Title: HEMOSTATIC MATERIAL

Abstract: The present invention relates to hemostatic powders comprising a chitosan salt together with at least one inert material. The present invention also relates to hemostatic powders into which fluid penetrability is 0.5 cm or more within 1 minute. At least one medical surfactant may optionally be included. The hemostatic powders may be incorporated into wound dressings.
Hemostatic Material

The present invention relates to a hemostatic material for use in controlling bleeding.

Traditionally the primary technique adopted for stemming blood flow is the application of continuous pressure to the wound. This enables clotting factors to collect at the wound site and form a congealed blood mass to stem blood flow. However, this technique is not suitable for severe wounds and wounds having multiple bleeding points. Therefore, bleeding out continues to be a major cause of death.

Death caused by bleeding out is a particular problem on the battlefield. Typically, wounds arising in this situation are accompanied by significant bleeding, and many result in death. Bleeding out is also a significant cause of death amongst the civilian population following trauma.

Attempts have been made to provide products which facilitate the stemming of blood flow from a wound. These include a product sold under the brand name Quick-clot®. Quick-clot® comprises a zeolite compound which absorbs water from the blood flowing from a wound such that the clotting factors present in the blood become concentrated and the blood coagulates more quickly thereby the zeolite and the coagulated blood together form a coagulum to stem blood flow.

Whilst effective Quick-clot® is not without problems. After application to the wound and as the zeolite absorbs water Quick-clot® generates heat. In fact, Quick-clot®
quickly reaches temperatures of around 50°C. As it is necessary to apply constant pressure to the wound site following application of Quick-clot® such temperatures make the application of pressure very difficult with medics needing to separate themselves from the wound site with any available material to prevent the discomfort accompanied with the heat generation. Furthermore, as the medic reaches for material to put between himself and the hot wound area he has to release the pressure. This can lead to channels appearing in the developing coagulum through which blood can escape. If this happens then it is necessary to remove Quick-clot® and start again. Ideally, a second person is required to ensure constant compression is applied. Other problems associated with Quick-clot® also relate to the heat generated upon contact with water. For example, as the product is a powder inevitably some settles on the skin surrounding the wound. If the skin is wet the heat generated can cause burns. Using Quick-clot® in wet and windy weather is also problematic as it may cause discomfort or even burns to a person standing nearby.

A further product which comprises chitosan is described in WO 02/102276. The product is a sheet dressing comprising a chitosan layer. The dressing is applied to the site of a wound and forms a seal. The chitosan causes the blood to coagulate which together with the seal formed by the sheet stems the blood flow. However, such products must be applied directly to the source of bleeding, i.e. to an artery. Such application requires skill and accuracy. Military medics and first responders do not have the necessary skills to identify the source of bleeding and apply the dressing thereto. In any event, it would be extremely difficult to perform such a delicate operation on a battlefield or at a trauma site.
GB 2 095 995 and GB 2 129 300 disclose the use of pure chitosan acetate as a hemostatic material. However, the gel which forms from the pure salt is very thin as only the outermost surface of the material is available to act in a short period of time. Quite often this material fails to stop bleeding and even when it does, the clot is very thin and weak so that when the patient is moved, the clot is compromised and bleeding resumes.

Therefore, it is an object of the present invention to provide a hemostatic material which quickly stems the flow of blood from a wound and which is easy and safe to use.

According to the present invention there is provided a hemostatic powder comprising a chitosan salt together with at least one inert material.

Advantageously, the hemostatic powder of the present invention can be applied by a person with only basic training. It is a matter of simply applying the powder to the wound area followed by pressure.

Furthermore, the powder of the present invention does not generate heat following application to the wound site. Therefore, the aforementioned disadvantages of the Quick-clot® product are not seen with the powder of the present invention.

Products which take advantage of biological processes tend to be temperature dependent. Often patients suffering blood loss are either very hot due to exertions on
the battlefield or very cold as they have been exposed to cold conditions. Currently available powder products are less effective at such temperature extremes. Advantageously the powder of the present invention is not affected by temperature fluctuations and therefore works equally well at temperatures above and below normal body temperatures (37°C).

