Title: A MULTILAYER MATERIAL

Abstract: The invention relates to a multilayer material comprising at least two layers of web and at least one layer of particles, said particles being arranged between said at least two layers of web. According to the invention at least a part of said multilayer material is made of bioactive glass and said particles are sol-gel derived silica particles. The invention also relates to different uses of said multilayer material.
A MULTILAYER MATERIAL

FIELD OF THE INVENTION

This invention relates to a multilayer material comprising at least two layers of web and at least one layer of particles, said particles being arranged between said at least two layers of web. The invention also relates to different uses of said multilayer material.

BACKGROUND OF THE INVENTION

The publications and other materials used herein to illuminate the background of the invention, and in particular, the cases to provide additional details respecting the practice, are incorporated by reference.

The use of bioactive glasses in medicine is now widely known. In this application, by bioactive glass is meant a material that has been designed to induce specific biological activity in body tissue. The term biodegradable in this context means that it is degradable upon prolonged implantation when inserted into the mammal body. By biomaterial a non-viable material used in a medical device is meant, that is, a material that is intended to interact with biological systems.

Bioactive glasses react in aqueous systems and develop layers on their surfaces resulting in bonding between the device and the host tissue. Unlike most other bioactive materials, the rate of chemical reactions of bioactive glasses can be easily controlled by changing the chemical composition of the glass. Therefore, bioactive glasses are interesting in particular in clinical applications and have indeed been used for example to treat cranio-facial injuries, to replace the small bones (ossicles) in the middle ear and in orthopaedic surgery to fill defects in bone.

The document US 6,743,513 discloses a tape cast multilayer ceramic and metal composite. In this material, a bioactive layer is first cast on a tape and the metal layers, or thin metal foils, are then laminated on the bioactive layer. For casting of the bioactive layer, fine particles of
bioactive glass, organic binder as well as plasticizers and binders are mixed to form a homogeneous slurry which is then cast on a tape. The organic compounds are then removed before sintering of the material.

OBJECTS AND SUMMARY OF THE INVENTION

An object of this invention is to provide a material suitable for use as a bioactivity enhancing material that has also sufficient structural strength and stability.

A further object of this invention is to provide a material that may be used for tissue culture in vitro and that allows the transfer of the tissue without damaging it.

Another object of the present invention is to provide a material that may act as a sensor giving signals under stress such as under bending or pressure.

An object is also to provide a material that is useful in the treatment of gingivitis. In addition, one object of the present invention is to provide a material that is easy and convenient to use.

The present invention relates to a multilayer material comprising at least two layers of web and at least one layer of particles, said particles being arranged between said at least two layers of web. The invention is typically characterised in that at least a part of said multilayer material is made of bioactive glass and that said particles are sol-gel derived silica particles.

The present invention also relates to various uses of said multilayer material.

DETAILED DESCRIPTION OF THE INVENTION

The invention is disclosed in the appended independent claims.

The multilayer material according to the invention comprises at least two layers of web and at least one layer of particles, said particles being arranged between said at least two layers of web. The invention is typically characterised in that at least a part of said multilayer
material is made of bioactive glass and that said particles are sol-gel derived silica particles.

Thus, the invention concerns a material comprising at least two structural layers made of web and at least one intermediate layer made of sol-gel derived silica particles that hold the two layers of web at a distance from each other. The present invention thus provides a material suitable for use as a bioactivity enhancing material that has also sufficient structural strength and stability.

According to the invention, the multilayer material may comprise two, three, four, five, six, seven or more layers of web. By web, it is meant materials such as woven tissues, nonwoven tissues or veils. The material thus has, on a microscopic level, a net-like structure. By net-like structure, it is to be understood both uniform and non-uniform net structures.

The multilayer material may also comprise one, two, three, four, five, six or more layers of particles. Within a layer, the particles are preferably arranged at a distance from each other. Also, according to a preferred embodiment of the invention, one layer of particles is arranged between each two layers of web, in order to keep them at a distance from each other. The particles thus act as "space-keepers" in the multilayer material.

