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Datasheet for the decision of 10 December 2007

Case Number: T 0078/06 - 3.3.08

Application Number: 97303147.9

Publication Number: 0806667

IPC: G01N 33/569

Language of the proceedings: EN

Title of invention:
Immunoassay for H. pylori in fecal specimens

Patentee:
MERIDIAN BIOSCIENCE, INC.

Opponents:
MEDIC S.R. L. and
HISS Diagnostics GmbH
Connex Gesellschaft zur Optimierung von Forschung
IMMUNDIAGNOSTIK AG

Headword:
Pylori/MERIDIAN

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

Keyword:
"Main request - added subject-matter (no)"
"Novelty - yes"
"Inventive step - yes"
"Sufficiency of disclosure - yes"

Decisions cited:
-

Catchword:
-

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Case Number: T 0078/06 - 3.3.08

D E C I S I O N
of the Technical Board of Appeal 3.3.08
of 10 December 2007

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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted 6 December 2005 rejecting the opposition filed against European patent No. 0806667 pursuant to Article 102(2) EPC.**

Composition of the Board:

Chairman: L. Galligani
Members: P. Julià
T. Karamanli

Summary of Facts and Submissions

I. European patent No. 0 806 667 was opposed by four opponents on the grounds as set forth in Article 100(a),(b) and (c) EPC. The opposition division considered that the claims as granted fulfilled the requirements of the EPC and, accordingly, rejected the oppositions (Article 102(2) EPC).

II. The opponents 01, 03 and 04 (appellants I, II and III, respectively) lodged notices of appeal and each filed a statement setting out the grounds of appeal.

III. With letter dated 16 June 2006, Dako Italia S.p.A. filed a notice of intervention under Article 105 EPC.

IV. With letter dated 25 August 2006, appellant III requested accelerated proceedings because of pending infringement proceedings.

V. The patentee (respondent) replied to the grounds of appeal with letter of 25 October 2006 and filed therewith a first auxiliary request.

VI. Dako Italia S.p.A withdrew its notice of intervention with letter dated 5 February 2007 and therefore, it was no longer party to the proceedings.

VII. With summons to the oral proceedings, the board sent a communication under Article 11(1) of the Rules of Procedure of the Boards of Appeal (RPBA) (OJ EPO 2003, 89), wherein the parties were informed of the board's preliminary opinion on the relevant issues.

VIII. The respondent replied to this communication and filed a second auxiliary request with letter dated 26 October 2007.

IX. With letter dated 12 November 2007, appellant III made further submissions which, with letter of 13 November 2007, the respondent requested the board to disregard.

X. On 23 November 2007, appellant I informed the board that it would not attend the oral proceedings.

XI. Oral proceedings took place on 10 December 2007 in accordance with Rule 71(2) EPC in the absence of appellant I as announced in its letter, appellant II and opponent 02, a party as right to the appeal proceedings (Article 107 EPC), who were all duly summoned.

XII. At the oral proceedings, the respondent withdrew its main request (claims as granted) and filed a new main request, which differed from the claims as granted only in the deletion of claim 12 directed to a kit. Claim 1 of the **main request** read as follows:

"1. A process for the determination of *H. pylori* in a fecal specimen which comprises:

(a) dispersing a fecal specimen suspected of carrying *H. pylori* in a sample diluent;
(b) contacting the fecal specimen in the diluent with a first polyclonal antibody for *H. pylori* antigen to form a complex of the antibody and the antigen;
(c) separating said specimen and said complex;

(d) exposing the complex to a second polyclonal antibody for said antigen and a portion of the antibody reacting with said complex, one of said first and second antibody being bound to a solid carrier and the other being labelled with a detection agent; and
(e) determining the presence of the labelled antibody and in turn determining the presence of *H. pylori* antigen in said fecal specimen."

Claims 2 to 9 were directed to particular embodiments of claim 1. Independent claims 10 and 11 related to processes for the determination of *H. pylori* in a faecal specimen which comprised several steps, including step (a) of claim 1 and a step (b) that required to contact the faecal specimen in the diluent with a first polyclonal antibody for *H. pylori* antigen bound to a solid support (claim 10) or produced by a first antibody producing species and bound to a solid carrier to form a complex of the antibody and the antigen (claim 11). The last step (d) of claim 10 read as step (e) of claim 1, whereas the last step (g) of claim 11 required only to determine the presence of *H. pylori* antibody in the faecal specimen.