Chitosan is a derivative of solid waste from shell fish processing and can be extracted from fungus culture. Chitosan is a water insoluble cationic polymeric material. Therefore, chitosan for use with the present invention is first converted into a water soluble salt. Therefore, the chitosan salt is soluble in blood to form a gel which stems blood flow.

Chitosan salts are ideally suited for the applications described herein as chitosan is readily broken down in the body. Chitosan is converted to glucosamine by the enzyme lysosyme and is therefore excreted from the body naturally. It is not necessary to remove chitosan from the body.

Furthermore, chitosan salts exhibit mild antibacterial properties and as such their use reduces the risk of infection.

Chitosan salts suitable for use with the present invention include any of the following either alone or in combination: acetate, lactate, succinate, malate, sulphate, acrylate. The foregoing examples are provided by way of example only and are not intended to be limiting in any way.
Preferably, the chitosan salt of the present invention is chitosan succinate.

The chitosan salt is prepared by combining chitosan with the appropriate acid. The acid may be any inorganic or organic acid which yields a soluble chitosan salt. For example, chitosan phosphate is insoluble and so phosphoric acid is unsuitable.

The chitosan salt preferably constitutes at least 5% by weight of the powder of the present invention.

Most preferably the chitosan salt constitutes at least 20% by weight of the powder of the present invention.

Surprisingly, it has been found that by adding at least one inert material to a chitosan salt the performance of the powder is enhanced.

The inert material may comprise any material which does not gel quickly, that is a material that gels in greater than 30 sees to 1 minute of application to a bleeding wound.

Suitable inert materials for use with the present invention include, but are not limited to any of the following either alone or in combination: cellulose, fumed silica, sand, clay, alginate, micro crystalline cellulose, oxidised regenerated cellulose, polyethylglycol, guar gum, xanthan gum, chitosan, chitosan derivatives, chitin, sucrose, lactose, pectin, some grades of carboxymethylcellulose, ground corn meal,
collagen, gelatine, polyvinylalcohol, acrylic acid, Carbopol®, crosslinked acrylic
acid-based polymers, barium sulphate, clay, lactose, sucrose, starch.

Ideally the inert material will have a known metabolic pathway in order that the body
can degrade of and dispose of said material if the powder remains in situ.

Said inert materials preferably constitute from at least 30% by weight of the present
invention.

Most preferably the inert materials constitute at least 30% by weight of the present
invention.

Advantageously, the presence of an inert material gives rise to excellent wetting out
properties. The way in which the powder of the present invention wets out is crucial
to its performance. That is, if the powder initially absorbs the blood quickly, then
blood and powder mix without sufficient gellation having occurred to form a gel layer
or block form, then a large strong gel clot forms which is capable of blood flow
stemming. On the other hand, if the powder absorbs the blood too slowly gellation
occurs in only a small amount of the powder, generally the first few millimetres depth
of the powder closest to the wound site, hi this case the gel clot which forms is weak
and not sufficiently dense to robustly stem the blood flow for a sufficient period of
time to allow the patient to be moved to a medical centre. Typically, such a gel clot
will break up under any motion such as when the patient is moved and bleeding will
resume.
Another factor which has been found to be important to the performance of the powder is the particle size of the chitosan salt. The particle size is measured by the size of sieve which it will go through or is retained by.

Preferably, the chitosan salt has a particle size in the range such that it will pass through a 5 mesh screen but be retained by a 80 mesh screen.

More preferably, the chitosan salt has a particular size in the range such that it will pass through a 20 mesh screen but be retained by a 50 mesh screen.

Most preferably, the particle size of the inert material will match that of the chitosan salt.

The correct particle size is achieved by grinding the chitosan salt and sorting by any suitable means for example sieving. Such sizing processes are well known to those skilled in the art and will not be described further.

It has been found that by adding at least one medical surfactant to the powder the performance of the powder is actually enhanced. The medical surfactant appears to further enhance the properties of the inert material.

