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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PROCESSES FOR THE PREPARATION OF STABLE POLYMORPH OF SERTRALINE HYDROCHLORIDE

(57) Abstract: The invention relates to a process for the preparation of a polymorph of sertraline hydrochloride. More particularly, it relates to the preparation of a stable polymorph of sertraline hydrochloride and pharmaceutical compositions that include the stable polymorph of sertraline hydrochloride. The invention also relates to use of said compositions for treating anxiety related disorders.

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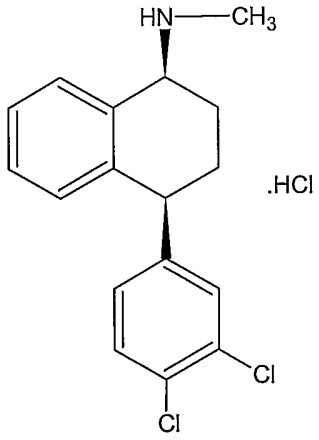
PROCESSES FOR THE PREPARATION OF STABLE POLYMORPH OF SERTRALINE HYDROCHLORIDE

Field of the Invention

The field of the invention relates to processes for the preparation of a polymorph of sertraline hydrochloride. More particularly, it relates to the preparation of a stable polymorph of sertraline hydrochloride and pharmaceutical compositions that include the stable polymorph of sertraline hydrochloride. The invention also relates to use of the compositions for treating anxiety related disorders.

Background of the Invention

Chemically, sertraline hydrochloride is (1S-cis)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthalenamine hydrochloride having the structural Formula I. It is useful in the treatment of anxiety-related disorders (U.S. Patent No. 4,962,128), symptoms associated with premenstrual disorders (U.S. Patent No. 5,789,449) and late luteal phase dysphoric disorder (U.S. Patent No. 5,744,501).



FORMULA I

Sertraline hydrochloride is known to exhibit polymorphism and exists in several crystalline forms and amorphous form having different physical properties. These different solid-state physical forms may be obtained by controlling the conditions under which the sertraline hydrochloride is obtained in the solid form. The solid-state form of a compound is also known to affect its behavior on compaction and its storage stability. Several processes have been reported for the preparation of various polymorphs of sertraline hydrochloride.

U.S.Patent No. 4,536,518 discloses a process for the preparation of sertraline hydrochloride having a melting point of 243-245°C by treating an ethyl acetate/ether solution of the free base with gaseous hydrogen chloride.

U.S. Patent No. 5,248,699 discloses processes for the preparation of five crystalline forms of sertraline hydrochloride, designated Form I, Form II, Form III, Form IV and Form V by rapid crystallization of sertraline hydrochloride from an organic solvent. The patent also discloses that Forms II, III, IV and V are metastable, and that granulation of Forms II, III or IV in isopropyl alcohol, ethyl acetate, hexane at a temperature from about 40-60°C causes conversion to Form I.

WO 00/32551 and WO 03/51818 describe processes for the preparation of various polymorphic forms of sertraline hydrochloride and their conversion to each other. These applications disclose the preparation of Form II by dissolving sertraline mandelate or free sertraline base in an organic solvent and treating with hydrogen chloride at ambient to reflux temperature.

U.S. Patent No. 6,495,721 discloses several processes for the preparation of Form II of sertraline hydrochloride. One of the processes disclosed for the preparation of Form II involves dissolving sertraline hydrochloride in an organic solvent such as acetone, cyclohexanol and dimethylformamide and heating the solution for sufficient time to effect the transformation to Form II of sertraline hydrochloride followed by isolation of Form II.

WO 01/32601 discloses processes for the preparation of sertraline hydrochloride polymorphic form II from a solution of sertraline free amine with some seeding crystals of form II before the addition of a solution of hydrogen chloride; or from a stirred suspension of sertraline hydrochloride polymorphic form V with some seeding crystals of sertraline hydrochloride polymorphic form II; or by drying a sertraline hydrochloride alcohol solvate at temperatures from about 0 to 30°C in high vacuum (less than I mbar); or from stirred suspensions of sertraline hydrochloride polymorphic form CSC1, CSC2 or T1 with some seeding crystals of sertraline hydrochloride polymorphic Form II. Furthermore, Sertraline hydrochloride polymorphic form II may be formed according to a process in which a solution of sertraline free amine is seeded with some crystals of polymorphic form II and a solution of hydrogen chloride is added.