XIII. The first auxiliary request was identical to the granted claims except for claims 1 and 10 which instead of reading "*determining the presence of the labelled antibody*" read "*determining the amount of the labelled antibody*" in steps (e) and (d) of claims 1 and 10, respectively. The second auxiliary request read as the first auxiliary request except for the deletion of claim 12 directed to a kit.

XIV. The following documents are cited in the present decision:

D1: US 5 403 924 (Publication date: 4 April 1995);

D2: WO 95/01445 (Publication date: 12 January 1995);

D4: J.B. Thomas et al., The Lancet, 1992, Vol. 340, pages 1194 to 1195;

D19: A.A. van Zwet et al., J. Clin. Microbiol., 1994, Vol. 32, pages 1346 to 1348;

D21: H. Enroth and L. Engstrand, J. Clin. Microbiol., 1995, Vol. 33, pages 2162 to 2165;

D33: J.D. Monfort et al., Veterinary Res. Comm., 1994, Vol. 18, pages 85 to 92;

D36: J.P. Gisbert et al., Aliment. Pharmacol. Ther., 2004, Vol. 19, pages 923 to 929.

XV. The arguments of the appellants given in writing related to the claims as granted but they also apply to the respondent's main request filed at the oral proceedings (cf. Section XII *supra*). These arguments and, for appellant III, the arguments given also during the oral proceedings, insofar as relevant to the present decision, may be summarized as follows:

Main request
Article 123(2) EPC

By using the term "*amount*", claims 1 and 10 as filed were directed to quantitative immunoassays for detecting *H. pylori* in faecal samples. The presence of *H. pylori* in a sample was inferred if the amount of labelled antibody was greater than a certain background. The replacement of the term "*amount*" by the term "*presence*" changed the nature of these quantitative methods to qualitative immunoassays, which comprised techniques that were not contemplated within the original quantitative assays. The reference to "*the presence of labelled antibody*" found in the description was made in the context of an immunometric assay, i.e. a quantitative assay.

Article 54 EPC

Document D2 disclosed specific antibodies against *H. pylori* and their use in immunologic assays for detecting *H. pylori* in faeces. These immunoassays were known in the art and therefore, it was not necessary to describe them in more detail. Faeces were explicitly identified as appropriate samples and thus, no selection was required. Since these samples were known to be (semi)solid, they always required a portioning and conditioning. The dispersion of faecal samples in a sample diluent was necessarily contemplated before contact with the antibodies. The claimed processes did not exclude the presence of intermediate (additional) manipulations of the faecal samples once they were dispersed in a sample diluent and before contact with the antibodies.

Document D1 disclosed the detection of *H. pylori* by contacting a fluid sample with an antibody. The described enzyme-linked immunosorbent assay (ELISA) was identical to the claimed processes except that faeces were not explicitly mentioned as body fluids. However, document D1 referred in general terms to body fluids and the disclosed list of body fluids was not exhaustive. Thus, the term "fluid" encompassed not only those body fluids mentioned in the list but other fluids that were known to contain *H. pylori*, such as faeces. In fact, stool was identified as a body fluid in the context of nucleic acid detection and diagnostic kits. The fact that faeces were mentioned in this context emphasized that, even when this type of sample (known to contain PCR inhibitors) was used, *H. pylori* could be detected.

Since intermediate manipulations were not excluded in the claimed processes, these processes were anticipated by document D4, which disclosed the isolation and detection of *H. pylori* from faeces using an ELISA immunoassay. The faeces were dispersed in a buffer, the components separated by centrifugation and faecal bacteria were cultured before detection by immunoassays.

The genomes of *Helicobacter pylori* and *Campylobacter jejuni* showed a close relationship between them. In fact, *H. pylori* had been reclassified as *Campylobacter pylori*. Since their antigens were almost identical and showed strong cross-reactivity, the detection of *C. jejuni* in document D33 (using an ELISA assay and faeces) inherently anticipated the claimed processes.

