having informed the board of its intention not to attend.

VIII. The submissions of appellant I as made in writing and at the oral proceedings, insofar as they are relevant to the decision, may be summarized as follows:

The claimed method consisted of two steps which were both **technical** in character, the first one because it involved **an in vitro assay of a pregnant woman's blood** (for free beta human chorionic gonadotrophin (hCG) and possibly alpha fetoprotein (AFP)), and the second one because it involved **a biochemical analysis** of reference maternal blood samples. The second step created a new **technical effect** in combination with the technical features represented by the first step. The invention did not solely reside in a mathematical method for the analysis of data obtained by a known assay. Therefore, the claimed method was patentable within the meaning of Article 52(1) EPC.

Each of claims 1, 4 and 9 of the main request was directed to an in vitro diagnostic method, as now emphasized by the presence of the term "in vitro" in the claims.

The disclosure was enabling. The required technical means such as antibodies specifically recognising free beta hCG were available in the prior art. A patient's specific risk parameters to be taken into consideration when determining the probability of Down syndrome were disclosed in the patent in such a way that all the

embodiments of the claimed invention were reproducible, more particularly whatever the gestational age. In this last respect document D36 (see section X, infra) was cited.

The subject-matter of claims 1 to 9 was new over document D8 (see section X, infra). Also the subject-matter of claim 10, which associated means for assaying for free beta hCG and means for comparing the measured level of the free beta hCG to a set of reference data, was new over the state of the art.

Document D1 (see section X, infra) being taken as the closest prior art, the technical problem underlying the invention was the provision of improved means and methods for determining the risk of a pregnant woman carrying a fetus with Down syndrome. The solution to this problem relied primarily on the determination in the maternal serum of the free beta hCG level. None of the cited prior art documents would have prompted the person skilled in the art to attempt this solution.

The same observations applied to the first auxiliary request. In particular the subject-matter of the amended claim 10 was sufficiently disclosed, was new and involved an inventive step.

IX. The written submissions of appellant II were in respect of claims 1 to 17 as maintained by the opposition division. No submissions were made in respect of the requests at issue. The submissions on file are summarised here, insofar as they are relevant to the decision:

The method of claim 1 contained both a technical

feature, namely the step of determining the level of free beta hCG, and a non-technical feature, namely the indication of an increased risk for the pregnant woman of carrying a fetus with Down syndrome. The technical feature was known, in particular in view of document D3 (see section X, infra). The non-technical feature was part of the exclusions of Article 52(2) EPC, because it related to a mathematical method which employed a computer program and a presentation of information. The technical problem solved by claims 1 and 2 was the analysis and treatment of the free beta hCG level measured with the view of reformulating it in the form of a value indicative of a risk of Down syndrome. Said problem was not of a technical nature. Nor was its result. Therefore, the subject-matter of **claims 1 and 2** was not patentable within the meaning of Article 52(1) EPC (cf decision T 775/92 of 7 April 1993).

The screening method of **claims 1 to 9** required that a physician be involved and resulted in the taking of a medical decision. Therefore, it was an excluded diagnostic method as referred to in Article 52(4) EPC (cf decision T 385/86 OJ 1988, 308).

The disclosure of the claimed invention as a whole was insufficient in that it failed to indicate which essential maternal factors were to be taken into consideration. Also the gestational age was not duly relied on with the exception of 14 to 16 weeks. Accordingly, the person skilled in the art was not in a position to perform the screening process of the invention during the first and third trimesters of gestation. In this last respect, in particular, document D31 (see section X, infra) was cited.

The subject-matter of **claims 1 to 4, 9 and 10** was not new in view of document D8 (see section X, infra). Document D15 (see section X, infra) was an irrelevant letter dated 2 April 1991 and relating not to a "â-hCG method" but to an "hCG method" as explicitly mentioned therein without the indication of the particular question the letter was supposed to answer. At the publication date of document D8 (see section X, infra), the expression "âhCG" was used to mean not "intact hCG plus free âhCG" but "free beta hCG".

Document D1 (see section X, infra) represented the closest prior art. The problem solved was the provision of a screening method permitting improved detection of Down syndrome. The person skilled in the art would have regarded it as obvious to measure free beta hCG instead of intact hCG in view of a combination of documents D1 and D7 or D1 and D28 (see section X, infra). Therefore, the subject-matter of **claims 1 to 9** did not involve an inventive step. In view of documents D2, D3 and D4 (see section X, infra), again the subject-matter of **claim 10** was not inventive. As the use of a computer did not require inventive skill, the subject-matter of **claims 11 to 17** was not inventive in view of documents D7 and D9 (see section X, infra).