According to another embodiment of the present invention, the material may further comprise particles selected from the group consisting of sol-gel derived titanium oxide particles, bioactive glass particles, particles made of a sintered mixture of hydroxyl apatite and bioactive glass as well as mixtures thereof. The material may thus comprise also other particles than sol-gel derived silica particles. The particles, particularly the sol-gel derived particles may comprise silica (sillicium oxide) and/or titanium oxide up to 100 mol-%, calcium up to 50 mol-%, phosphorous up to 15 mol-%, proteins or other therapeutically active agents up to 20 mol-%. The particles may also consist of mixtures of these different materials. When hydroxyl apatite is used, it may be for example in the form of powder or granules and it may be combined with calcium phosphate.
The particles may be in the form of spheres or particles having a more non-uniform shape. The particles may also be in the form of very short fibers. The diameter of the particles is preferably 10-1000 μm.

The degradation rate of the particles may vary. For example, part of the particles may degrade and/or dissolve at a high rate, such as within a week when placed within the body of a mammal. According to an embodiment of the invention, the degradation rate of at least a part of said particles is higher than the degradation rate of the webs. It is naturally also possible to use webs having different rates of degradation as well as to use webs comprising different fibers having different rates of degradation.

The material according to the present invention may be deformed in certain limits. The bending, folding or deformation by pressure of the material may be used to induce zones of different activity, since the force (compression or elongation) increases the potential at the surface of the material and thus creates polarities. These polarities are then used to enhance the growth of the tissue. The material may thus comprise particles or fibers that have piezoelectric properties.

Usefull piezoelectric materials are biocompatible piezoelectric materials such as SiO₂ in quartz form and/or other piezoelectric materials such as BaTiO₃, PbZrTiO₅ and LiSO₄. One preferred material is SiO₂ in the form of particles. It is also possible to use partial coatings of SiO₂ or fibers that have piezoelectric properties per se. It is furthermore possible to use the above-mentioned materials or for example ZnO for coating of the silicon nanoparticles or a Si/SiO₂ nanolayers in order to render them both light producing and piezoelectric. As an example, it can be mentioned that the piezoelectric coefficient of SiO₂ in quartz form is 2,3 pC/N, whereas when a silicon particle is coated with a thin layer of ZnO, a piezoelectric coefficient of 10,6 pC/N can be obtained. The thickness of said coating may be for example in the order of 0,01-100 μm.

By piezoelectric materials it is meant particles, crystals or coatings that acquire a charge when compressed, twisted or distorted. The function of these piezoelectric particles is thus to create a tension as the
prepreg is deformed (bent, twist, compressed etc), thus creating a piezoelectric effect.

The piezoelectric effect may be local in a microscopic scale or macroscopic scale. On macroscopic scale, the piezoelectric effect may be obtained by a larger sensor structures. The information given by piezoelectric effect may be used for analysis either locally or at distance.

According to yet another embodiment of the invention, at least a part of said particles may comprise an agent selected from the group consisting of therapeutically active agents, proteins and mixtures thereof. The multilayer material may thus be used for delivery of different agents or the said agents may be incorporated in the material to induce a specific reaction beneficial for example for the attaching of the material to body tissue. It is also possible to use proteins that enhance the tissue growth.

Some examples of therapeutically active agents useful in the present invention are heparin, antibiotics, anti-inflammatory agents, growth factors, other proteins, stem cells, cancer drugs. The therapeutically active agents may be used for systemic or local application.

According to an embodiment of the invention, the layers of web are made of fibers selected from the group consisting of bioactive glass fibers, E-glass fibers, carbon fibers, aramid fibers, polyethylene fibers, polypropylene fibers and mixtures thereof. Any other known fibers may also be used. Preferably the fibers are biocompatible. The diameter of said fibers is typically 1 μm – 1000 μm, for bioactive glass fibers typically 1 μm – 200 μm. The fibers may also consist of several layers, for instance having several different coating layers.