Article 56 EPC

The presence of *H. pylori* in faecal samples and its detection by immunological assays was known in the art. The advantages of using faecal samples were evident to the skilled person. The closest prior art, document D2, disclosed antibodies raised against *H. pylori* and their use in immunoassays for detecting *H. pylori* in faecal samples. The technical problem to be solved was to put into practice these teachings. Document D33 disclosed the detection of *Campylobacter* bacteria (related to *H. pylori*) using merely diluted faecal samples in ELISA immunoassays. There was no prejudice against the use of merely diluted faecal samples in these immunoassays. The absence of a prejudice was also shown by document D1, which disclosed the use of faecal samples for detecting *H. pylori* in ELISA immunoassays. Neither document D1 nor document D2 referred to a sample manipulation and there was no indication in these documents that, when faeces were used as samples, an amplification step was necessarily required for carrying out the immunoassays.

On the one hand, the culture of bacteria from faecal samples was performed in the prior art in order to identify viable *H. pylori*, since this prior art was concerned with studies on possible oral-faecal routes of *H. pylori* infection (document D4). A prejudice against the use of merely diluted faecal samples for detecting (viable and non-viable) *H. pylori* was not derivable therefrom. On the other hand, the prior art concerned with PCR detection of *H. pylori* in faecal samples was technically so different from prior art concerned with immunoassays that any information

deduced from the former could not be applied to the latter. The PCR prior art showed the presence of PCR inhibitors in faecal samples and their advantageous elimination for detecting *H. pylori* but it did not demonstrate any prejudice against the use of merely diluted faecal samples in immunoassays. Document D21 disclosed a method for removing PCR inhibitors by immunomagnetic separation (IMS). This method comprised steps (a), (b) and (c) of the claimed process and only differed therefrom by the absence of steps (d) and (e), i.e. the use of a second labelled antibody in the determination of the *H. pylori* antigens.

There was no demonstration on file showing that the culture or amplification of *H. pylori* in faecal samples before the ELISA test was detrimental to obtaining reliable results. An inventive step could not be based on the provision of improved clinical data and/or a better diagnosis, since the patent in suit failed to provide any data (specificity, sensitivity and reliability). The teachings of the patent did not differ from the instructions given in a textbook for carrying out an ELISA test and they did not go beyond the disclosure of document D2. If the particulars for carrying out the assay to detect *H. pylori* in faeces (which were not disclosed in the patent in suit) could be found in a textbook or available by routine experimentation, then the claimed processes were derivable from document D2 in an obvious manner. Otherwise, if the information derived from document D2 was not sufficient to achieve these processes, then the disclosure of the patent was also not sufficient.

Article 83 EPC

According to the patent in suit, several difficulties identified in the prior art (strain variation, low levels of *H. pylori* in faeces, cross-reactivity) raised serious doubts on the feasibility of a specific, sensitive and reliable ELISA for direct detection of *H. pylori* in faecal samples. However, the claimed processes were identical to those described in the prior art for detecting bacterial antigens in faecal samples (document D33). The patent only disclosed known steps of an ELISA immunoassay, without providing further information for achieving the required sensitivity and reliability. Neither the work-up of the sample nor the composition of the sample diluent or the assay conditions were disclosed. Example 4 only gave very general advices and it did not even define when a sample was deemed to be positive for *H. pylori*. Moreover, only calibrated samples were used and the source of the clinical samples were not specified. The properties of an immunoassay were defined by the specific antigen used and the selection of the first (capture) and second (detection) antibodies. However, this information was missing in the patent in suit. The first antibody was raised against a sonicated bacterial supernatant of *H. pylori* cells and therefore, it was not specific since not all *H. pylori* strains shared the same antigens and it cross-reacted with *Campylobacter*. The specificity had to be provided by a second antibody, which, however, was only identified as being "a previously accepted rabbit anti-*H. pylori*". No reproducibility could be associated with this disclosure. The post-published "Premium Platinum HpSA" test was not disclosed in the patent and it did not provide reliable results.

Adaptation of the description

The term "assay(s)" was ambiguous since it could be understood as comprising a kit. In order to be clear, it had to be replaced by the term "immunomethod(s)" or "immunoprocess(es)".

