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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

— *with sequence listing part of description (Rule 5.2(a))*

(88) Date of publication of the international search report:
23 June 2011

(54) Title: ALBUMIN VARIANTS

(57) Abstract: The present invention relates to variants of a parent albumin having altered plasma half-life compared with the parent albumin. The present invention also relates to fusion polypeptides and conjugates comprising said variant albumin.

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2010/066572

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07K14/765
ADD.

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)
C07K

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, BIOSIS, Sequence Search, EMBASE, WPI 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 2006/051859 A1 (FU YAN [US] ET AL) 9 March 2006 (2006-03-09) abstract; sequence 12 paragraphs [0024], [0025], [0039], [0043], [0047], [0060], [0069], [0070] -----	2,3,5, 8-12,16, 18
A	MINCHIOTTI LORENZO ET AL: "Mutations and polymorphisms of the gene of the major human blood protein, serum albumin", HUMAN MUTATION, vol. 29, no. 8, 1 August 2008 (2008-08-01) , pages 1007-1016, XP002520020, JOHN WILEY & SONS, INC, US ISSN: 1059-7794, DOI: 10.1002/HUMU.20754 abstract figure 1 -----	1-3,5, 7-12, 16-18
	-/--	

[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 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
25 March 2011	03/05/2011

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, Fax: (+31-70) 340-3016	Montrone, Marco

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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 95/23857 A1 (DELTA BIOTECHNOLOGY LTD [GB]; KERRY WILLIAMS SEAN MARTIN [GB]; GILBERT) 8 September 1995 (1995-09-08) abstract page 6, line 23 - page 7, line 12	1-3,5, 7-12, 16-18
A	SHEFFIELD W P ET AL: "Modulation of clearance of recombinant serum albumin by either glycosylation or truncation.", THROMBOSIS RESEARCH, vol. 99, no. 6, 15 September 2000 (2000-09-15), pages 613-621, XP002616651, ISSN: 0049-3848 abstract	1-3,5, 7-12, 16-18
A	IWAO Y ET AL: "Oxidation of Arg-410 promotes the elimination of human serum albumin", BIOCHIMICA ET BIOPHYSICA ACTA (BBA) - PROTEINS & PROTEOMICS, ELSEVIER, vol. 1764, no. 4, 1 April 2006 (2006-04-01), pages 743-749, XP025123234, ISSN: 1570-9639, DOI: 10.1016/J.BBAPAP.2006.01.011 [retrieved on 2006-04-01] abstract	1-3,5, 7-12, 16-18
A	ISHIMA YU ET AL: "S-Nitrosylation of human variant albumin Liprizzi (R410C) confers potent antibacterial and cytoprotective properties", JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, vol. 320, no. 3, 1 March 2007 (2007-03-01) , pages 969-977, XP002510092, AMERICAN SOCIETY FOR PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, US ISSN: 0022-3565, DOI: 10.1124/JPET.106.114959 abstract	1-3,5, 7-12, 16-18
X	WO 2007/021494 A2 (HUMAN GENOME SCIENCES INC [US]; ROSEN CRAIG [US]; BELL ADAM [US]; MOOR) 22 February 2007 (2007-02-22) abstract; sequences 496,519 page 24 - page 25; table 2 page 30, paragraph 79-81 page 39, paragraph 149 - page 40, paragraph 157 page 56, paragraph 274	2-4,6, 8-12,16, 18

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE UniProt [Online] 24 July 2007 (2007-07-24), "SubName: Full=Uncharacterized protein;", XP002629970, retrieved from EBI accession no. UNIPROT:A6NBZ8 Database accession no. A6NBZ8 abstract; compound -----	2-4,6,8, 9
X	WO 2004/011499 A1 (UNIV EDINBURGH [GB]; BEREZENKO STEPHEN [GB]; SADLER PETER JOHN [GB]; S) 5 February 2004 (2004-02-05) abstract; table 1 -----	2-4,6,8, 9
Y	IWAO ET AL: "Changes of net charge and alpha-helical content affect the pharmacokinetic properties of human serum albumin", BIOCHIMICA ET BIOPHYSICA ACTA (BBA) - PROTEINS & PROTEOMICS, vol. 1774, no. 12, 1 December 2007 (2007-12-01), pages 1582-1590, XP022385158, ELSEVIER, NETHERLANDS ISSN: 1570-9639, DOI: 10.1016/J.BBAPAP.2007.09.001 abstract figures 1,2 table 2 page 1587, column 2, paragraph 2 - page 1589, column 2, paragraph 2 -----	1-12, 16-18
Y	KENANOVA V. ET AL: "HSA Domain III as a protein scaffold with defined serum pharmacokinetics", THE JOURNAL OF NUCLEAR MEDICINE , vol. 50, no. Suppl. 2 15 May 2009 (2009-05-15), XP002629971, Retrieved from the Internet: URL:http://jnumedmtg.snmjournals.org/cgi/c ontent/meeting_abstract/50/2_MeetingAbstra cts/1582 [retrieved on 2011-03-22] abstract ----- -/--	1-12, 16-18