WO 02/096859 discloses processes for the preparation of sertraline hydrochloride Form II by extracting or dissolving the sertraline base into ethyl acetate, adding isopropanol as a solvent, adding hydrogen chloride dissolved in ethyl acetate or in gaseous form, and isolating the sertraline hydrochloride polymorphic Form II.

WO 03/93217 discloses sertraline hydrochloride Form II which is substantially free of other polymorphic forms.

The inventors have found that the prior art approach for the preparation of polymorph form II is not suitable from a commercial point of view because the sertraline hydrochloride so obtained has a tendency to undergo discoloration upon storage.

The present invention provides a process which results in a storage stable polymorph form II of sertraline hydrochloride. The polymorph form II of sertraline hydrochloride when made by the process of the present invention is easy to isolate and handle, thus making the process amenable for commercial scale use.

Summary of the Invention

In one general aspect there is provided a storage stable polymorph form II of sertraline hydrochloride.

The Form II of sertraline hydrochloride may have, for example, the X-ray powder diffraction pattern of Figure 1.

In another general aspect there is provided a pharmaceutical composition that includes a therapeutically effective amount of the storage stable polymorph form II of sertraline hydrochloride; and one or more pharmaceutically acceptable carriers, excipients or diluents.

In another general aspect there is provided a process for the preparation of stable polymorph form II of sertraline hydrochloride. The process includes obtaining a suspension of sertraline hydrochloride in a solvent comprising one or more of methyl isobutyl ketone, N,N-dimethylacetamide or N,N-dimethylformamide; heating the suspension; and recovering the stable Form II of sertraline hydrochloride by the removal of the solvent.

Removing the solvent may include, for example, one or more of filtration, filtration under vacuum, decantation and centrifugation. The process may include further forming of the product so obtained into a finished dosage form.

The process may include further drying of the product obtained.

In one general aspect, the solution may be cooled before filtration to obtain better yields of the stable Form II of sertraline hydrochloride.

In another general aspect, the solution may be seeded with crystals of Form II resulting in the precipitation of the Form II of sertraline hydrochloride and removing the solvent there from by filtration, filtration under vacuum, decantation or centrifugation.

The sertraline hydrochloride which is used as the starting material may be obtained by any of the known processes, for example, processes as disclosed in U.S. Patent No. 4,536,518; U.S. Patent No. 5,248,699; WO 00/32551; and WO 01/32601.

In another general aspect there is provided a process for the preparation of storage stable Form II of sertraline hydrochloride. The process includes washing the Form II of sertraline hydrochloride with a dilute solution of an antioxidant in a solvent; and recovering the storage stable Form II of sertraline hydrochloride by the removal of the solvent.

The solvent may be, for example, one or more of methyl isobutyl ketone, N,N-dimethylacetamide, N,N-dimethylformamide, or mixtures thereof.

The antioxidant may be any conventional antioxidant used in the pharmaceutical industry, for example, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), hydroquinone, propyl gallate, ascorbyl palmitate, octyl gallate, dodecyl gallate, tocopherols, sodium or calcium ascorbate, tert-butylated hydroquinone, and the like.

Removing the solvent may include, for example, one or more of filtration, filtration under vacuum, decantation and centrifugation. The process may include further forming of the product so obtained into a finished dosage form.

The process may include further drying of the product obtained.

In one general aspect, the washing may be carried out by making a slurry in the dilute solution of an antioxidant in a solvent.

In one general aspect, wet solid Form II sertraline hydrochloride obtained from the process of its preparation may be washed before drying the product.

In another general aspect, the form II sertraline hydrochloride may be dried before washing with a dilute solution of an antioxidant in a solvent.

The sertraline hydrochloride Form II may be obtained by any of the processes known in the art, for example, U.S. Patent No. 4,536,518. The stable Form II sertraline hydrochloride prepared above may be used for the preparation of storage stable Form II sertraline hydrochloride.

The process may produce a storage stable Form II sertraline hydrochloride having the X-ray diffraction pattern of Figure 1, and which does not undergo discoloration during its shelf-life.

In another general aspect there is provided a method for treating the anxiety related disorders in a warm-blooded animal, the method comprising providing the warm-blooded animal a pharmaceutical composition that includes the storage stable Form II sertraline hydrochloride.

The details of one or more embodiments of the inventions are set forth in the description below. Other features, objects and advantages of the inventions will be apparent from the description and claims.

Description of the Drawings

Figure 1 is an X-ray powder diffraction pattern of stable Form II of sertraline hydrochloride.

