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Datasheet for the decision of 27 May 2008

Case Number: T 1823/06 - 3.3.08

Application Number: 01310782.6

Publication Number: 1221620

IPC: G01N 33/86

Language of the proceedings: EN

Title of invention:
Method for performing activated clotting time test with reduced sensitivity to the presence of aprotinin and for assessing aprotinin sensitivity

Applicant:
Sienco, Inc.

Opponent:
-

Headword:
Aprotinin clotting test/SIENCO

Relevant legal provisions:
EPC Art. 56

Relevant legal provisions (EPC 1973):
-

Keyword:
"Main and first auxiliary requests - inventive step (no)"
"Second auxiliary request - inventive step (yes)"

Decisions cited:
-

Catchword:
-

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Case Number: T 1823/06 - 3.3.08

D E C I S I O N
of the Technical Board of Appeal 3.3.08
of 27 May 2008

Appellant: Sienco, Inc.
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Representative: Smaggasgale, G.H.
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 11 July 2006 refusing European application No. 01310782.6 pursuant to Article 97(1) EPC 1973.**

Composition of the Board:

Chairman: L. Galligani
Members: P. Julià
C. Heath

Summary of Facts and Submissions

I. European patent application No. 01 310 782.6, published as EP 1 221 620 with the title "Method for performing activated clotting time test with reduced sensitivity to the presence of aprotinin and for assessing aprotinin sensitivity", was refused by the examining division pursuant to Article 97(1) EPC 1973 on the grounds that the main request and the first and second auxiliary requests did not fulfil the requirements of Article 56 EPC.

II. Claim 1 of the main request refused by the examining division read as follows:

"1. An *in vitro* diagnostic process for measuring blood coagulation, the process comprising the steps of:

providing a test container for holding a blood sample;

providing one or more additive reagents for contact activation of said blood sample, and

providing a further additive reagent selected to reduce the sensitivity of the process and variability to aprotinin in heparinized blood."

The first auxiliary request defined the "further additive reagent" as being selected from "shale, illite, bentonite, montmorillonite, rectorite and/or dickite". The second auxiliary request defined the "one or more additive reagents" as being selected from "celite, kaolin and/or glass beads" and the "further additive reagent" as in the first auxiliary request.

III. The examining division considered that, insofar as inventive step was solely based on the achievement of technical effects, all the embodiments of the claims had to exhibit these effects. The application showed that these effects were achieved only for a limited number of specific combinations. However, the requests were not restricted to these combinations. Furthermore, claim 1 of the main and first auxiliary requests contravened Article 84 EPC because the corresponding subject-matter could be defined in more concrete terms.

IV. The applicant (appellant) filed an appeal against the decision of the examining division and paid the appeal fee. With letter dated 8 November 2006, the appellant filed a statement setting out the grounds of appeal and maintained all requests underlying the decision under appeal. Oral proceedings were also requested in the event that none of these requests could be met.

V. The examining division did not rectify the contested decision and referred the appeal to the board of appeal (Article 109 EPC 1973).

VI. The board sent a communication as annex to the summons to oral proceedings stating its preliminary, non-binding opinion.

VII. With letter dated 28 April 2008, the appellant replied to the board's communication, withdrew all previous requests and filed a new main request and a new auxiliary request. The appellant further indicated its intention to withdraw the request for oral proceedings

in the event that one of these requests was found allowable by the board.

VIII. On 19 May 2008 the board sent a fax to the appellant indicating its preliminary opinion on the requests then on file and maintaining the oral proceedings.

IX. With a fax dated 23 May 2008, the appellant replied to the board and filed a new main request and new first and second auxiliary requests. The request for oral proceedings was withdrawn and the appellant requested the board to take a decision based on these new requests.

X. Oral proceedings took place on 27 May 2008 in the absence of the appellant.

XI. Appellant's **main request** contained a single claim that read as follows:

"1. An *in vitro* diagnostic process for measuring blood coagulation, the process comprising the steps of:

providing a test container for holding a blood sample;
providing a reagent system selected from:

kaolin for contact activation of the blood sample and illite to reduce the sensitivity of the process and variability to aprotinin in heparized [*sic*] blood;

celite for contact activation of the blood sample and shale to reduce the sensitivity of the process and variability to aprotinin in heparinized blood;

celite for contact activation of the blood sample and bentonite to reduce the sensitivity of the process and variability to aprotinin in heparinized blood; or

kaolin for contact activation of the blood sample and bentonite to reduce the sensitivity of the process and variability to aprotinin in heparinized blood."

XII. Claim 1 of the **first auxiliary request** read as the only claim of the main request except for the deletion of the reagent system consisting of kaolin and illite. Claim 2 was directed to the use of a reagent system in an *in vitro* diagnostic process for measuring blood coagulation, wherein the reagent system was selected from the four combinations of claim 1 in the main request. The **second auxiliary request** comprised only one claim identical to claim 1 of the first auxiliary request.

