Title: A SPACER FOR INERTIAL REMOVAL OF THE NON-RESPIRABLE FRACTION OF MEDICINAL AEROSOLS

Abstract: The invention comprises a medicinal inhaler spacer (100, 200) OR actuator comprising a chamber (130, 230) having a proximal end (132, 232) closed by a proximal plate (140, 240), a tangentially aligned inlet (110, 210) on the proximal end (132, 232) of the chamber (130, 230), a tapered distal end (134, 234), and an outlet (120, 220) extending through the proximal plate (140, 240) into and communicating with the chamber (130, 230). Spacers (100, 200) of the present invention may be used to increase the respirable fraction of a medicinal aerosol inhaler. The invention also comprises medicinal aerosol inhalers and methods of delivering drug to the lung of a mammal employing these spacers.
SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

**Declarations under Rule 4.17:**

— as to applicant’s entitlement to apply for and be granted a patent (Rule 4.17(iii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SI, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPPO patent (GH, GM, KE, LS, MW, MZ, SD, SI, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

— as to the applicant’s entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations

**Published:**

— with international search report

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.
A SPACER FOR INERTIAL REMOVAL OF THE NON-RESPIRABLE FRACTION OF MEDICINAL AEROSOLS

The present invention relates to a spacer or actuator for inertial removal of the non-respirable fraction of medicinal aerosols. The present invention also relates to medicinal aerosol inhalers employing a spacer or actuator for inertial removal of the non-respirable fraction of the medicinal aerosol.

Background of the Invention

Medicinal aerosol inhalers are commonly used to treat a number of medical conditions. It is well known that medicinal aerosols, whether they originate from a metered dose inhaler (MDI), dry powder inhaler (DPI), or a nebulizer, consist of a distribution of particles with varying sizes. For a particle to be considered respirable, meaning it will have a high probability of depositing in the lung upon inhalation, it should have an aerodynamic diameter of less than about 4.7 micrometers. Larger, non-respirable particles can be deposited in a patient's mouth and/or throat, which can lead to undesirable effects. Mouth and/or throat deposition can lead to a displeasing taste, as well as potentially causing side effects related to drug dosing by a non-inhalation route. It is thus desirable to provide an aerosol dose to a patient that consists primarily or entirely of respirable particles, that is, a dose that has a high respirable fraction.

In the development and manufacture of medicinal aerosol formulations, however, there are many factors that need to be taken into consideration, for example, drug solubility and/or stability in a suitable medium, the ability to prepare small particles, and the necessary dosage. Oftentimes, it is not possible or practical to make a medicinal aerosol where all of the particles delivered by a conventional device are respirable. A number of efforts have been made to develop spacers or actuators that provide either a longer or more tortuous path between the formulation reservoir and the patient to either remove non-respirable material or disperse larger aggregates into smaller particles. Medicinal inhaler spacers have incorporated additional distance and/or various configurations of baffles as a method for removal of non-respirable particles (U.S. 5,676,130, Gupte et al.; WO 92/04066, Bisgaard). Rotational motion of an airflow stream has also been proposed (U.S. 6,073,629, Hardy et al.) and in particular airflows described
as cyclonic wherein the airflow travels from inlet to outlet by spiraling in one direction along a central axis (U.S. 5,476,093, Lankinen; WO 01/00262, Hamer et al.).

Summary of the Invention

It has now been found that certain types of cyclone spacers can be a highly effective, compact, and robust way to increase the respirable fraction of a medicinal aerosol. Non-respirable particles that enter the inlet of the spacer are preferentially removed from the airstream through inertial deposition onto the interior surfaces of the spacer, thereby increasing the respirable fraction of the medicinal aerosol.

The present invention provides a medicinal inhaler spacer comprising a chamber having a proximal end closed by a proximal plate, a tangentially aligned inlet on the proximal end of the chamber, a tapered distal end, and an outlet extending through the proximal plate into and communicating with the chamber.

The present invention further comprises a medicinal aerosol inhaler comprising a medicinal inhaler spacer of the invention where the inlet of the spacer is in fluid communication with an aerosol generation system and the outlet of the spacer is in fluid communication with a mouthpiece.

The invention also further comprises a method of delivering a medicinal aerosol to the lung of a mammal using this medicinal inhaler.