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ANDERSEN JAN T ET AL: "Ligand binding and antigenic properties of a human neonatal Fc receptor with mutation of two unpaired cysteine residues", FEBS JOURNAL, vol. 275, no. 16, August 2008 (2008-08), pages 4097-4110, XP002629972, ISSN: 1742-464X abstract	1-12, 16-18
Y	CHAUDHURY CHAITY ET AL: "Albumin binding to FcRn: distinct from the FcRn-IgG interaction.", BIOCHEMISTRY, vol. 45, no. 15, 18 April 2006 (2006-04-18), pages 4983-4990, XP002629973, ISSN: 0006-2960 abstract page 4983, column 1, paragraph 2 - column 2, paragraph 1 page 4988, column 2, paragraph 2 - page 4989, paragraph 5	1-12, 16-18
Y	ANDERSEN JAN TERJE ET AL: "The versatile MHC class I-related FcRn protects IgG and albumin from degradation: implications for development of new diagnostics and therapeutics.", DRUG METABOLISM AND PHARMACOKINETICS, vol. 24, no. 4, 10 September 2009 (2009-09-10), pages 318-332, XP002629974, ISSN: 1880-0920 abstract page 318, column 1, paragraph 1 - column 2, paragraph 2 page 320, column 2, paragraph 3 page 321, column 1, paragraph 3 page 323, column 1, paragraph 4 page 326, column 1, paragraph 1 - column 2, paragraph 1	1-12, 16-18

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KRAGH-HANSEN U ET AL: "Effect of genetic variation on the thermal stability of human serum albumin", BIOCHIMICA ET BIOPHYSICA ACTA (BBA) - PROTEINS & PROTEOMICS, vol. 1747, no. 1, 14 February 2005 (2005-02-14), pages 81-88, XP004725430, ELSEVIER, NETHERLANDS ISSN: 1570-9639, DOI: 10.1016/J.BBAPAP.2004.09.025 abstract page 83, column 2, paragraph 2; tables 1,2	2-4,8,9
Y	OLAFSEN TOVE ET AL: "Tunable pharmacokinetics: modifying the in vivo half-life of antibodies by directed mutagenesis of the Fc fragment", NATURE PROTOCOLS, NATURE PUBLISHING GROUP, GB, vol. 1, no. 4, 1 January 2006 (2006-01-01) , page 2048, XP001537674, ISSN: 1750-2799, DOI: DOI:10.1038/NPROT.2006.322 abstract page 2048, column 1, paragraph 1 - page 2049, column 1, paragraph 1	1-12, 16-18
Y,P	KENANOVA VANIA E ET AL: "Tuning the serum persistence of human serum albumin domain III: diabody fusion proteins", PROTEIN ENGINEERING DESIGN & SELECTION, vol. 23, no. 10, October 2010 (2010-10), pages 789-798, XP002629975, ISSN: 1741-0126 abstract	1-12, 16-18
Y	ANDERSEN JAN TERJE ET AL: "A receptor-mediated mechanism to support clinical observation of altered albumin variants.", CLINICAL CHEMISTRY, vol. 53, no. 12, December 2007 (2007-12), page 2216, XP002629976, ISSN: 0009-9147 abstract	1-12, 16-18

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CARLSON J ET AL: "ALLOALBUMINEMIA IN SWEDEN STRUCTURAL STUDY AND PHENOTYPIC DISTRIBUTION OF NINE ALBUMIN VARIANTS", PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, vol. 89, no. 17, 1992, pages 8225-8229, XP002629977, ISSN: 0027-8424 abstract page 8227; table 1 page 8228, column 1, paragraph 4 -----	1-12, 16-18