XIII. The appellant's arguments, insofar as relevant to the present decision, may be summarized as follows:

Main request
Article 123(2) EPC

The application as filed explicitly disclosed the combinations of kaolin and illite, celite and shale, and celite and bentonite. After describing the addition of illite to either pure kaolin or kaolin containing an illite impurity, the application described the use of various clay minerals, including bentonite as a further additive reagent, and concluded that bentonite had the greatest ion exchange capacity of all tested minerals and that bentonite activated clotting time (ACT)

results on heparinized blood were substantially unaffected by aprotinin. A combination of kaolin and bentonite was thus also derivable from the application as filed.

Patentability

There were no quantitative requirements associated with the reduction of sensitivity and the variability to aprotinin in claim 1, nor were the amounts of the reagents defined in this claim. However, claim 1 specifically required the illite to reduce the sensitivity of the process and the variability to aprotinin in heparinized blood. Thus, an essential feature of the claim was that the illite had to be present in an amount sufficient to provide the desired function, namely to reduce the sensitivity of the process and variability to aprotinin in heparinized blood. Claim 1 included thereby a functional limitation that was allowable since it could not be defined more precisely without unduly restricting the scope of the claim. The result of the functional limitation could be directly verified by tests known to the skilled person and no undue experimentation was required. It would be nothing more than routine trial and error for a skilled person - knowing the teachings of the application - to arrive at appropriate amounts of reagents for a particular blood sample.

Kaolin #2 was the kaolin least affected by aprotinin from all commercial kaolin formulations tested. However, it was not consistently unaffected between patients. The application disclosed the characteristics of kaolin #2 and optimized these features for producing a test

that was unaffected by aprotinin over the entire patient population. Kaolin #2 contained illite impurities, i.e. trace amounts, that were insufficient to obtain the desired insensitivity to aprotinin. Illite had to be added to kaolin #2 (overshadowing thereby the amount of natural illite impurities) for achieving the desired results. Kaolin #2 did not meet the functional requirement defined in the claim.

First and second auxiliary requests
Patentability

The subject-matter of claim 1 of the first and second auxiliary requests (the sole claim of this second auxiliary request) was directed to an *in vitro* diagnostic process with a reagent system selected from those combinations for which novelty and inventive step had been acknowledged.

Since kaolin #2 did not have sufficient illite to provide the reagent system for use in an *in vitro* diagnostic process for measuring blood coagulation, claim 2 of the first auxiliary request was also novel and provided an inventive contribution.

XIV. The appellant (applicant) requested that the decision under appeal be set aside and that a patent be granted on the basis of the main request or the first or second auxiliary request, all filed on 23 May 2008.

Reasons for the Decision

Main request

Article 123(2) EPC

1. The application as filed discloses the use of a reagent system consisting of kaolin - either pure or with natural illite impurities - and illite in an activated clotting time (ACT) assay of heparinized blood samples containing the bleeding inhibitor aprotinin. Whereas kaolin acts as a contact activator to trigger clot formation, illite reduces the sensitivity of the ACT assay and the variability to aprotinin in the heparinized blood (cf. *inter alia* page 6 of the published application). The combinations of celite and shale as well as celite and bentonite (the preferred formulation) are also explicitly disclosed in the application (cf. paragraphs [0041] to [0045] and Figures 7 and 8 of the published application). The application further states that bentonite is the preferred additive for the activation formulation to reduce aprotinin sensitivity (cf. paragraph [0042] of the published application) and thus, since both kaolin and celite are disclosed as suitable contact activators (the latter being preferred), a combination of kaolin and bentonite is also directly derivable from the application as filed.

2. No objections were raised under Article 123(2) EPC in the decision under appeal and the board has none of its own. Therefore, the requirements of Article 123(2) EPC are considered to be fulfilled.

Patentability of the claimed process

3. The reagent system referred to in claim 1 contains two different components, the first (kaolin or celite) for contact activation of the blood sample and the second (illite, shale or bentonite) to reduce the sensitivity of the process and variability to aprotinin in heparinized blood. There is, however, no requirement in the claim for any specific amount of any of the two components. Nevertheless, their amount must be sufficient to enable them to perform the functions defined in the claim, i.e. to activate the blood clotting and to reduce the sensitivity of the process and variability to aprotinin. Similarly, there is no quantitative requirement associated with these functions and their value is therefore left entirely open and might well comprise small reductions in the sensitivity of the process and in the variability to aprotinin.

4. The application reports studies for aprotinin sensitivity performance measuring the performance of two known commercial kaolin formulations, namely USP grade kaolin from Mallinckrodt Chemical, Inc. (kaolin #1) and kaolin manufactured by International Technidyne Corporation (kaolin #2) which are normally used for the activated clotting time (ACT) assay. Although none of these formulations provides aprotinin sensitivity results meeting the expectations for a safe and effective ACT for heparinized blood samples containing aprotinin, significantly different results are obtained between the two formulations, the average ACT results for kaolin #2 being less affected by aprotinin than those for kaolin #1 (cf. paragraphs [0029] and [0030]).