Therefore, the present invention optionally comprises at least one medical surfactant.
Suitable medical surfactants include any of the following either alone or in combination: block copolymers based on ethylene oxide and propylene oxide (e.g. BASF Pluronics®), lauric acid, oleic acid, other fatty acids and fatty acid salts, silicone based surfactants and emulsifiers.

The medical surfactant preferably constitutes at least 0.01% by weight of the total composition.

Preferably the surfactant is dissolved during manufacturing such that the surfactant forms a coating around the particles of the powder. That said, the surfactant may be added in the form of a solid.

The powder of the present invention preferably has a pH of from 3.5 to 6.0.

It has been observed that hemostatic powders into which fluid can penetrate by 0.5cm or more have superior hemostatic effect. This is a surprising observation, since it had previously been widely accepted that hemostasis is a surface effect such that only the 0.5cm closest to the bleed point would be important. This is now shown not to be the case.

Thus, according to a further aspect of the present invention there is provided a hemostatic powder comprising a chitosan salt, wherein fluid penetrability into the hemostatic powder is 0.5cm or more within 1 minute.
The hemostatic powder may include at least one inert material, and may comprise any of the compositions as hereinbefore described.

The fluid penetrability into the hemostatic powder may be lcm or more within 1 minute, more preferably 1.5cm or more within 1 minute.

The present invention also provides a method of stemming blood flow.

Therefore, according to a further aspect of the present invention there is provided a method of stemming blood flow comprising the steps of: cleaning a wound area where possible; applying to said wound area a hemostatic powder comprising at least one chitosan salt together with at least one inert material; and applying constant pressure to wound area until a gel clot forms.

Compression is preferably applied to the wound area for about 3 minutes or more.

The present invention may be incorporated into a chitosan fibre. The fibres may then be used to prepare a wound dressing for superficial non-life threatening bleeding or life threatening bleeding.

Therefore, according to a further aspect of the present invention there is provided a hemostatic powder for use in the manufacture of a hemostatic wound dressing, said powder comprising at least one chitosan salt together with at least one inert material.
According to a further aspect of the present invention there is provided a hemostatic wound dressing comprising at least one chitosan salt together with at least one inert material.

During the manufacture of the material of the present invention an active base is prepared by preparing a mixture of chitosan and acid in a solvent in which the chitosan is insoluble (usually 80:20 ethanol:water). Where used a surfactant may also be added to this mixture. The solvent is evaporated to provide a substantially dry active base material. The active base material is then combined with other materials such as inert materials to provide the powder of the present invention.

The invention will now be described further by way of example only with reference to the following examples and figures:

Figure 1 is a diagrammatic representation of the penetrability test described herein.

Fig. 1 shows a rest tube 1 comprising an aqueous layer 2 and a layer of hemostatic powder 3. the distance travelled by the aqueous layer 2 is shown as band 4.
Example 1 - powder process

The ethanol (or any other solvent in which chitosan will not dissolve) and the water are mixed. The acid is dissolved in the ethanol and water combination. The surfactant is dissolved in the same solution.

The raw chitosan powder is added to the solution and mixed in a dough style mixer for 15 minutes.

The resulting slurry is dried at 60°C to remove the ethanol and water.

The resulting solids are passed through a grinding mill to produce the required particle size.

This chitosan salt can then be mixed and blended with the dry inert powder to produce the final hemostat.

Table 1 shows some of the various blends prepared and their hemostatic efficacy penetrability.

The 'Active Base 15' is prepared by forming a pre-mix of 59% chitosan and 41% succinic acid in an 80:20 ethanol: water solution. The solvent is then removed by drying at 60°C.
**Example 2 - fibre coating**

A solution of chitosan in water with the required acid is made. Surfactants and or plastiziers can be added.

This can then be applied to an existing fabric such as gauze by spraying or coating etc.

The resulting fabric is then dried.

A final texturising process can be used to soften the fabric.
**Example 3 - chitosan fabric**

The ethanol (or any other solvent in which chitosan will not dissolve) and the water are mixed. The acid is dissolved in the ethanol and water combination. A surfactant/plasticiser may be dissolved in the same solution.