According to an embodiment of the invention, different layers of web may be made of different fibers. Also, it is possible that one web comprises two or more different kinds of fibers. For example, for tissue guiding use, the nature of the fibers and their location is selected so as to induce a precisely localized degradation and thus tissue growth in a predetermined direction.
According to another embodiment of the invention, the fibers are at least partly coated with a coating selected from the group consisting of polymeric coating, sol-gel derived silica coating, sol-gel derived titanium dioxide coating and mixtures thereof. The coating may be biodegradable or non-biodegradable. The coating may also be doped with calcium and/or phosphate.

The polymeric coating may be for example a coating that binds the fibers together and/or binds the fibers to the particles. Examples of such polymers are acrylates, derivatives thereof, polylactides, ε-caprolactone, polylactic acid, polyglycolic acid, silanes, copolymers and mixtures thereof. The polymers may be bioactive or bioinert. A sol-gel derived silica coating is typically used when it is desired to further enhance the bioactivity of the multilayer material. A sol-gel derived titanium dioxide coating is used for example when it is desired to obtain a good contact and adhesion with soft tissues. The different layers of web may be coated differently and one layer may comprise different coatings at different locations or sides of the web. It is naturally also possible to coat only a part of said webs or all of them fully.

One bioactive glass composition that is useful in the present invention comprises SiO₂, Na₂O, CaO, K₂O, MgO, P₂O₅ and B₂O₃, wherein the amount of

- SiO₂ is 51-58 wt-% of the starting oxides,
- Na₂O is 7-9 wt-% of the starting oxides,
- CaO is 21-23 wt-% of the starting oxides,
- K₂O is 10-12 wt-% of the starting oxides,
- MgO is 1-4 wt-% of the starting oxides,
- P₂O₅ is 0.5-1.5 wt-% of the starting oxides, and
- B₂O₃ is 0-1 wt-% of the starting oxides,

provided that the total amount of Na₂O and K₂O is 17-20 wt-% of the starting oxides. This is called composition A in this specification.

Another type of suitable bioactive glass composition is disclosed in WO 96/21628. A typical composition of these glasses is

\[
\text{SiO}_2 \quad 53 - 60 \text{ wt-% of the starting oxides},
\]
Na₂O 0 - 34 wt-% of the starting oxides,
K₂O 1 - 20 wt-% of the starting oxides,
MgO 0 - 5 wt-% of the starting oxides,
CaO 5 - 25 wt-% of the starting oxides,
B₂O₃ 0 - 4 wt-% of the starting oxides and
P₂O₅ 0.5 - 6 wt-% of the starting oxides,

provided that

Na₂O + K₂O = 16 - 35 wt-% of the starting oxides,
K₂O + MgO = 5 - 20 wt-% of the starting oxides and
MgO + CaO = 10 - 25 wt-% of the starting oxides.

According to one embodiment, the fibers are made of a bioactive glass having the following composition: Na₂O 6 wt-% of the starting oxides, K₂O 12 wt-% of the starting oxides, MgO 5 wt-% of the starting oxides, CaO 20 wt-% of the starting oxides, P₂O₅ 4 wt-% of the starting oxides and SiO₂ 53 wt-% of the starting oxides. Another suitable bioactive glass composition is Na₂O 6 wt-% of the starting oxides, K₂O 12 wt-% of the starting oxides, MgO 5 wt-% of the starting oxides, CaO 15 wt-% of the starting oxides, P₂O₅ 4 wt-% of the starting oxides and SiO₂ 58 wt-% of the starting oxides.

In the compositions above, the amount of different oxides is given as weight percent of the starting oxides because some elements, such as sodium, evaporate during the heating. The amounts of the final oxides are however close to those of the starting oxides and in any case, the difference between the starting amounts and the final amounts is less than 5 percentage units, preferably less than 3 percentage units.