X. The following documents are referred to in the present decision:

(D1) Mark H. Bogart et al., Prenat. Diagn., Vol. 7, 1987, Pages 623 to 630

(D2) English translation of the Japanese patent application with publication number 54-126723 published on 2 October 1979

(D3) Mehmet Ozturk et al., Endocrinol., Vol. 120, No. 2, 1987, Pages 549 to 558

(D4) Copy of a commercial brochure presenting the "â HCG-RIA-100" kit manufactured by IRE with a letter attached thereto from the "Commissariat à l'énergie atomique" to the "Ministère de la santé et de la famille" dated 31 December 1980

(D7) R. Bharathur et al., Am. J. Hum. Gen., Vol. 43, No. 3, Suppl., September 1988, Page A226, Abstr. 0901

(D8) H. Arab et al., Am. J. Hum. Gen., Vol. 43, No. 3, Suppl., September 1988, Page A225, Abstr. 0896

(D9) Nicholas J. Wald et al., BMJ, Vol. 297, 8 October 1988, Pages 883 to 887

(D10) B. B. Butler et al., Am. J. Hum. Gen., Vol. 41, No. 3, Suppl., September 1987, Page A268, Abstr. 798

(D15) Letter of Prof. P.Y. Wong to Dr. James N. Macri dated 2 April 1991 together with a copy of the cover page of a commercial brochure relating to the "hCG MAIA Clone" kit of Serono Diagnostics

(D28) U. Gaspard et al., Ann. Endocrinol. (Paris), Vol. 45, 1984, Pages 269 to 280

(D29) Ulf-Hakan Stenman et al., Scand. J. Clin. Lab. Invest., 1993, Vol. 53, Suppl. 216, Pages 42 to 78

(D31) Document reproducing information presented in the internet site of NTD Laboratories Inc. dated 3 to 5 May 1999 with 14 pages hand-numbered as page 1 to page 14

(D36) Copy of a commercial brochure of CIS bio international entitled "Free Beta Screen / A strategy for prenatal screening of trisomy 21", with a cover page and pages 1 to 28, undated but containing citations dated 1992

XI. Appellant I requested that the decision under appeal be set aside and the patent be maintained on the basis of the main request or one of the two auxiliary requests all filed on 28 February 2003.

XII. Appellant II requested that the decision under appeal be set aside and the patent be revoked.

Reasons for the Decision

Main request

Article 123(2) EPC

1. In order to overcome the novelty objection against claim 10 which led to the refusal of the main and auxiliary requests by the opposition division, claim 10 has been amended in the new main request at issue. The question thus arises whether the application as filed disclosed an assay kit which contains, in addition to means for assaying a pregnant woman's blood for free beta hCG, not only the means referred to in claim 10 as granted but also means for comparing the measured level of the free beta hCG to a set of reference data.

2. An assay kit as commonly used in the field of medical diagnosis may be regarded as a set of **reagents** selected and pre-conditioned in such a way that they represent **means** appropriate for the determination of a particular analyte.

3. Whereas the description as filed contains an implicit disclosure of a kit containing reagents for assaying a pregnant woman's blood for free beta hCG (indeed, examples of such reagents are described in detail on pages 26 and 27, the reagents being (i) an antibody specific to the free beta hCG, (ii) a wash buffer, and (iii) a blocking solution), there is by contrast no disclosure (implicit or explicit) of a kit additionally including reagent means for comparing the measured level of the free beta hCG to a set of reference data.

4. Therefore, the board concludes that claim 10 as granted has been amended in such a way that claim 10 of the main request does not comply with the requirements of Article 123(2) EPC, and, consequently, the main request as a whole is not allowable.

First auxiliary request

Article 123(3) EPC

5. The board notes that the scope of claims 4, 9 and 10, the only amended claims (compared to the claims as granted) of this request is narrower than that of the corresponding granted claims. Indeed, claims 4 and 9 have been amended by specifying that the claimed method is an "in vitro" method and claim 10 is directed not to an assay kit as previously claimed but to the use of the same. Therefore, the requirements of Article 123(3)

EPC are met.

Article 123(2) EPC

6. The added term "in vitro" in claims 4 and 9 only confirms the nature of the screening methods of the invention, which, because they are practised on a blood sample, are in vitro diagnostic methods (see points 12 to 17, infra). Since there is no doubt that a kit as defined in claim 10 was disclosed in the application as filed (see point 3 supra), support exists therein for the use of such a kit. Therefore, the said claims comply with the requirements of Article 123(2) EPC.