The resulting solution can be applied to a fibre or a fabric made of the fibres or a blend of chitosan fibres with any other fibre.

The resulting wet fibre mass is dried to remove the ethanol and water.

If necessary a final texturising process can be used to soften any resulting fabric.

The hemostatic efficacy and penetrability properties of the present invention were determined by the following tests:

**Penetrability**

5mls of distilled water were added to a test tube. A drop of red food dye was added to the water. 3g of hemostatic powder were gently tipped on top of the water such that a layer was formed (see Fig. 1).

After 1 minute the distance travelled by the water into the hemostatic powder was measured.

The sample was monitored for gel blocking.
A distance of 0.5cm or more indicates an effective hemostat for the purposes of the present invention.

**Hemostatic efficacy**

The ability of a hemostat to bond with particles like bentonite is a measure of its hemostatic efficacy.

To a container containing 30ml of distilled water was added 0.5g of hemostatic powder. The mixture was stirred moderately for 3 minutes using a magnetic stirring bar and stirrer. The stirred mixture was then filtered through a Whatman #1 filter paper.

The amount of filtrate required to flocculate 50ml of a settled 0.5% Bentonite® solution was determined.

The use of less than 1mI of the filtrate indicates an effective hemostat for the purposes of the present invention.

The following table 2 shows various active base compositions, together with the results of the penetrability and hemostatic efficacy tests:
The active base comprising surfactant absorbs more dye in the penetrability test indicating that the base will provide a more stable and robust clot in practice.

The active base comprising surfactant required less fluid to meet the requirements of the hemostatic efficacy test indicating that the base will minimise flow of blood from a wound.

**In vivo hemostatic efficacy**

The hemostatic powders were tested in vivo in a porcine model. The wounds were complete severs of a femoral artery. The powder was applied to the wound bowl and compression applied for 5 minutes.

In test 'Ui', 'Formula D' was prepared using an active base formed from a pre-mix of 59% chitosan and 41% succinic acid in a solvent solution in which the chitosan is insoluble. The solvent solution was removed by drying.
It is of course to be understood that the present invention is not intended to be restricted to the foregoing examples which are described by way of example only.

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<th>Test</th>
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<th>Penetrability</th>
<th>No. wounds treated</th>
<th>Results</th>
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<tbody>
<tr>
<td>i</td>
<td>100% Active base 15</td>
<td>0.3 cm</td>
<td>3</td>
<td>Partially successful. One wound would not stop bleeding. Two wounds stopped but re-bleed after some minutes.</td>
</tr>
<tr>
<td>ii</td>
<td>50% Active base 15 + 50% inert chitin</td>
<td>2.65 cm</td>
<td>2</td>
<td>100% successful</td>
</tr>
<tr>
<td>iii</td>
<td>Formula D</td>
<td>1.2 cm</td>
<td>6</td>
<td>100% successful</td>
</tr>
</tbody>
</table>
CLAIMS

1. A hemostatic powder comprising a chitosan salt together with at least one inert material.

2. A hemostatic powder according to claim 1, wherein the chitosan salt comprises one or more of the group consisting of: chitosan acetate, chitosan lactate, chitosan succinate, chitosan malate, chitosan sulphate, chitosan acrylate.

3. A hemostatic powder according to claim 2, wherein the chitosan salt comprises chitosan succinate.

4. A hemostatic powder according to any one of the preceding claims, wherein the chitosan salt constitutes at least 5% by weight of the hemostatic powder.

5. A hemostatic powder according to claim 4, wherein the chitosan salt constitutes at least 20% by weight of the hemostatic powder.

6. A hemostatic powder according to any one of the preceding claims, wherein the at least one inert material comprises one or more of the group consisting of: cellulose, fumed silica, sand, clay, alginate, micro crystalline cellulose, oxidised regenerated cellulose, polyethylglycol, guar gum, xanthan gum, chitosan, chitosan derivatives, chitin, sucrose, lactose, pectin, carboxymethylcellulose, ground corn meal, collagen, gelaatine, polyvinylalcohol, acrylic acid, crosslinked acrylic acid-based polymers, barium sulphate, clay, lactose, sucrose, starch.