It is obvious to a person skilled in the art that the amounts of the oxides can be freely chosen within the above-mentioned limits. Indeed, the amount of SiO₂ can be for example 51,5, 52, 53,5, 55 or 56 wt-% of the starting oxides, the amount of Na₂O can be for example 7, 7,3, 7,7, 8, 8,5 or 9 wt-% of the starting oxides, the amount of CaO can be for example 21, 21,4, 21,7, 22, 22,6 or 23 wt-% of the starting oxides, the amount of K₂O can be for example 10, 10,5, 10,6, 11, 11,3, 11,7 or 12 wt-% of the starting oxides, the amount of MgO can be for example 1, 1,3, 1,9, 2,4, 2,7, 3,5 or 4 wt-% of the starting oxides, the
amount of P$_2$O$_5$ can be for example 0.5, 0.7, 1, 1.2 or 1.5 wt-% of the starting oxides, and the amount of B$_2$O$_3$ can be for example 0, 0.4, 0.6, 0.9 or 1 wt-% of the starting oxides.

When the composition A is used, according to an embodiment of the invention, the amount of SiO$_2$ is 54 - 56 wt-% of the starting oxides.

According to another embodiment of the invention in relation to composition A, the glass composition further comprises Al$_2$O$_3$ up to 1 wt-% of the starting oxides provided that the total amount of B$_2$O$_3$ and Al$_2$O$_3$ is 0.5 - 2.5 wt-% of the starting oxides.

According to yet another embodiment of the invention in connection to composition A, the decrease in the amount of Na$_2$O and/or K$_2$O is compensated by the increase of the amount of Al$_2$O$_3$ and/or B$_2$O$_3$.

The bioactive glass having a composition of the type A described above may be processed with any conventional methods. A particularly preferred method for the treatment is heating with laser since it allows localized yet high temperatures to be used in the melting of the glass.

The glass composition A that may be used in the present invention is advantageously prepared in atmospheric pressure and at temperatures of about 1360 °C. The heating time for making the glass melt is typically three hours. No protection gas is needed. When preparing the glass composition A, the constituents are first melted together and then cooled down. The resulting solid material is then crushed and remelted in order to obtain a homogeneous material.

The present glass composition A may advantageously be used in the form of fibres. Indeed, the composition A may be drawn to a fibre at higher temperatures than other known bioactive glass compositions. Typically, the manufacturing temperature may be even 100 °C higher than for the conventional bioactive glass compositions. Higher manufacturing temperatures lead to fibres having a smaller diameter since the viscosity of the glass melt decreases with increasing temperature. Also, the manufacturing temperature is critical for the resulting fibre product since it is close to the softening temperature of the glass, thus close to the crystallization temperature. A fibre
manufactured from the present composition A that has been heat-treated three times still has the described properties.

The bioactive glass composition A useful in the present invention is disclosed in the application EP 02079105.9, the contents of which are incorporated by reference herein.

The material according to the present invention may for example be in the form of a sheet, a tissue, a tube such as a stent, a ring or a band. The different forms may be obtained by using webs that are already in the desired form, such as a woven tube, or by forming them starting from a sheet, by any technique known per se.

The stiffness and strength of the multilayer material depends on the nature of the materials used for webs and particles as well as on the diameter of the fibers and the attaching of the fibers to the particles. The stiffness may be designed from highly stiff to easily foldable. Preferably, the structure is elastic, i.e. it can be deformed to at least a certain extent. The multilayer material according to the present invention may also be sewable, i.e. it may be possible to sew the different layers of web to each other, to form a tube by rolling the multilayer material and then sew it into shape, or to sew the multilayer material directly onto a body tissue.

Also the thickness of the multilayer material as well as its weight per surface unit may vary depending on the application.

The fibers of the web may be attached to the particles by sintering, especially when glass materials are used. Sintering may also be used to attach the edges of a sheet of multilayer material according to the present invention in order to form a tube. Furthermore, also gluing and other techniques may be used for attaching the layers of web and particles to each other as well as the edges of the material to each other.