In another embodiment the invention comprises a medicinal aerosol inhaler comprising an aerosol generation system, a cyclone chamber, and a mouthpiece, wherein the inlet of the cyclone chamber is in fluid communication with the aerosol generation system and the outlet of the cyclone chamber is in fluid communication with the mouthpiece. The cyclone chamber has a tapered distal end and an outlet extending through the proximal end.

Brief Description of the Drawings

Preferred embodiments of the invention will now be described in greater detail below with reference to the attached drawings, wherein:

Fig. 1 is a perspective view of a medicinal inhaler spacer.

Fig. 2 is a perspective view of a medicinal inhaler spacer.

Fig. 3 is a perspective view of a medicinal inhaler spacer with a schematic diagram of an airflow pattern.
Detailed Description of the Invention

FIG. 1 shows a perspective view of a preferred embodiment of a medicinal inhaler spacer 100 of the present invention.

The spacer 100 comprises an inlet 110 that is located tangentially on a circumferential outer surface of a chamber 130. The inlet 110 adjoins the chamber 130 along the proximal end 132 of the chamber. As shown in FIG. 1 the inlet 110 is cylindrical, but it may also be rectangular, oval, tubular, or any like shape that will provide for an opening into the chamber 130 through which air may flow.

The chamber 130 preferably has rounded sides and the proximal end 132 of the chamber is more preferably in the shape of a cylinder that defines a central axis 150. The chamber 130 has a taper over its distal end 134, preferably in the form of a distally converging cylinder. As shown in FIG. 1 this distally converging cylinder may be closed at its distal end. Alternatively, as shown in FIG. 2, the distal end 234 of the chamber 230 tapers towards a point making the distal end of the chamber conical, as opposed to the truncated conical distal end shown in FIG. 1.

The proximal end 132 of the chamber is capped with a proximal plate 140. As shown in FIG. 1 the proximal plate 140 may be flat, but the intended function is to cap the proximal end of the chamber and so, for example, it may also be rounded or curved in shape. The proximal plate 140 may be a separate piece that is attached to the chamber 130 or it may be made integral with the chamber 130.

An outlet 120 extends through the proximal plate 140 and communicates with the interior of the chamber 130. In a preferred embodiment the outlet 120 extends into the chamber 130 to a level below the bottom of the inlet 110 opening. In another preferred embodiment the ratio of the distance of the outlet extension into the chamber to the length of the proximal end 132 of the chamber is between about 0.5 and 2.0, and more preferably between 0.75 and 1.5. As shown the outlet 120 is cylindrical in shape, but it may also be oval, tubular, rectangular, or any like shape that will provide for an opening into the chamber 130 through which air may flow.

The central axis 150 preferably passes through the outlet 120 where the outlet 120 passes through the proximal plate 140. In a more preferred embodiment the outlet 120 defines an outlet axis that is substantially coaxial with the central axis 150, and is most preferably coaxial with the central axis 150, as shown in FIG. 1.
In use, an airstream flows into the inlet, passes through the chamber, and flows out of the outlet. The airflow passing through the chamber preferably undergoes rotational flow around the central axis 150, and more preferably undergoes rotational flow of more than 360 degrees around the central axis 150. The extension of the outlet into the chamber inhibits a direct linear airflow from inlet to outlet and aids in allowing the airstream to undergo multiple rotations, which leads to greater efficiency of removal of non-respirable particles. Although non-limiting to the scope of the invention, it is theorized that in this embodiment the airflow 160 enters the inlet 110, simultaneously rotates around the central axis 150 and translates distally in the chamber 130, until becoming constricted by the distal taper. After becoming constricted, the airflow 160 is then redirected along the central axis 150 and out of the outlet 120. The combination of the distal rotational motion along with the reversal of direction of the airflow caused by the constricting taper leads to efficient removal of non-respirable particles. This airflow pattern is shown schematically in FIG. 3.

The inlet 110 is defined on a circumferential outer surface of the chamber adjoining the proximal end 132 of the chamber, such that it is tangentially aligned with the proximal end 132 of the chamber. More preferably, the inlet 110 adjoins the proximal end 132 of the chamber where the proximal end 132 connects to the proximal plate 140. It should be understood that the inlet is preferably adapted to direct an inlet airflow in a substantially circumferential direction in the chamber and therefore allow for the creation of a rotational airflow and that this would include minor modifications in the position of the inlet in relation to the chamber.