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2010/066572

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2006051859 A1	09-03-2006	NONE	
WO 9523857 A1	08-09-1995	AT 260338 T	15-03-2004
		AU 683728 B2	20-11-1997
		AU 1818395 A	18-09-1995
		CA 2183241 A1	08-09-1995
		DE 69532603 D1	01-04-2004
		DE 69532603 T2	05-01-2005
		DK 749478 T3	28-06-2004
		EP 0749478 A1	27-12-1996
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		GB 2301365 A	04-12-1996
		JP 3795073 B2	12-07-2006
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		PT 749478 E	30-07-2004
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		BR PI0614761 A2	19-05-2009
		CA 2618476 A1	22-02-2007
		EC SP088262 A	30-05-2008
		EP 1924596 A2	28-05-2008
		JP 2009504157 T	05-02-2009
		KR 20080071119 A	01-08-2008
WO 2004011499 A1	05-02-2004	AU 2003248949 A1	16-02-2004
		CA 2493347 A1	05-02-2004
		CN 1684980 A	19-10-2005
		EP 1525222 A1	27-04-2005
		JP 2006515156 T	25-05-2006
		NZ 537998 A	30-06-2008
		US 2007185315 A1	09-08-2007
		ZA 200500888 A	22-02-2006

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2010/066572

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

2. ☒ Claims Nos.: 13-15
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:

see FURTHER INFORMATION sheet PCT/ISA/210

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:

see additional sheet

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 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.:

1-12, 16-18

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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-3, 5-12, 16-18(all partially)

A method for preparing a variant of albumin, fragments thereof or fusion polypeptide comprising said variant albumin or fragment thereof, comprising following steps:
a. Providing a nucleic acid encoding a parent albumin having at least 80% sequence identity to SEQ ID NO: 2;
b. Modifying the sequence of step a., to encode a variant albumin, fragments thereof or fusion polypeptide comprising said variant albumin or fragment thereof having one or more substitutions corresponding to the substitutions in SEQ ID NO: 2 selected among:Q417A,C,D,E,F,G,H,I,K,L,M,N,P,R,S,T,V,W,Y
c. Introducing the modified sequence of step b., in a suitable host cell;
d. Growing the cells in a suitable growth medium under condition leading to expression of the variant of albumin, fragments thereof or fusion polypeptide comprising said variant albumin or fragment thereof; and
e. Recovering the variant of albumin, fragments thereof or fusion polypeptide comprising said variant albumin or fragment thereof from the growth medium; wherein the variant of albumin, fragments thereof or fusion polypeptide comprising said variant albumin or fragment thereof, has an altered plasma half-life compared with the parent albumin, fragments thereof or fusion polypeptide comprising said variant albumin or fragment thereof;
Variants of HSA comprising said modification at Q417, conjugates, and pharmaceutical compositions thereof.

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2. claims: 1-3, 5-12, 16-18(all partially)

A method for preparing a variant of albumin, fragments thereof or fusion polypeptide comprising said variant albumin or fragment thereof, comprising following steps:
a. Providing a nucleic acid encoding a parent albumin having at least 80% sequence identity to SEQ ID NO: 2;
b. Modifying the sequence of step a., to encode a variant albumin, fragments thereof or fusion polypeptide comprising said variant albumin or fragment thereof having one or more substitutions corresponding to the substitutions in SEQ ID NO: 2 selected among:
K500A,C,D,E,F,G,H,I,K,L,M,N,Q,R,S,T,V,W,Y
c. Introducing the modified sequence of step b., in a suitable host cell;
d. Growing the cells in a suitable growth medium under condition leading to expression of the variant of albumin, fragments thereof or fusion polypeptide comprising said variant albumin or fragment thereof; and
e. Recovering the variant of albumin, fragments thereof or fusion polypeptide comprising said variant albumin or

fragment thereof from the growth medium; wherein the variant of albumin, fragments thereof or fusion polypeptide comprising said variant albumin or fragment thereof, has an altered plasma half-life compared with the parent albumin, fragments thereof or fusion polypeptide comprising said variant albumin or fragment thereof;
Variants of HSA comprising said modification at K500, conjugates, and pharmaceutical compositions thereof.

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3. claims: 1-12, 16-18(all partially)

A method for preparing a variant of albumin, fragments thereof or fusion polypeptide comprising said variant albumin or fragment thereof, comprising following steps:
a. Providing a nucleic acid encoding a parent albumin having at least 80% sequence identity to SEQ ID NO: 2;
b. Modifying the sequence of step a., to encode a variant albumin, fragments thereof or fusion polypeptide comprising said variant albumin or fragment thereof having one or more substitutions corresponding to the substitutions in SEQ ID NO: 2 selected among:
D550A,C,E,F,G,H,I,K,L,M,N,P,Q,R,S,T,V,W,Y
c. Introducing the modified sequence of step b., in a suitable host cell;
d. Growing the cells in a suitable growth medium under condition leading to expression of the variant of albumin, fragments thereof or fusion polypeptide comprising said variant albumin or fragment thereof; and
e. Recovering the variant of albumin, fragments thereof or fusion polypeptide comprising said variant albumin or fragment thereof from the growth medium; wherein the variant of albumin, fragments thereof or fusion polypeptide comprising said variant albumin or fragment thereof, has an altered plasma half-life compared with the parent albumin, fragments thereof or fusion polypeptide comprising said variant albumin or fragment thereof;
Variants of HSA comprising said modification at D550, conjugates, and pharmaceutical compositions thereof.