The presence of impurities in the kaolin samples was investigated as a possible cause for the wide range of activation characteristics among these kaolin samples. As a result of these studies, the application states that ACT results using kaolin with illite impurities - as found in some kaolin #2 samples and also in kaolin from J.T. Baker Co. (cf. paragraphs [0031] and [0032]) - achieve an average performance that is substantially unaffected by aprotinin in heparinized samples. Nevertheless, ACT results using kaolin with little impurities has a bimodal statistical distribution function: most samples are unaffected by aprotinin but other blood samples can be strongly affected by aprotinin (cf. paragraphs [0033] and [0034]).

5. The application further states that the addition of illite to either pure kaolin or to the combination of kaolin and natural illite provides some reduction in sensitivity to aprotinin. However, in the reported kaolin plus illite tests, some patients still show a delay in the presence of both heparin and aprotinin in comparison to heparin alone (cf. paragraph [0038]). Thus, contrary to appellant's argumentation (cf. Section XIII supra), there are no differences in the ACT results between a formulation of kaolin with natural illite impurities and a formulation of pure kaolin with illite added. Nor are these formulations significantly different in their composition when the amount of illite added is small. Since there is no requirement in the claim for a particular amount of illite or for a specific degree of reduction of sensitivity of the process and variability to aprotinin (cf. point 3 *supra*), it is not possible to differentiate - either by their composition or by the

ACT results - a reagent system based on some commercial kaolin formulations (International Technidyne Corporation or J.T. Baker Co.) from one based on pure kaolin with (small amount of) illite added.

6. The side effect of aprotinin in ACT tests, namely a prolongation of activated ACT results in the presence of heparin, and the use of kaolin as a clot activator in ACT tests were already known in the art, as acknowledged in the application (cf. paragraphs [0004] and [0008]). Starting from this prior art knowledge, the technical problem to be solved is seen in the provision of an improved ACT formulation with a consistent response to the anticoagulant heparin regardless of the absence or presence of aprotinin, which is in fact the problem referred to in the application (cf. paragraph [0015]). The examples of the application show, however, that this technical problem is not solved by all four claimed embodiments, in particular not by the combination of kaolin and illite.

7. The application shows that the desired formulation is achieved when using celite as a preferred contact activator and bentonite as a preferred additive to reduce aprotinin sensitivity (cf. paragraphs [0042] to [0045]). Thus, in agreement with the decision of the examining division (cf. page 6, first full paragraph of the decision under appeal), an inventive contribution is acknowledged for an *in vitro* diagnostic process for measuring blood coagulation wherein use is made of a reagent system containing the preferred formulation of celite and bentonite, and also the exemplified combination of celite and shale. Moreover, since there is no evidence on file to suggest that similar results

are not achieved with a reagent system containing kaolin and the preferred bentonite, this combination is also considered to be inventive.

8. Nevertheless, as explained in point 5 *supra*, no improvement is achieved by a reagent system containing a combination of kaolin and illite. At least for some of these combinations (pure kaolin with small amounts of illite added), the results obtained in the ACT tests are identical to those obtained with some of the commercial kaolin formulations (International Technidyne Corporation or J.T. Baker Co.). No inventive contribution can be seen for these particular combinations and therefore, the technical problem is considered not to be solved over the whole scope of the claim.

9. It follows from the above that the main request does not fulfil the requirements of the EPC.

First auxiliary request

10. The subject-matter of claim 1 of this request is directed to an *in vitro* diagnostic process for measuring blood coagulation comprising a reagent system based only on combinations for which an inventive contribution has been acknowledged (cf. point 7 *supra*). These combinations are also referred to in claim 2 of this first auxiliary request which is directed to the use of these reagent systems in an *in vitro* diagnostic process for measuring blood coagulation. However, in addition to them, claim 2 comprises a further reagent system based on the combination kaolin and illite (cf. Section XII *supra*).

11. The change of a claim relating to a process (*in vitro* diagnostic process) using a composition (reagent system with a combination of products) into a claim relating to the use of this composition in such a process is formally acceptable but it does not add any inventive element to a claim which involves the same operations as the previous one. For the reasons already outlined above, for the embodiment based on the combination of kaolin and illite no inventive contribution can be seen, since it does not provide any improvement over the prior art.

12. Hence, because of claim 2, the first auxiliary request does not fulfil the requirements of the EPC.

Second auxiliary request

13. The sole claim of this request is identical to the subject-matter of claim 1 of the first auxiliary request for which patentability has already been acknowledged in points 7 and 10 *supra*. The second auxiliary request fulfils thus all the requirements of the EPC.

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 grant a patent on the basis of the second auxiliary request filed on 23 May 2008 and a description and figures to be adapted thereto.

The Registrar: The Chairman:

A. Wolinski L. Galligani