Detailed Description of the Invention

The inventors have developed processes for the preparation of the stable Form II of sertraline hydrochloride. The Form II sertraline hydrochloride is characterized by its X-ray diffraction pattern as shown in Figure 1. The inventors have developed a process for the preparation of the stable Form II of sertraline hydrochloride by obtaining a suspension of sertraline hydrochloride in a solvent comprising one or more of methyl isobutyl ketone, N,N-dimethylacetamide or N,N-dimethylformamide; heating the suspension; and recovering the stable Form II of sertraline hydrochloride by the removal of the solvent. The inventors have also developed pharmaceutical compositions that contain the stable

Form II of sertraline hydrochloride in admixture with one or more solid or liquid pharmaceutical diluents, carriers, and/or excipients.

In general, the suspension of sertraline hydrochloride may be obtained by suspending sertraline hydrochloride in a suitable solvent. Alternatively, such a suspension may be obtained directly from a reaction in which sertraline hydrochloride is formed. The suspension containing sertraline hydrochloride may be heated to obtain a solution. It may be heated from about 30°C to about 200°C, for example from about 50°C to about 150°C. It may be heated from about 10 minutes to about 24 hours. More particularly, it may be heated for about 2-3 hours.

The sertraline hydrochloride can be prepared by methods described in U.S. Patent No. 4,536,518; U.S. Patent No. 5,248,699; WO 00/32551; and WO 01/32601.

The term "sertraline hydrochloride" includes all polymorphic forms, amorphous form, solvates, hydrates, or mixtures thereof.

The solvent may be removed from the solution by a technique which includes, for example, filtration, filtration under vacuum, decantation and centrifugation.

In one aspect the solution may be cooled before filtration to obtain better yields of the stable Form II of sertraline hydrochloride. It may be cooled from about 100°C to about -50°C, for example from about 50°C to about -10°C.

In another aspect, the solution may be seeded with crystals of Form II resulting in the precipitation of the Form II of sertraline hydrochloride and removing the solvent there from by filtration, filtration under vacuum, decantation or centrifugation.

The product obtained may be further or additionally dried to achieve the desired moisture values. For example, the product may be further or additionally dried in a tray drier, dried under vacuum and/or in a Fluid Bed Dryer.

The inventors have developed a process for the preparation of the storage stable Form II of sertraline hydrochloride. The process includes washing the Form II of sertraline hydrochloride with a dilute solution of an antioxidant in a solvent; and recovering the storage stable Form II of sertraline hydrochloride by the removal of the solvent.

In general, the Form II of sertraline hydrochloride in dry solid state may be washed. Alternatively, wet solid Form II of sertraline hydrochloride obtained from the process to prepare Form II sertraline hydrochloride may directly be washed without drying it.

In general, the washing involves making a slurry of Form II sertraline hydrochloride in a dilute solution of an antioxidant in a suitable solvent.

The term "solvent" includes any solvent or solvent mixture in which Form II sertraline hydrochloride is insoluble or very slightly soluble or sparingly soluble, including, for example methyl isobutyl ketone, N,N-dimethylacetamide, N,N-dimethylformamide, or mixtures thereof.

The antioxidant may include conventional antioxidants used in the pharmaceutical industry, for example butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), hydroquinone, propyl gallate, ascorbyl palmitate, octyl gallate, dodecyl gallate, tocopherols, sodium or calcium ascorbate, tert-butylated hydroquinone, and the like.

The resulting storage stable Form II of sertraline hydrochloride does not get discolored during its entire shelf life. It may be formulated into ordinary dosage forms such as, for example, tablets, capsules, pills, solutions, etc. In these cases, the medicaments can be prepared by conventional methods with conventional pharmaceutical excipients.

The compositions include dosage forms suitable for oral, buccal, rectal, and parenteral (including subcutaneous, intramuscular, and ophthalmic) administration. The oral dosage forms may include solid dosage forms, like powder, tablets, capsules, suppositories, sachets, troches and lozenges as well as liquid suspensions, emulsions, pastes and elixirs. Parenteral dosage forms may include intravenous infusions, sterile solutions for intramuscular, subcutaneous or intravenous administration, dry powders to be reconstituted with sterile water for parenteral administration, and the like.

The storage stable Form II of sertraline hydrochloride can be administered for the treatment of anxiety-related disorders, symptoms associated with premenstrual disorders and late luteal phase dysphoric disorders, in a warm-blooded animal.