7. A hemostatic powder according to any one of the preceding claims, wherein the at least one inert material constitutes at least 30% by weight of the hemostatic powder.
8. A hemostatic powder according to any one of the preceding claims, wherein the chitosan salt comprises particles that will pass through a 5 mesh screen but be retained by a 80 mesh screen.

9. A hemostatic powder according to claim 8, wherein the chitosan salt comprises particles that will pass through a 20 mesh screen but be retained by a 50 mesh screen.

10. A hemostatic powder according to any one of the preceding claims, wherein the particle size of the chitosan salt and the particle size of the at least one inert material are substantially equivalent.

11. A hemostatic powder according to any one of the preceding claims, wherein the hemostatic powder further comprises at least one medical surfactant.

12. A hemostatic powder according to claim 11, wherein the at least one medical surfactant comprises one or more of the group consisting of: block copolymers based on ethylene oxide and propylene oxide, fatty acids, fatty acid salts, silicone based surfactants and emulsifiers.

13. A hemostatic powder according to claim 12, wherein the at least one medical surfactant is a fatty acid selected from lauric acid and oleic acid.

14. A hemostatic powder according to any one of claims 11 to 13, wherein the at least one medical surfactant constitutes at least 0.01% by weight of the hemostatic powder.

15. A hemostatic powder according to any one of claims 11 to 14, wherein the at least one medical surfactant is present in the form of a coating around particles of the hemostatic powder.
16. A hemostatic powder according to any one of the preceding claims, wherein the hemostatic powder has a pH of from 3.5 to 6.

17. A hemostatic powder comprising a chitosan salt, wherein fluid penetrability into the hemostatic powder is 0.5cm or more within 1 minute.

18. A hemostatic powder according to claim 17, wherein fluid penetrability into the hemostatic powder is 1cm or more within 1 minute.

19. A hemostatic powder according to claim 18, wherein fluid penetrability into the hemostatic powder is 1.5cm or more within 1 minute.

20. A hemostatic powder according to any one of claims 17 to 19, wherein the hemostatic powder further comprises at least one inert material.

21. A hemostatic powder according any one of claims 17 to 20, wherein the chitosan salt comprises one or more of the group consisting of: chitosan acetate, chitosan lactate, chitosan succinate, chitosan malate, chitosan sulphate, chitosan acrylate.

22. A hemostatic powder according to claim 21, wherein the chitosan salt comprises chitosan succinate.

23. A hemostatic powder according to any one of claims 17 to 20, wherein the chitosan salt constitutes at least 5% by weight of the hemostatic powder.

24. A hemostatic powder according to claim 23, wherein the chitosan salt constitutes at least 20% by weight of the hemostatic powder.
25. A hemostatic powder according to any one of claims 20 to 24, wherein the at least one inert material comprises one or more of the group consisting of: cellulose, fumed silica, sand, clay, alginate, micro crystalline cellulose, oxidised regenerated cellulose, polyethylglycol, guar gum, xanthan gum, chitosan, chitosan derivatives, chitin, sucrose, lactose, pectin, carboxymethylcellulose, ground corn meal, collagen, gelatine, polyvinylalcohol, acrylic acid, crosslinked acrylic acid-based polymers, barium sulphate, clay, lactose, sucrose, starch.

26. A hemostatic powder according to any one of claims 20 to 25, wherein the at least one inert material constitutes at least 30% by weight of the hemostatic powder.

27. A hemostatic powder according to any one of claims 17 to 26, wherein the chitosan salt comprises particles that will pass through a 5 mesh screen but be retained by a 80 mesh screen.

28. A hemostatic powder according to claim 27, wherein the chitosan salt comprises particles that will pass through a 20 mesh screen but be retained by a 50 mesh screen.