XVI. The respondent's arguments given in writing and during oral proceedings, insofar as relevant to the present decision, may be summarized as follows:

Main request
Article 123(2) EPC

In the light of the prior art relating to ELISA assays, the application as a whole taught that the disclosed processes were not merely restricted to the detection of specific amounts of *H. pylori*. The term "*amount*" was to be understood as any "*amount over zero*".

Article 54 EPC

According to the case law, a generic disclosure did not take away the novelty of a specific disclosure. Neither document D1 nor document D2 disclosed a specific immunotest for the detection of *H. pylori* in faecal samples. Document D1 was a general disclosure for the identification of *H. pylori* in several samples, whilst the claims were specific for faecal samples. The reference to stool as a body fluid was only made in the context of nucleic acid detection and not of antigen detection. There was no support for including faeces in the list of body fluids cited in the immunologic

methods. In view of the prior art disclosing the difficulties of *H. pylori* detection in faecal samples, these samples were not expected to contain sufficient levels of *H. pylori* for a direct detection using immunologic methods. The omission of faeces as samples for these methods was thus conspicuous and deliberate.

The features characterizing the claimed processes were only mentioned in isolation and as potential alternatives in document D2, which was concerned with a marker protein rather than with a methodology or the type of sample to be tested. The disclosure of several assays using this marker was only generic and it did not address the situation of the patent in suit. To arrive at the embodiments of the patent, a selection was required and, even if the skilled person selected faecal samples and one of the listed immunoassays, a large number of sample treatments were still possible. The mere dilution of faecal samples was not a straight manipulation but rather other manipulations were to be considered for an immunoassay to be effective, such as sample amplification and cross-reactivity removal. Since document D2 stated that the genes encoding the *H. pylori* HAP antigen and the *V. cholerae* HAP protein were 99% similar, a risk of cross-reactivity was identified and therefore, the likely need to carry out further sample manipulations (other than a mere dilution) for removing possible cross-reactants. The claimed processes excluded, however, any intermediate manipulation of the sample.

Document D4 disclosed an amplification step comprising the culture of faecal bacteria and their subsequent identification. The identification of a microorganism

grown from a faecal sample (bacterial culture) was different from a process identifying this microorganism in the faecal sample itself. Document D33 did not detect *H. pylori* but only *Campylobacter* bacteria. The major antigens of these bacteria were different and polyclonal antibodies raised against each of them were unique and specific. There was evidence on file showing that no cross-reactivity was found with *Campylobacter* strains when using polyclonal antibodies raised against several *H. pylori* strains. No cross-reactivity was detected with the processes of the patent and antigens from four *Campylobacter* strains, including *C. jeuni*.

Article 56 EPC

The prior art showed that the detection of *H. pylori* in faeces was very difficult and required amplification steps (PCR or culture). In those cases in which success was reported, the level of detection was very low and not reliable. This prior art, in particular document D4, represented the closest prior art since it concerned the detection of *H. pylori* in faeces and addressed the same problem as the patent in suit. Although faecal samples were recognized as advantageous over other more inconvenient samples, this prior art reflected a prejudice against testing *H. pylori* in faecal samples.

The selection as closest prior art of documents concerned with the immunological detection of organisms other than *H. pylori* in faecal samples and the suggestion to replace the antibodies used therein for antibodies raised against *H. pylori* was only effective with hindsight. Similarly, the selection of document D2 as closest prior art was not objective in the light of

the problem to be solved, namely the provision of a test for convenient, accurate and rapid identification of *H. pylori* in faecal samples. Document D2 did not address the difficulties associated with the detection of *H. pylori* in faecal samples. The teachings of this document were generic and directed to a specific *H. pylori* marker. Even if document D2 was selected as closest prior art, the only teaching derived from this document was to use the specific *H. pylori* marker. Although faeces were identified as possible samples, no indication was given as to how these samples were to be treated. Therefore, the skilled person had to look in the prior art for these indications. In doing so, the skilled person encountered a large body of prior art concerned with the detection of *H. pylori* in faecal samples. However, from this prior art it was only derivable that such a detection required always an amplification step.

There was evidence on file showing that a commercial product based on the claimed processes provided reliable results and therefore, that the patent in suit solved the technical problem. Contrary to the prejudice in the art, the amplification steps were detrimental to the detection of *H. pylori* and a direct ELISA assay with faecal samples provided reliable results.