The material according to the present invention may have any kind of shape and size. It may for example be used in units as small as in the millimetre range, up to the range of tens of centimetres. It is also possible to manufacture larger devices by combining several smaller parts. The smaller parts may then have different constitutions
according to the intended use of the device, which may also be called a functional web.

One method of introducing the present multilayer material in a tube form into the body is to position the material in tube form over a rod, to introduce the rod into the desired location wherein the material attaches to the surrounding tissue, to remove the rod whereby the multilayer material stays in place.

The present invention further relates to different uses of the multilayer material disclosed above. The material may be used for example for delivery of therapeutically active agents, for tissue repair, for coating of an implant, for the manufacture of a device for curing gingivitis as well as for support material for tissue culture. The material may also be used in the manufacture of devices for delivery of therapeutically active agents and/or in the manufacture of devices for tissue repair.

An example of delivery of therapeutically active agents is a stent made of the present multilayer material in which the inside of the stent comprises heparin and the outside of the stent comprises an agent that enhances the attaching of the stent into the body tissue. The use of the present multilayer material for tissue repair and for tissue guiding has been disclosed above. It is also possible to coat an implant with the material according to the present invention by attaching the material on the surface of the implant by for example sintering or gluing. A device for curing gingivitis is disclosed more in detail below. The present multilayer material is advantageous also as a support material for tissue culture, since once the culture is ready to be transferred, the material offers support during the transfer and may enhance the attaching of the new tissue to the target tissue.

In this specification, except where the context requires otherwise, the words "comprise", "comprises" and "comprising" means "include", "includes" and "including", respectively. That is, when the invention is described or defined as comprising specified features, various embodiments of the same invention may also include additional features. Also, the reference signs should not be construed as limiting the claims.
The invention is described below in greater detail by the following, non-limiting drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 illustrates a perspective view of a first embodiment of a multilayer material according to the present invention.

Figure 2 illustrates a side view of a second embodiment of a multilayer material according to the present invention.

Figure 3 illustrates a side view of a third embodiment of a multilayer material according to the present invention.

Figure 4 illustrates a use according to a fourth embodiment of a multilayer material according to the present invention.

Figure 5 illustrates a positioning device of a multilayer material according to a fifth embodiment of the present invention.

Figure 6 illustrates a use according to a sixth embodiment of a multilayer material according to the present invention.

DETAILED DESCRIPTION OF THE DRAWINGS

Figure 1 illustrates a perspective view of a first embodiment of a multilayer material according to the present invention. In this embodiment, the material consist of layers 1, 2, 3 of web and of particles 4 positioned between the layers 1, 2 and 3. The layers 1, 2, 3 may be made of same or different materials and each layer may comprise one or more constituents.

Figure 2 illustrates a side view of a second embodiment of a multilayer material according to the present invention. In this second embodiment, the layers 5 are spaced apart in such a way that the distance from one layer to another layer is substantially equal on the total thickness of the material. The diameter of the particles 6 varies and some of the particles are essentially regular in shape, for example spheres, and some of the particles are of a more irregular shape.
Figure 3 illustrates a side view of a third embodiment of a multilayer material according to the present invention. In this embodiment, a tissue guiding material is presented. The layers 7 comprise parts 11 (here illustrated, for the sake of clarity, by thicker lines) that have a faster degradation rate than the rest of the layer. The layers are separated by particles 8, 9 and 10. The particles 8 have a higher degradation rate than the particle 9 and 10, typically essentially the same degradation rate as parts 11. These particles are positioned between the parts 11 of each layer. Particles 9 and 10 are of different type and here also of different shape.

Figure 4 illustrates a use according to a fourth embodiment of a multilayer material according to the present invention. In this embodiment, a device 12 for curing gingivitis has been manufactured from the material according to the present invention. The device 12 consists of a multilayer material in a ring form. The gingival 13 around a tooth 14 is cut open, as illustrated on one side of the tooth 14, the device 12 is positioned around the tooth and the gingival 13 is sewed close. In this embodiment, the multilayer material is preferably fully made of biodegradable materials.