In a preferred embodiment a particle collecting means, not shown, may be provided within or adjacent to the distal end of the chamber. Particles may, for example, be collected in the distal end of the chamber by adhesive means, such as a tape, glue, gel, or a high viscosity liquid. Particles may also be collected in or adjacent to the distal end of the chamber by mechanical means, such as one or more small openings in the distal part of the chamber 130 that allow particles to easily fall through the openings and into a collection reservoir adjacent to the distal end, the openings being sized so as to make it difficult for particles to pass from the collection reservoir back into the chamber. Collection of particles at the base of or adjacent to the distal end of the chamber allows
repeated use of the spacer without need for cleaning or emptying, and prevents or limits re-entrainment of non-respirable particles into airflows generated by subsequent dosing.

In use, an airflow comprising an aerosol that passes through the inlet 110 into the chamber 130 will undergo centrifugal forces that can lead to solid or liquid particles of the aerosol impacting the surfaces of the chamber 130. In particular, larger particles have more inertia and a greater tendency to deviate from the airflow and are therefore more likely to impact on the chamber surfaces. It should be understood that one skilled in the art will appreciate that size and shape of the inlet 110, outlet 120, and chamber 130 can be adjusted to change the likelihood that particles of a given size will impact upon the chamber surface. In particular, the spacer can be sized such that for given parameters of airflow velocity and particle density, a "cut-off" size can be estimated. Particles larger than the "cut-off" size will be expected to impact the chamber surface and particles smaller than the "cut-off" size will be expected to pass through the chamber 130 and leave the outlet 110. Although theoretically scalable to any size, it will be appreciated that the height and width of the spacer should be of a size that is convenient for a patient to handle, and these dimensions will preferably be between 1 and 20 cm, and more preferably between 2 and 5 cm.

The present invention further comprises a medicinal aerosol inhaler comprising a medicinal inhaler spacer of the invention where the inlet of the spacer is in fluid communication with an aerosol generation system and the outlet of the spacer is in fluid communication with a mouthpiece. In a preferred embodiment the aerosol generation system comprises a pressurized aerosol canister, a dry powder generation system, or a nebulization system.

**Examples**

**Particle Collection Testing**

Particle collection characteristics were tested using a Model 160 Marple Miller Impactor (MMI) coupled with a USP throat (United States Pharmacopeia, USP 24 <601> Aerosols, Metered Dose Inhalers, and Dry Powder Inhalers, Figure 4) and a volumetric flow rate of 60 L/min. Aerosol generation was provided by a Turbohaler® DPI (manufactured by Astra Pharmaceuticals), a commercially available dry powder delivery device. For all testing, the stage cups of the MMI were coated with a surfactant to prevent particle bounce and re-entrainment.
The outlet of the dry powder delivery device was connected to the inlet of the spacer and the outlet of the spacer was connected to the USP throat.

The amount of drug deposited in the spacers and in each individual component of the MMI apparatus was determined by rinsing the component with a measured volume of an appropriate solvent and subjecting the rinsate to standard HPLC analysis to determine concentration. Data that was returned from HPLC analysis was analyzed to determine the average amount of drug collected per delivered dose. The resulting mass values were then normalized to the fraction of delivered dose collected in each individual component of the testing assembly.

Using the individual component values, the amount of throat deposition, the respirable mass, and the respirable fraction was calculated for each device. Throat deposition is defined as the percent of the total delivered dose that deposits in the USP throat. Respirable mass is defined as the percentage of the total delivered dose that is measured to be smaller than the respirable limit of 4.7 micrometers in aerodynamic diameter. Respirable fraction is defined as the percentage of a delivered dose that reaches the entry of the throat and is smaller than the respirable limit. When using the MMI, respirable mass is collected in cups 2, 3, 4, and on the filter. Mass collected in the throat and cups 0 and 1 are considered non-respirable.

Example 1
A spacer of the general design depicted in FIG. 2 was constructed with the following dimensions: inlet port of diameter 1.0 cm; chamber inside diameter 4.0 cm; nontapered end of chamber height 2.4 cm; tapered end of chamber height 4.8 cm with a taper angle of 22.6 degrees; outlet port diameter 2.0 cm with an extension of 2.0 cm into the chamber.