Article 84 EPC

7. The amendments contained in claims 4, 9 and 10 have not introduced any unclarity and are supported by the description. Therefore, those claims comply with the requirements of Article 84 EPC.

Article 52(1) EPC

8. Claim 1 is directed to an in vitro screening method which primarily relies on an activity of assaying a pregnant woman's blood for free beta hCG, ie a concrete activity requiring a skilled practitioner to accomplish material (as opposed to mental) acts using technical means generally available in a laboratory. Based on this activity the invention provides free beta hCG as an independent marker for determining if a pregnant woman is carrying a fetus with Down syndrome and thereby solves a technical problem. Therefore, claim 1 is technical in character.

9. Adding to that activity of assaying an activity of comparing, which as defined in dependent claim 2 comprises not only material acts associated with the use of technical means such as computer means but also mental acts, does not alter the nature of the invention which still solves the same technical problem. Therefore, claim 2 is also technical in character.

10. In support of these submissions appellant II referred to decision T 775/92 of 7 April 1993. In that decision, it was said that when examining whether the three step method of an independent claim may be considered to be an invention within the meaning of Article 52(1) EPC, it has to be assessed whether non-technical steps (b) and (c) involve a contribution to the field not excluded from patentability. Therefore, that decision applies the so-called contribution approach for which it has been recognised in the later decision T 931/95 (OJ 2001, 441; see point 6 of the reasons) that there is no basis in the EPC. For that reason the present board considers that decision T 775/92 (supra) is not relevant in the present case.

11. Therefore, the subject-matter of claims 1 and 2 is patentable under Article 52(1) EPC.

Article 52(4) EPC

12. Article 52(4) EPC is meant to exclude from patent protection all methods **practised on the human or animal body** which relate to diagnosis or which are of value for the purposes of diagnosis (see T 964/99, OJ EPO 2002, 4, point 4.4. of the reasons).

13. The methods according to claims 1 to 9 are not

practised on the body of the pregnant woman but on a sample of her blood. Furthermore, none of the claims contain a sampling step. Moreover, each of the claims contains the explicit mention that it relates to an **in vitro** method.

14. The activities, as referred to in the claims, of assaying a blood sample for free beta hCG or alpha fetoprotein and of using computer means for comparing the measured levels to a set of reference data taking into account the gestational age of the woman can undoubtedly be carried out by a laboratory assistant without requiring the actual intervention of a physician.

15. Furthermore, whereas it is accepted that a preliminary interview may be carried out by a physician and that it is the duty of also a physician to counsel a patient on the basis of the results provided by any screening method of the invention and, if necessary, a further diagnostic test to confirm the presence of Down syndrome, these activities of the physician take place respectively **before** and **after** the claimed method is performed and should not be restrained by patent rights.

16. Decision T 385/86 (OJ 1988, 308) which was referred to by appellant I relates to a different factual framework, the claims examined relating to a medical diagnosis in which not a sample of a body fluid but **a whole, intact, living animal or human body is examined** (using magnetic resonance). Consequently, decision T 385/86 (supra) is not applicable to the present case.

17. Therefore, claims 1 to 9 meet the requirements of

Article 52(4) EPC.

Article 83 EPC

18. Appellant II objected that no antibodies were disclosed in the patent which were appropriate for the determination of free beta hCG.

19. Indeed, no particular such antibodies are disclosed in the description which, however, states that "[t]he maternal blood level of free beta-hCG is then measured by conventional analytical methods such as immunological methods known to the art" (see page 4, lines 32 to 34 of the patent specification). As a matter of fact, document D3 discloses such a method which relies on the use of monoclonal antibody FBT11, an antibody which recognises antigenic determinants present only on free beta hCG (see left-hand column of page 551). Therefore, at the priority date means for the determination of free beta hCG were available to the person skilled in the art.

20. The board is also satisfied that the other technical means required for the performance of the various aspects of the invention, such as means for the determination of alpha fetoprotein and appropriate computer software, were similarly available.

21. Appellant II mainly based its objection of insufficiency of disclosure on the allegation that the patent failed to disclose sufficiently the patient's specific risk parameters to be taken into consideration when determining the probability of Down syndrome.

22. Risk parameters such as maternal age, gestational age,

levels of intact hCG and/or alpha fetoprotein and/or unconjugated estriol, and the manner of incorporating them in a set of reference data are referred to in many places in the patent (see, in the patent specification, the passage in the description from line 45 of page 3 to line 1 of page 4 and the "Detailed description of the invention" on pages 4 to 7). The person skilled in the art is thereby advised that, depending on the degree of detection efficiency that is sought, one or more of those parameters can be incorporated into the set of reference data to refine the screening process.