Figure 5 illustrates a positioning device of a multilayer material according to a fifth embodiment of the present invention. The material 16 according to the invention is placed over the positioning device 15, a rod or the like. The positioning device 15 is then inserted into the tissue and as the material 16 reacts with the tissue and becomes attached to it, the positioning device 16 can be removed.

Figure 6 illustrates a use according to a sixth embodiment of a multilayer material according to the present invention. In this embodiment, a stent 17 has been manufactured from the material according to the present invention.
CLAIMS

1. A multilayer material comprising at least two layers of web and at least one layer of particles, said particles being arranged between said at least two layers of web, characterized in that at least a part of said multilayer material is made of bioactive glass and that said particles are sol-gel derived silica particles.

2. Multilayer material according to claim 1, characterized in that said material further comprises particles selected from the group consisting of sol-gel derived titanium oxide particles, bioactive glass particles, particles made of a sintered mixture of hydroxyl apatite and bioactive glass as well as mixtures thereof.

3. Multilayer material according to claim 1 or 2, characterized in that said layers of web are made of fibers selected from the group consisting of bioactive glass fibers, E-glass fibers, carbon fibers, aramid fibers, polyethylene fibers, polypropylene fibers and mixtures thereof.

4. Multilayer material according to claim 3, characterized in that said fibers are at least partly coated with a coating selected from the group consisting of polymeric coating, sol-gel derived silica coating, sol-gel derived titanium dioxide coating and mixtures thereof.

5. Multilayer material according to any of the preceding claims, characterized in that the degradation rate of at least a part of said particles is higher than the degradation rate of the webs.

6. Multilayer material according to any of the preceding claims, characterized in that at least a part of said particles comprises an agent selected from the group consisting of therapeutically active agents, proteins and mixtures thereof.

7. Use of a multilayer material according to any of the claims 1-6 for delivery of therapeutically active agents.

8. Use of a multilayer material according to any of the claims 1-6 for the manufacture of a device for tissue repair.
9. Use of a multilayer material according to any of the claims 1-6 for coating of an implant.

10. Use of a multilayer material according to any of the claims 1-6 for the manufacture of a device for curing gingivitis.

11. Use of a multilayer material according to any of the claims 1-6 as support material for tissue culture.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7: A61L 27/10, 27/30, 27/42, 27/58, 31/12, B32B 5/30
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
IPC 7: A61L, A61C, B32B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
FI, SE, NO, DK classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-internal, WPI, PAJ, MEDLINE, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<th>Category*</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
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<td>Y</td>
<td>WO 0115751 A1 (BIOXID OY et al.) 08 March 2001 (08.03.2001)</td>
<td>1-6, 8-11</td>
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<td>Y</td>
<td>US 6743513 B2 (MECHLOSKY JOHN J et al.) 01 June 2004 (01.06.2004)</td>
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<td>US 2004115239 A1 (SHASTRI VENKATRAM P et al.) 17 June 2004 (17.06.2004)</td>
<td>1-6, 8-11</td>
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☐ Further documents are listed in the continuation of Box C. ☑ See patent family annex.

* Special categories of cited documents:
*"A" document defining the general state of the art which is not considered to be of particular relevance
*"E" earlier application or patent but published on or after the international filing date
*"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
*"O" document referring to an oral disclosure, use, exhibition or other means of establishing the public knowledge of the subject matter before the priority date claimed
*"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
*"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
*"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
*"&" document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report
29 September 2005 (29.09.2005)

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Form PCT/ISA/210 (second sheet) (April 2005)
INTERNATIONAL SEARCH REPORT

Box No. II  Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☑ Claims Nos.: 7
   because they relate to subject matter not required to be searched by this Authority, namely:
   Claim 7 relates to a method for treatment of the human or animal body by therapy (PCT Rule 39.1 (iv))

2. ☐ Claims Nos.:
   because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III  Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant’s protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant’s protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (2)) (April 2005)
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