Particle collection characteristics were determined by attaching the spacer to a Turbohaler® and are shown in Table 1. The particle collection characteristics for a Turbohaler® connected directly to the USP throat are shown for comparison.

Example 2
A spacer of the general design depicted in FIG. 2 was constructed with the following dimensions: inlet port of diameter 0.75 cm; chamber inside diameter 3.0 cm;
non-tapered end of chamber height 1.8 cm; tapered end of chamber height 3.6 cm with a taper angle of 22.6 degrees; outlet port diameter 1.5 cm with an extension of 1.5 cm into the chamber.

Particle collection characteristics were determined by attaching the spacer to a Turbohaler® and are shown in Table 1. The particle collection characteristics for a Turbohaler® connected directly to the USP throat are shown for comparison.

Example 3
A spacer of the general design depicted in FIG. 2 was constructed with the following dimensions: inlet port of diameter 0.5 cm; chamber inside diameter 2.0 cm; non-tapered end of chamber height 1.2 cm; tapered end of chamber height 2.4 cm with a taper angle of 22.6 degrees; outlet port diameter 1.0 cm with an extension of 1.0 cm into the chamber.

Particle collection characteristics were determined by attaching the spacer to a Turbohaler® and are shown in Table 1. The particle collection characteristics for a Turbohaler® connected directly to the USP throat are shown for comparison.

<table>
<thead>
<tr>
<th>Table 1</th>
</tr>
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<tbody>
<tr>
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<tr>
<td>Throat Deposition (% of total)</td>
</tr>
<tr>
<td>Respirable Mass (% of total)</td>
</tr>
<tr>
<td>Respirable Fraction (% of total inhaled)</td>
</tr>
</tbody>
</table>

Example 4
A spacer of the general design depicted in FIG. 1 was constructed with the following dimensions: inlet port of diameter 1.02 cm; chamber inside diameter 5.08 cm; non-tapered end of chamber height 1.27 cm; tapered end of chamber height 1.27 cm with a taper angle of 56.3 degrees; cyclone body base diameter of 1.27 cm; outlet port diameter 2.03 cm with an extension of 1.78 cm into the chamber.
Particle collection characteristics were determined by attaching the spacer to a Turbohaler® and are shown in Table 2. The particle collection characteristics for a Turbohaler® connected directly to the USP throat are shown for comparison.

**Example 5**

A spacer of the general design depicted in FIG. 1 was constructed with the following dimensions: inlet port of diameter 1.02 cm; chamber inside diameter 5.08 cm; non-tapered end of chamber height 1.27 cm; tapered end of chamber height 1.27 cm with a taper angle of 56.3 degrees; cyclone body base diameter of 1.27 cm; outlet port diameter 2.03 cm with an extension of 1.27 cm into the chamber.

Particle collection characteristics were determined by attaching the spacer to a Turbohaler® and are shown in Table 2. The particle collection characteristics for a Turbohaler® connected directly to the USP throat are shown for comparison.

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<tr>
<th></th>
<th>Turbohaler®</th>
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<th>Example 5</th>
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<tr>
<td>Throat Deposition</td>
<td>53.4</td>
<td>0.1</td>
<td>0.2</td>
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<tr>
<td>(% of total)</td>
<td></td>
<td></td>
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<tr>
<td>Respirable Mass</td>
<td>39.5</td>
<td>25.8</td>
<td>23.5</td>
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<tr>
<td>(% of total)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respirable Fraction</td>
<td>35.0</td>
<td>99.6</td>
<td>99.0</td>
</tr>
<tr>
<td>(% of total inhaled)</td>
<td></td>
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</tbody>
</table>
We claim:

1. A medicinal inhaler spacer comprising:
   a chamber having a proximal end closed by a proximal plate, a tangentially aligned
   inlet on the proximal end of the chamber, a tapered distal end, and an outlet
   extending through the proximal plate into and communicating with the chamber.

2. The spacer of claim 1, wherein the chamber has only one inlet and one outlet.

3. The spacer of claim 1, wherein the proximal end of the chamber is cylindrical.

4. The spacer of claim 1, further comprising a particle collecting means within or adjacent
   to the distal end of the chamber.