23. Appellant II also argued that the screening method of the invention could not be performed at a gestational age other than the second trimester of pregnancy. In support of their submission, they referred to document D31 (see page 4) which contains the indication that AFP is not an efficient marker during the first trimester. The board notes, that whereas this observation may have an impact on the cost-efficiency of a Down syndrome screening using both AFP and free beta hCG as markers performed during the first trimester, it has no impact on the reproducibility of such screening because, as AFP and free beta hCG are separately measured, free beta hCG will in any case permit the achievement of an accurate screening.

24. The board notes that the description contains no disincentive to the person skilled in the art from performing the invention not only during the well-documented second trimester of gestation but also during the first and third trimesters.

25. The board also notes that document D31 (see page 4) which was cited by appellant II also readily

illustrates that free beta hCG may be used as an efficient marker for the screening of Down syndrome whatever the gestational age, including the first trimester. Similarly document D36 (see page 26) contains the observation that free beta hCG levels are also high in the first trimester of pregnancies complicated by trisomy 21 (Down syndrome). Appellant II itself (as the editor of document D36) admits that this observation offers the real prospect of screening for trisomy 21 in the first trimester.

26. The board concludes that at the priority date the person skilled in the art was in a position to reproduce the basic core of the invention, ie the determination of free beta hCG in the maternal serum, and additionally to take into consideration one or more risks parameters to reproduce each and every aspects of the claimed invention.

27. Therefore, the requirements of Article 83 EPC are met.

Article 54 EPC

28. An essential technical feature of the invention as defined in independent claims 1 to 4 and 9 is the step of assaying a pregnant woman's blood for **free** beta human chorionic gonadotropin. As pointed out in the patent specification (see in particular, page 9, lines 53 to 58) free beta hCG and intact hCG are regarded in the patent as **distinct markers** which are determined independently. Therefore, there can be no doubt that the gist of the invention is the use of means which recognize specifically the free beta hCG subunits and do not recognize the intact hCG, thereby measuring the concentration of such subunits in the

maternal serum.

29. Document D8, which is the only document cited by appellant II as being novelty-destroying, is an abstract which briefly reports that the determination of maternal serum beta hCG combined with maternal serum alpha-fetoprotein (AFP) is superior for prenatal screening for Down syndrome to either test alone. The maternal serum beta human chorionic gonadotropin assays were performed using a commercially available monoclonal antibody immunoradiometric assay kit.

30. It is important to note the fact that there is no indication in the document that the **beta hCG** assayed for was in its unbound form.

31. Appellant II expressed the view that, despite the fact that document D8 did not refer explicitly to the "free" beta hCG, one could not exclude that the unbound form of beta hCG was actually assayed for in the experiments reported therein.

32. This submission is no more than mere speculation. What is not questionable is that as early as 1984 and still in 1993, ie years after the priority date, there was uncertainty as to the precise meaning of the commonly used expressions "beta hCG assay" (or alternative expressions such "âhCG assay" and hCGâ assay"), such an assay concerning either the determination of the intact HCG plus the free beta hCG subunits or the determination of only the free beta subunits (see document D28, page 270, right-hand column and in document D29, the sentence bridging pages 50 and 51).

33. At the priority date, the person skilled in the art

would not have been in a position to identify which kit was meant in document D8 by the term "a commercially available monoclonal antibody immunoradiometric assay kit". Moreover, against the unsupported hypothesis made by appellant II that a kit permitting determination of the free â hCG was used in the experiments of document D8, one can set the attestation made in document D15 by an author of document D8 that in "the 1988 study" a "hCG MAIAclone kit" from Serono was used, which according to document D29 (see Table 3 on page 65) allows the determination of the intact hCG.

34. In view of these remarks, the board considers that appellant II has not proved that a kit which allows the determination of free beta hCG was used in the experiments of document D8.

35. Therefore, the subject-matter of claims 1 to 4, 9 and 10 is new.

Article 56 EPC

Claims 1, 4 and 9

36. Both parties agreed that document D1 represented the closest prior art. This was also the opinion of the opposition division.

37. The purpose of the study presented in document D1 was to evaluate the possibility of using serum hCG levels as a screening test for potential chromosomally abnormal pregnancies. Serum samples were collected from 25 women carrying a fetus with a chromosome abnormality. In 17 cases this abnormality was trisomy 21, ie Down syndrome. A prior art

radioimmunoassay was used which employed an antibody recognizing intact hCG and free beta hCG but the results are expressed only in terms of hCG levels expressed in IU/ml. Two other radioimmunoassays were used for the determination of alpha fetoprotein (AFP) and of alpha-hCG. It was concluded that determination of hCG and alpha-hCG levels was a superior screening procedure to AFP determination for detecting chromosomally abnormal fetuses. Nevertheless, the authors noted that association of both high and low concentrations of [intact] hCG with fetal abnormalities was enigmatic (see document D1, page 629, third full paragraph).