Article 83 EPC

There was no evidence on file showing that the claimed processes could not be carried out with the information of the patent in suit. On the contrary, evidence was provided for an effective commercial product on the market and based on these processes. The skilled person

was made aware that a prejudice in the art was incorrect and that *H. pylori* could be identified with standard ELISA assays using faecal samples. The essential teaching was that such identification had to take place by direct contact of the faecal sample in a diluent with the assay material (antibody) and that no amplification steps were required. No more information was needed with regard to the subsequent ELISA assay since this information was available in the prior art or could be determined using routine experimentation. Although there were certain circumstances in which the claimed processes could be improved, this did not mean that they were not reliable for testing faecal samples in the majority of circumstances.

Adaptation of the description

The term "(immuno)assay(s)" as used in the description referred to processes, not to any product (kit). The term "immunoassay(s)" was well-known in the art and was found both in the patent in suit and in the application as filed with reference to the method proposed for detecting *H. pylori*.

XVII. There were no arguments and requests on file from opponent 02.

XVIII. The appellants (opponents 01, 03, 04) requested that the decision under appeal be set aside and that the patent be revoked.

XIX. The respondent (patentee) requested that the decision under appeal be set aside and the patent be maintained in amended form on the basis of the main request filed

during the oral proceedings, or in the alternative, on the basis of the first auxiliary request filed with a letter dated 25 October 2006 or the second auxiliary request filed with a letter dated 26 October 2007.

Reasons for the Decision

Main request
Article 123(2) EPC

1. According to Article 123(2) EPC a European patent may not be amended in such a way that it contains subject-matter which extends beyond the content of the application as filed. Regarding the concept of the content of the application as filed, it is established case law that it relates to the parts of the European patent application which determine the disclosure of the invention, namely the description, the claims and the drawings (cf. "Case Law of the Boards of Appeal of the EPO", 5th edition 2006, III.A.1.1, page 235).

2. Although claims 1 and 10 as filed were directed to quantitative assays ("*determining the amount of the labelled antibody*"), the description as filed, taken as a whole, was not limited to these quantitative assays but contemplated possible qualitative assays as well. In the description of Example 4 reference is made to the determination of the mere presence of the labelled antibody associated with the solid support without further reference to any quantitative determination thereof (cf. column 7, lines 45 to 46). Said example states that "*quantitative determinations* ***can be made*** *by comparing the measure of labelled antibody with that obtained for calibrating samples containing known*

quantities of antigen" (in bold by the board) (cf. column 8, lines 21 to 24), thereby defining the quantitative assays as a possible option only. It is also worth noticing that the last step (g) of claim 11 as filed required only to determine the presence of antigen in the faecal sample without reference to any amount of labelled antibody. It is further noted that determining the amount of a given product in a sample necessarily presupposes determining its presence therein.

3. The subject-matter of claims 1 and 10 is considered thus to fulfil the requirements of Article 123(2) EPC.

Article 54 EPC
The disclosure of the patent in suit

4. The patent in suit discloses several immunoassays for the detection of *H. pylori* in faecal specimens. There is no restriction whatsoever on the nature of the (first and second) polyclonal antibodies used in these immunoassays nor any limitation of the immunoassay conditions. Nevertheless, the patent in suit describes, firstly, how to prepare the faecal sample, namely by dispersion in a protein-based sample diluent that might be formulated and buffered to minimize cross-reactivity (cf. paragraph [0017]). Secondly, it further teaches to use the so prepared sample in a direct and straightforward manner in these immunoassays. Steps (a) and (b) of the claimed processes require to bring the diluted faecal sample into direct contact with the (first) polyclonal antibody used in the immunoassays and they exclude any intermediate (additional) manipulation of the diluted faecal sample. There is no

reference in the description of the patent in suit to such an intermediate manipulation of the diluted sample.

5. The board does not agree with the appellants that in the sequence of steps (a) to (d) of the claimed processes there may be also comprised further intermediate manipulations or additional treatments of the diluted faecal sample. The patent in suit teaches to exclude further manipulations of the diluted sample, this disclosure being the actual gist of the patent.