5. The spacer of claim 1, wherein the outlet extends into the chamber to a level below the
   bottom of the inlet opening.

6. The spacer of claim 5, wherein the tapered distal end is formed as a converging
   cylinder.

7. The spacer of claim 6, wherein the proximal end of the chamber is cylindrical.

8. The spacer of claim 7, wherein the outlet is positioned such that the central axis defined
   by the cylindrical proximal end passes through the outlet.

9. The spacer of claim 8, adapted to provide a rotational flow around the central axis of at
   least a portion of an airstream passing from the inlet through the chamber to the
   outlet.

10. The spacer of claim 9, adapted to provide a rotational flow of more than 360 degrees

11. A medicinal aerosol inhaler comprising:
    an aerosol generation system;
    the medicinal inhaler spacer of claim 1; and
    a mouthpiece,

    wherein the inlet of the spacer is in fluid communication with the aerosol generation
    system and the outlet of the spacer is in fluid communication with the mouthpiece.

12. A medicinal inhaler of claim 11, wherein the aerosol generation system comprises a

13. A medicinal inhaler of claim 11, wherein the aerosol generation system comprises a
    dry powder generation system.
14. A medicinal inhaler of claim 11, wherein the aerosol generation system comprises a nebulization system.

15. A method of delivering a medicinal aerosol to the lung of a mammal comprising administering an aerosol formulation to the mammal using the medicinal inhaler of claim 11.

16. A method of delivering a medicinal aerosol to the lung of a mammal according to claim 15 wherein the respirable fraction of the medicinal aerosol delivered to the lung is greater than the respirable fraction of medicinal aerosol that would be delivered to the lung in the absence of the medicinal inhaler spacer.

17. A medicinal inhaler spacer comprising:
   a cylindrical chamber having a proximal end closed by a proximal plate, a tangentially aligned inlet on the proximal end of the chamber, a tapered distal end formed as a converging cylinder, and an outlet extending through the proximal plate into and communicating with the chamber; and a mouthpiece,
   wherein the inlet of the spacer is in fluid communication with the aerosol generation system and the outlet of the spacer is in fluid communication with the mouthpiece.

18. A medicinal aerosol inhaler comprising:
   an aerosol generation system;
   a cyclone chamber with a tapered distal end and an outlet extending through the proximal end; and a mouthpiece,
   wherein the inlet of the cyclone chamber is in fluid communication with the aerosol generation system and the outlet of the cyclone chamber is in fluid communication with the mouthpiece.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61M15/00

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 A61M

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 forms used)

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<th>Relevant to claim No.</th>
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<td>US 5 476 093 A (LANKINEN TAPIO) 19 December 1995 (1995-12-19) cited in the application abstract; figures column 4, line 15-35 column 5, line 53 -column 6, line 1 column 6, line 41-63 column 7, line 56-61 column 8, line 3 -column 9, line 17</td>
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<td>EP 0 682 955 A (RITZAU PARI WERK GMBH PAUL) 22 November 1995 (1995-11-22) abstract; figures column 4, line 9-67 column 6, line 1-53</td>
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Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Category 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 (to be 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
* Y' 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
* X' document member of the same patent family

Date of the actual completion of the international search 15 July 2003

Date of mailing of the international search report 06/08/2003

Name and mailing address of the ISA European Patent Office, P B, 5818 Patentilaan 2 NL - 2280 HU Rijswijk Tel. (+31-70) 340-2049, Te 31 651 epo nl, Fax. (+31-70) 340-3016

Authorized officer Lager, J

Form PCT/ISA/210 (second sheet) (July 1992)
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<td>A</td>
<td>WO 01 00262 A (CAMBRIDGE CONSULTANTS; EASON STEPHEN WILLIAM (GB); HARMER QUENTIN) 4 January 2001 (2001-01-04) cited in the application abstract; figures page 3, line 19 -page 4, line 8 page 6, line 36 -page 7, line 30</td>
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<td>A</td>
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Form PCT/RM/210 (continuation of second sheet) (July 1992)
INTERNATIONAL SEARCH REPORT

Box I Observations where certain claims were found unsearchable (Continuation of item 1 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.: 15-16
   because they relate to subject matter not required to be searched by this Authority, namely:
   Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

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 II Observations where unity of invention is lacking (Continuation of item 2 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.

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