38. It can be derived from document D1 that, as the same antibody was capable of recognizing both the intact hCG and the free beta hCG, that antibody recognized an antigenic site available thereto whether the beta-subunit was bound to the alpha-subunit or not and, therefore, was not capable of specifically detecting only free beta hCG.

39. In view of document D1, the technical problem solved by the invention as defined in claims 1, 4 and 9 may be regarded as the provision of an improved screening assay for Down syndrome. The solution to this problem is a screening assay which focuses on the use of free beta hCG as a distinct marker, the beta hCG subunits being measured independently from the intact hCG.

40. Only two other prior art documents, namely documents D8 and D9, deal with the **screening of Down syndrome** based on the determination of intact hCG or the subunits thereof **in maternal serum**. The content of document D8 has been already discussed (see point 29, supra).

Document D9 reports on a study aiming at improving the effectiveness of antenatal screening for Down syndrome by measuring hCG concentrations in maternal serum. The samples were assayed for hCG, with the Serono MAIA-clone kit which as already noted (see point 33 supra) allows the determination of intact hCG. Document D9 also recites a mathematical method of estimating the risk of a Down syndrome term pregnancy.

41. None of documents D1, D8 and D9 suggests that a correlation may exist between the level of free beta-hCG and the suspicion of a fetus with Down syndrome. The finding of such a correlation being hindered in the prior art by the fact that, free beta hCG being a minor component compared to the intact hCG during normal and abnormal pregnancy (see document D3, pages 553 to 555), the studies of the prior art concerned with the screening of Down syndrome have focused on the evaluation of the intact hCG.

42. Free beta hCG was first recognized as a valuable independent marker for Down syndrome screening by the inventor without any incentive from the prior art.

43. Appellant II put a particular emphasis on documents D7 and D28 and attempted to combine each of them with document D1.

Document D7 is an abstract which briefly reports that amniotic fluid beta hCG levels were, on an average, higher in Down syndrome than in unaffected pregnancies. The information therein lacks any statement that this was based on the evaluation of free beta hCG. Moreover, the study was carried out not on maternal serum but on amniotic fluid.

Document D28 reports on a study in which each of intact hCG and free beta hCG was independently evaluated as a marker for several pregnancy disorders. Nevertheless, those disorders do not include Down syndrome. Moreover, free beta hCG is not recognized as a powerful diagnostic aid therefor.

Therefore, neither of documents D7 or D28 would have suggested to a person skilled in the art that the markers of document D1 might be replaced by free beta hCG.

44. Therefore, the subject-matter of independent claims 1, 4 and 9 involves an inventive step.

Claim 10

45. In addition to document D3 (see point 19, supra) appellant II referred to documents D2 and D4.

Document D2 describes the preparation of antibodies with specificity for free beta hCG. Said antibodies are susceptible of application in areas such as diagnosis of abnormal pregnancies, no preference for any of them being mentioned.

Document D4 relates to a commercial kit for the determination of free beta hCG in particular in maternal serum as an indicator for the survey of pregnancies. Abnormal pregnancies with a risk of carrying a fetus with Down syndrome are not referred to.

46. Although means for assaying a pregnant woman's blood for free beta hCG were known in the art (see documents

D2, D3 and D4), their use in a method for Down syndrome screening was in no way suggested, and thus the subject-matter of claim 10 also involves an inventive step.

Claims 11 to 17

47. In addition to document D9 (see point 40, supra) document D10 was cited by appellant II. Document D10 is an abstract which reports on a personal computer program for a maternal serum AFP screening program including, as a program function, calculation of parameters with interpretation of risk for Down syndrome.

48. As neither of documents D9 and D10 suggests the use of free beta hCG as an independent marker for screening of fetal chromosomal trisomies such as Down syndrome, at the priority date the person skilled in the art would have found no incentive to combine the means referred to in any of independent claims 11, 13, 14 and 17 in an apparatus and use said apparatus for the method of any of claims 1 to 9.

49. Therefore, the subject-matter of claims 11, 13, 14 and 17 involves an inventive step.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the first instance with the

order to maintain the patent on the basis of the first auxiliary request and the description and drawings as granted.

The Registrar: The Chairman:

P. Cremona L. Galligani