The prior art cited against the novelty of the claimed subject-matter

6. Document D2 discloses "*a method for the identification of H. pylori HAP protein antigenic determinants comprising contacting a sample to be tested with an antibody according to the present invention and detecting the presence of an antibody-antigen complex*" (cf. page 9, lines 2 to 7), wherein HAP stands for a specific haemagglutinin/protease enzyme closely related to the zinc metalloprotease enzymes of *Pseudomonas aeruginosa* and *Vibrio cholera* (cf. page 2, second full paragraph). Faeces are disclosed as a "*sample to be tested*" together with other four possible types of samples, namely dental plaque, saliva and gastric juices and mucosa (cf. page 9, lines 13 to 16). Further reference is made to the use of the antibodies "*in immunoassays to detect patients whom exhibit cross-reacting H. pylori HAP antigens*", wherein these "*immunoassays may be based on direct antigen-antibody reactions, competition, single or double sandwich assays*" (cf. page 9, line 28 to page 10, line 1). The use of these immunoassays for each and every "*sample to*

be tested" is thus considered to be contemplated in document D2, even though these combinations are disclosed only as possible alternatives and none of them is actually exemplified. Document D2 does not address however the issue of how to prepare the "*sample to be tested*" and there is no indication in this respect, let alone a guidance as to how to use a prepared faecal sample, i.e. whether to contact the sample directly with the antibodies or else other manipulations may be required.

7. In the absence of this information and in the light of the prior art concerned with the detection of *H. pylori* in faecal samples (cf. *infra*), the board does not consider that it is directly derivable from document D2 alone that a mere dispersion of the faecal sample and a straight contact of the so prepared sample with the antibodies is appropriate for carrying out the cited immunoassays.

8. Document D1 discloses a method for detecting the specific *H. pilori* tagA antigen (120-128 kDa) performed "*by contacting a fluid tissue or tissue sample*" with a purified antibody (cf. column 7, lines 21 to 38). In particular, a sandwich method is described using a primary antibody bound to a substrate and a secondary labelled antibody (cf. column 8, lines 22 to 52). Although a fluid sample is defined as "*any body fluid which would contain the antigen or cell containing the antigen*", it is arguable whether faeces are to be considered as a "*body fluid*" or as a more heterogeneous type of sample. Moreover, there is no indication in document D1 suggesting that faeces comprise the specific *H. pilori* tagA antigen. Nor does the presence

of nucleic acid specific for the *H. pylori* tagA antigen in stool (cf. column 12, lines 52 to 59 and column 14, lines 9 to 24) imply that the tagA antigen is also present in this type of sample. Furthermore, document D1 does not address the specific preparation of a faecal sample (by mere dilution), let alone the (direct) use of the prepared sample in the disclosed immunoassays.

9. Document D4 discloses the detection of viable *H. pylori* from human faeces using an ELISA immunoassay. The method however comprises a first step of culturing *H. pylori* and the subsequent detection of *H. pylori*. As stated in points 4 and 5 *supra*, the claimed processes exclude intermediate manipulations of the faecal sample.

10. Document D33 discloses the detection of the flagellar antigen of *Campylobacter jejuni* and *Campylobacter coli* (62 kDa) in faecal specimens using an ELISA immunoassay. Although the patent in suit refers to some of the antigens of the flagellar protein of *H. pylori* (60 KDa) as being non-specific and found in other bacteria such as *C. jeuni* and *C. coli* (cf. paragraph [0004]), there is no reference to *H. pylori* in document D33. This document states that the 62 kDa flagellar protein is only present in *C. jeuni* and *C. coli* (cf. page 85, last paragraph) and that the used monoclonal antibody MAB002 reacts "*with no other species tested*" (cf. page 86, last but one paragraph). This is also supported by evidence on file showing that the monoclonal antibody MAB002 does not cross-react with *H. pylori*.

11. It follows from the above that none of the cited documents anticipates the claimed subject-matter, which therefore fulfils the requirements of Article 54 EPC.

Article 56 EPC
The closest prior art and the technical contribution of the patent in suit

12. The board agrees with the respondent that the closest prior art should be chosen among documents concerned with the detection of *H. pylori* in faecal samples. Among them, the board considers document D2 to represent the best starting point: it refers to faecal samples as appropriate samples for the detection of an *H. pylori* antigen by way of immunoassay (cf. page 9, lines 13 to 16 and line 24 to page 10, line 1). The technical differences between the teaching of this document and the claimed subject-matter are in the preparation of the sample and in the absence of any intermediate manipulation of the faecal sample (cf. points 6 and 7 *supra*).