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4. claims: 1-5, 7-12, 16-18(all partially)

A method for preparing a variant of albumin, fragments thereof or fusion polypeptide comprising said variant albumin or fragment thereof, comprising following steps:
a. Providing a nucleic acid encoding a parent albumin having at least 80% sequence identity to SEQ ID NO: 2;
b. Modifying the sequence of step a., to encode a variant albumin, fragments thereof or fusion polypeptide comprising said variant albumin or fragment thereof having one or more substitutions corresponding to the substitutions in SEQ ID NO: 2 selected among:
K573A,C,D,E,F,G,H,I,L,M,N,P,Q,R,S,T,V,W,Y
c. Introducing the modified sequence of step b., in a

suitable host cell;
d. Growing the cells in a suitable growth medium under condition leading to expression of the variant of albumin, fragments thereof or fusion polypeptide comprising said variant albumin or fragment thereof; and
e. Recovering the variant of albumin, fragments thereof or fusion polypeptide comprising said variant albumin or fragment thereof from the growth medium; wherein the variant of albumin, fragments thereof or fusion polypeptide comprising said variant albumin or fragment thereof, has an altered plasma half-life compared with the parent albumin, fragments thereof or fusion polypeptide comprising said variant albumin or fragment thereof;
Variants of HSA comprising said modification at K573, conjugates, and pharmaceutical compositions thereof.

5-30. claims: 1-3, 5-12, 16-18(all partially)

A method for preparing a variant of albumin, fragments thereof or fusion polypeptide comprising said variant albumin or fragment thereof, comprising following steps:
a. Providing a nucleic acid encoding a parent albumin having at least 80% sequence identity to SEQ ID NO: 2;
b. Modifying the sequence of step a., to encode a variant albumin, fragments thereof or fusion polypeptide comprising said variant albumin or fragment thereof having one or more substitutions corresponding to the substitutions in SEQ ID NO: 2 selected among: H440A, A490C, E492A, V493A, D494A, E495A, T496A, P499A, E501A, N503A, A504C, E505A, T506A, H510A, H535A, K536A, P537A, K538A, T540A, K541A, E542A, K574A, Q580A, A581C, A582C, G584A including the further specifically claimed variants thereof
c. Introducing the modified sequence of step b., in a suitable host cell;
d. Growing the cells in a suitable growth medium under condition leading to expression of the variant of albumin, fragments thereof or fusion polypeptide comprising said variant albumin or fragment thereof; and
e. Recovering the variant of albumin, fragments thereof or fusion polypeptide comprising said variant albumin or fragment thereof from the growth medium; wherein the variant of albumin, fragments thereof or fusion polypeptide comprising said variant albumin or fragment thereof, has an altered plasma half-life compared with the parent albumin, fragments thereof or fusion polypeptide comprising said variant albumin or fragment thereof;
Variants of HSA comprising said modification at H440, A490, E492, V493, D494, E495, T496, P499, E501, N503, A504, E505, T506, H510, H535, K536A, P537A, K538, T540, K541, E542, K574, Q580, A581, A582, G584 conjugates, and pharmaceutical compositions thereof.

31-35. claims: 2, 3, 5-12, 16-18(all partially)

A variant of albumin, fragments thereof or fusion polypeptides comprising said variant albumin or a fragment thereof having altered plasma half-life compared with the parent albumin, fragment thereof or fusion polypeptide comprising said parent albumin or fragment thereof, comprising one or more substitutions in positions corresponding to the positions in SEQ ID NO:2 selected among: 464, 575, 577, 578, 579.

Continuation of Box II.2

Claims Nos.: 13-15

Present claims 13 to 15 relate to a compound which has a given desired property or effect, namely a variant of albumin which binding to FcRn is stronger than for the corresponding albumin or fragment. However, the description does not provide support and disclosure in the sense of Article 6 and 5 PCT for any such compound having the said property or effect and there is no common general knowledge of this kind available to the person skilled in the art. This non-compliance with the substantive provisions is to such an extent, that no search was carried for the subject-matter of these claims (PCT Guidelines 9.19 and 9.20).

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.2), should the problems which led to the Article 17(2) declaration be overcome.