For the purpose of this disclosure, a warm-blooded animal is a member of the animal kingdom possessed of a homeostatic mechanism and includes mammals and birds.

The present invention is further illustrated by the following examples which are provided merely to be exemplary of the invention and do not limit the scope of the invention. Certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

Example 1: Preparation of stable sertraline hydrochloride Form II

Sertraline hydrochloride (1.0 g) was suspended in methyl isobutyl ketone (20 ml) at room temperature and the reaction mixture was heated slowly to 80°C. The reaction mixture was stirred at 80°C for about 2 hours and then cooled to room temperature. The product was filtered and dried under vacuum.

The XRD pattern as per Figure 1 showed it to be a Form II of sertraline hydrochloride.

Example 2: Preparation of stable sertraline hydrochloride Form II

Sertraline hydrochloride (1.0 g) was dissolved in dimethylacetamide (20 ml) at room temperature and the reaction mixture was heated slowly to 80°C. The reaction mixture was stirred at 80°C for about 2 hours and then cooled to –5°C. The product was filtered and dried under vacuum.

The XRD pattern as per Figure 1 showed it to be a Form II of sertraline hydrochloride.

Example 3: Preparation of storage stable sertraline hydrochloride Form II

Sertraline hydrochloride (1.0 g) was suspended in methyl isobutyl ketone (20 ml) at room temperature and the reaction mixture was heated slowly to 80°C. The reaction mixture was stirred at 80°C for about 2 hours and then cooled to room temperature. The product was filtered and washed with a solution of butylated hydroxyanisole (0.1 g in 2 ml methyl isobutyl ketone) and then dried under vacuum.

The XRD pattern as per Figure 1 showed it to be a Form II of sertraline hydrochloride.

A measure of discoloration can be obtained by measuring UV absorbance. The UV absorbance of Example 3 (5% solution in methanol at about 380nm) was found to be 0.069 after storage for one year at 30°C and 55% humidity.

We Claim:

1. Storage stable Form II of sertraline hydrochloride, wherein after one year of storage at 30°C and 55% humidity the UV absorbance of a 5% solution of sertraline hydrochloride in methanol at about 380 nm does not exceed 0.1.

2. The storage stable Form II of sertraline hydrochloride of claim 1, wherein the sertraline hydrochloride has the X-ray diffraction pattern of Figure 1.

3. A pharmaceutical composition comprising:

a therapeutically effective amount of a storage stable Form II of sertraline hydrochloride; and

one or more pharmaceutically acceptable carriers, excipients or diluents.

4. A process for the preparation of stable Form II of sertraline hydrochloride, the process comprising:

obtaining a suspension of sertraline hydrochloride in a solvent comprising one or more of methyl isobutyl ketone, N,N-dimethylacetamide or N,N-dimethylformamide; heating the suspension; and

recovering the stable Form II of sertraline hydrochloride by the removal of the solvent.

5. The process of claim 4, wherein removing the solvent comprises one or more of filtration, filtration under vacuum, decantation, and centrifugation.

6. The process of claim 4 further comprising cooling before removing the solvent.

7. The process of claim 4, further comprising additional drying of the product obtained

8. The process of claim 4, further comprising forming the product obtained into a finished dosage form.

9. A process for the preparation of storage stable Form II of sertraline hydrochloride, the process comprising:

washing Form II of sertraline hydrochloride with a dilute solution of an antioxidant in a solvent; and

recovering the storage stable Form II of sertraline hydrochloride by the removal of the solvent.

10. The process of claim 9, wherein the antioxidant comprises one or more of butylated hydroxyanisole, butylated hydroxytoluene, hydroquinone, propyl gallate, ascorbyl palmitate, octyl gallate, dodecyl gallate, tocopherols, sodium ascorbate, calcium ascorbate, and tert-butylated hydroquinone.

11. The process of claim 9, wherein the solvent comprises one or more of methyl isobutyl ketone, N,N-dimethylacetamide, and N,N-dimethylformamide.

12. The process of claim 9, wherein removing the solvent comprises one or more of filtration, filtration under vacuum, decantation, and centrifugation..