29. A hemostatic powder according to any one of claims 17 to 28, wherein the particle size of the chitosan salt and the particle size of the at least one inert material are substantially equivalent.

30. A hemostatic powder according to any one of claims 17 to 29, wherein the hemostatic powder further comprises at least one medical surfactant.

31. A hemostatic powder according to claim 30, wherein the at least one medical surfactant comprises one or more of the group consisting of: block copolymers based
on ethylene oxide and propylene oxide, fatty acids, fatty acid salts, silicone based surfactants and emulsifiers.

32. A hemostatic powder according to claim 31, wherein the at least one medical surfactant is a fatty acid selected from lauric acid and oleic acid.

33. A hemostatic powder according to any one of claims 30 to 32, wherein the at least one medical surfactant constitutes at least 0.01% by weight of the hemostatic powder.

34. A hemostatic powder according to any one of claims 30 to 33, wherein the at least one medical surfactant is present in the form of a coating around particles of the hemostatic powder.

35. A hemostatic powder according to any one of claims 17 to 34, wherein the hemostatic powder has a pH of from 3.5 to 6.

36. A hemostatic powder according to any one of the preceding claims for use in the manufacture of a hemostatic wound dressing.

37. A hemostatic wound dressing comprising a hemostatic powder according to any one of the preceding claims.

38. A hemostatic wound dressing according to claim 37, wherein the hemostatic wound dressing comprises fibres.

39. A hemostatic wound dressing according to claim 38, wherein the fibres are chitosan fibres.
40. A method of manufacturing a hemostatic powder, comprising the steps of: preparing a mixture of chitosan and an acid in a solvent in which the chitosan is insoluble, evaporating the solvent, and mixing the resulting chitosan salt with at least one inert material.

41. A method according to claim 40, wherein the solvent is 80:20 ethanol:water.

42. A method according to either of claims 40 or 41, wherein the method includes the step of adding at least one medical surfactant.

43. A method of stemming blood flow, including the steps of: applying to a wound area a hemostatic powder according to any one of claims 1-36; and applying constant pressure to the wound area until a gel clot forms.

44. A method according to claim 43, wherein the step of applying constant pressure to the wound area is carried out for at least 3 minutes.
**INTERNATIONAL SEARCH REPORT**

**A. CLASSIFICATION**

INV.  A61K31/72  A61L15/22  A61L26/00

**According to International Patent Classification (IPC), also both national classification and IPC.**

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

A61L  A61K  A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

**Electronic data base consulted during the international search (name of data base and, where practical, search terms used)**

EPO-Internal, WPI Data, CHEMABS Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
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<td>X</td>
<td>US 5 836 970 A (PANDIT ABHAY S [US]) 17 November 1998 (1998-11-17) column 1, lines 39-47; column 2, lines 9-22; tables 2-4; column 7, lines 10-19</td>
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**X** Further documents are listed in the continuation of Box C.

**X** 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 document but published on or after the international filing date
- **L** document which may throw doubts on priority citaions or may 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
- **P** document published prior to the international filing date but later than 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 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
- **A** same patent family

**Date of the actual completion of the international search**

30 April 2007

**Date of mailing of the international search report**

11/05/2007

**Name and mailing address of the ISA**

European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 Hl RHENWIJK Tel. (+31-70) 340-2040, Tx 31 651 epo nl, Fax (+31-70) 340-3016

**Authorized officer**

Skjödebrand, Carl
<table>
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<td>A</td>
<td>GB 2 393 120 A (JOHNSON &amp; JOHNSON MEDICAL LTD [GB]) 24 March 2004 (2004-03-24) page 1, lines 16-21</td>
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INTERNATIONAL SEARCH REPORT

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

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|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.: because they relate to subject matter not required to be searched by this Authority, namely:

   Although claims 43 and 44 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

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 III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

1. □) All required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. □) All searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. □) Only some of the required additional search fees were timely paid by the applicant, this International Search Report

   restricted to the invention first mentioned in the claims, it is covered by 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

□) No protest accompanied the payment of additional search fees
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<td>US 5836970 A</td>
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