The technical problem to be solved and the solution proposed by the patent in suit

13. Starting from document D2, the technical problem to be solved is to put into practice the immunoassays using a faecal sample. The solution proposed by the claims at issue is a method characterized by the dispersion of the faecal sample in a protein-based diluent and by the direct contact of the so prepared faecal sample with the (first) polyclonal antibody of the immunoassay.

14. The appellants argue that there is no demonstration in the patent in suit that the technical problem has been solved, since there is no information on the source of the (clinical) samples used or on the (pre)treatment of these samples, and there is no comparison of (reliability, specificity) data with other methods (cf. Section XV *supra*). However, post-published evidence on file shows that the claimed processes actually solve the technical problem and that, although improvements are possible (use of monoclonal antibodies), no particular difficulties are encountered when using these processes for detecting *H. pylori* in faeces. The fact that these processes are more reliable and sensitive in certain diseases or groups of patients (dispeptic patients without upper intestinal bleeding) than in others (with upper intestinal bleeding, cf. document D36) might help to optimize their use but it does not call into question their validity.

15. The benefits of using (non-invasive) faecal samples over other types of (invasive) samples, such as gastric juice (cf. page 9, lines 14 and 15 in document D2), are evident to the skilled person. Similarly, the advantages of avoiding intermediate manipulations of the sample are also obvious to the person skilled in the art (quicker, easier and more reliable test). Thus, the board is satisfied that the technical problem is solved by the claimed method.

16. It remains the question whether, as argued by the respondent, there were reservations in the art or even a prejudice against the **direct use** of faecal samples when carrying out ELISA immunoassays.

Existence of reservations or prejudice in the state of the art

17. A large body of prior art documents is on file concerning the detection of *H. pylori* in faecal samples. None of them, however, applies immunoassay detection methods directly to faecal samples. In fact, before a detection takes place, the sample undergoes always an intermediate treatment, this involving either **i)** the (sub)culture of faecal *H. pylori* on selective media or **ii)** the amplification of a *H. pylori* nucleic acid by polymerase chain reaction (PCR).

18. The documents wherein a subculture of the faecal sample on selective media is used are essentially concerned with studies on the transmission of *H. pylori* infection which necessarily requires isolation of viable *H. pylori* (cf document D4), and often require optimisation of the culture conditions. It has been argued that no information can be derived from this prior art in respect of the detection of *H. pylori* since, in view of the culture, non-viable *H. pylori* is not taken into account.

19. In prior art document D21, paramagnetic beads coated with polyclonal antibodies which bind to both coccoid (non-viable) and rod-shaped forms (viable) of *H. pylori* (cf. abstract and page 2164, right-hand column) are used to isolate *H. pylori* from stool specimens, "*when most of the bacteria are possibly in the coccoid form*" (cf. page 2165, left-hand column second full paragraph). However, this step is only preliminary to the subsequent detection step in that it removes the inhibitory factors of the PCR present in the faeces (immunomagnetic separation, IMS) and so allows

detection of *H. pylori* by PCR. The document concludes that "*IMS followed by PCR is sensitive in stool and water specimens when the samples are spiked with cultures of H. pylori*" (cf. page 2165, left-hand column, last paragraph). Thus, even after isolation of both coccoid and rod-shaped *H. pylori* and removal of PCR inhibitors, the level of *H. pylori* in stool specimens is so low that spiking of the samples is still required for PCR amplification.

20. This is fully in line with the disclosure of other prior art documents (cf. eg. document D19) concerned with the detection of *H. pylori* in faeces by PCR amplification and which do not rely on the isolation of viable *H. pylori*. These documents report low levels of *H. pylori* in faeces and the difficulties associated with this detection. Even after removal of PCR inhibitory factors present in faecal samples and effective control of PCR inhibition by faeces, document D19 concludes that "*the use of fecal samples for the detection of H. pylori in patients is precarious*", since no detection was obtained with faecal samples of 24 infected patients (cf. page 1346, right-hand column, last two full paragraphs and page 1347, right-hand column, second full paragraph).