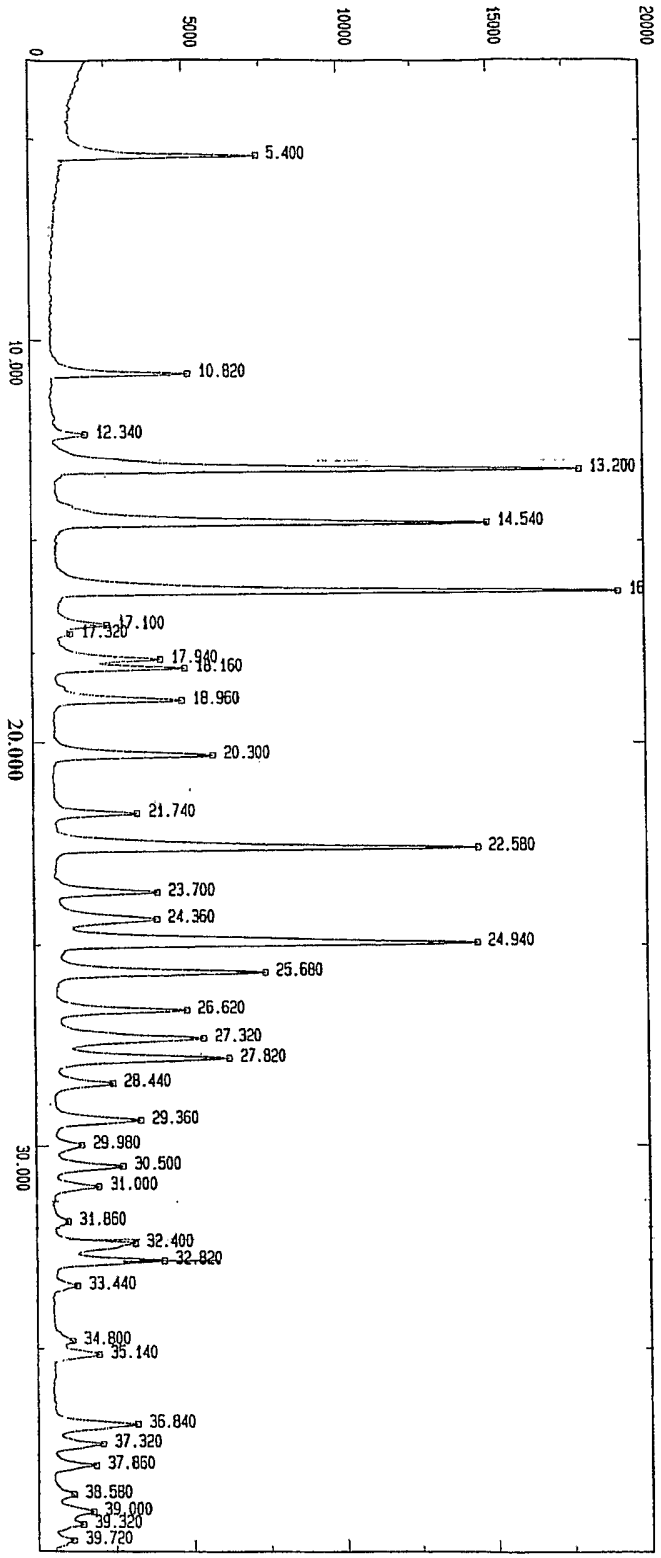
13. The process of claim 9, further comprising drying of the product obtained.

14. The process of claim 9, further comprising forming the product obtained into a finished dosage form.

15. The process of claim 9, wherein the Form II sertraline hydrochloride has the X-ray diffraction pattern of Figure 1.

16. A method of treating anxiety-related disorders, symptoms associated with premenstrual disorders and late luteal phase dysphoric disorder in a warm-blooded animal, the method comprising administering a pharmaceutical composition that includes a storage stable Form II of sertraline hydrochloride.

FIGURE 1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26.620
27.320
27.820
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32.820
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35.140
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37.320
37.860
38.580
39.000
39.320
39.720

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB2005/000612

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C211/42 A61K31/135 A61P25/22

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 C07C 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, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 495 721 B1 (EDUARD SCHWARTZ ET AL.) 17 December 2002 (2002-12-17) cited in the application column 4, line 38 - line 54; claim 9; examples 6,8,12	1-16
X	WO 03/093217 A (TEVA PHARMACEUTICAL INDUSTRIES LTD; TEVA PHARMACEUTICALS USA, INC; BOR) 13 November 2003 (2003-11-13) cited in the application claims 25-28; figure 1; examples 1-4	1-3,16

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in 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 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

"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 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
24 June 2005	04/07/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Zervas, B

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2005/000612

Box 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. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 16 is 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)

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 an additional fee, this Authority did not invite payment of any additional fee.

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.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern[redacted]al Application No
PCT/IB2005/000612

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