21. In the light of this prior art, the board considers that there were indeed reservations in the art (or even a prejudice) as regards the possibility of a direct use of faecal samples without previous treatment. As documents D2 fails to indicate how the faecal samples were to be treated in order to carry out the proposed immunoassays, the skilled person - in line with the prior art referred to above - would have necessarily

contemplated a preliminary treatment of the faecal sample. The omission of such a treatment, be it culture or amplification, would not have been obvious as there was no reasonable expectation to detect *H. pylori* in these faecal samples if the treatment was omitted.

22. Evidence on file shows that, contrary to the existing prejudice in the prior art, the omission of an intermediate manipulation results in the reliable and sensitive detection of *H. pylori* in faecal samples (cf. point 14 *supra*). The advantages of this omission are evident, since the assays are easier and quicker to perform with savings in time and costs.

Appellants' further arguments for lack of inventive step

23. Reference was made to prior art relating to the direct detection of several microorganisms (group A rotaviruses) in faecal samples and to other prior art disclosing the production of antibodies raised against *H. pylori* and their use in immunoassays. It has been argued that the combination of both types of prior art documents would have been obvious to the skilled person with the result that the patent in suit lacks inventive step (cf. Section XV *supra*). However, in the prior art relating to antibodies raised against *H. pylori*, there is no reference to the type and nature of the samples to be used in the immunoassays, let alone on the specific steps or manipulations of the samples. Nor is a reference to *H. pylori* found in the prior art relating to the direct detection of microorganisms other than *H. pylori* in faecal samples. There is no evidence on file showing that the presence of these microorganisms in faeces might also imply the presence

of *H. pylori* and its possible detection using similar immunoassays. Moreover, nowhere in this prior art is a suggestion that could motivate the skilled person to combine these two groups of prior art documents. There is no motivation to replace the antibodies raised against group A rotavirus with antibodies raised against *H. pylori*. Nor is there any reason in this prior art for expecting that the direct immunoassays useful for the detection of group A rotavirus would also be useful for the detection of *H. pylori*.

24. Document D33 has also been cited in the context of inventive step since this document discloses the detection of *C. jejuni* and *C. coli* antigens in faecal samples with an ELISA immunoassay and without any intermediate treatment of the samples (cf. Section XV *supra*). However, as stated in point 10 *supra*, there is no reference to *H. pylori* in this document and the antigens used in the immunoassay are described as being specific for these bacteria only. Moreover, the monoclonal antibody used in the immunoassay reacts "*with no other species tested*". Although *C. jejuni* and *H. pylori* might be phylogenetically related, they are specific pathogens with differences in their niches, survival, transmission and pathogenesis. Therefore, no conclusions for *H. pylori* can be drawn from the presence of *C. jejuni* in faecal samples. In view of the above conclusions (cf. points 17 to 22 *supra*), hindsight would be required for selecting this document as the closest prior art and arriving at the claimed processes starting therefrom.

25. Thus, the requirements of Article 56 EPC are considered to be fulfilled.

Article 83 EPC

26. There are post-published documents on file showing that the claimed processes result in the successful detection of *H. pylori* in faecal samples without carrying out any intermediate manipulation of the samples (document D36). The conditions referred to in these documents require only common general knowledge supplemented, if necessary, by routine tests. Although improvements and optimization of these processes might be possible (selection of antibodies, groups of patients, etc.) (cf. point 14 *supra*), there is no evidence on file casting serious doubts as to whether the claimed processes can successfully be put into practice. Thus, in line with the established case law of the Boards of Appeal (cf. "Case Law", *supra*, II.A.5.1.1, page 179), the requirements of Article 83 EPC are considered to be fulfilled.

Adapted description

27. In the light of the available prior art and of common general knowledge, it is clear that the term "*assay*" is understood by the skilled person as referring to a "*method*" or a "*process*" of testing or detection. It does not imply a "*product*", in particular a kit. In view thereof, the term is considered to leave no room for any ambiguous interpretation and there are no objections concerning the adapted description.

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 in amended form in the following version:

Description:
Columns 1-9 received during oral proceedings of 10 December 2007.

Claims:
No. 1 to 11 received during oral proceedings of 10 December 2007.

The Registrar: The Chairman:

A. Wolinski L. Galligani