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Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

E.

S.

D.

REF: Expediente No. PCT/10-048790

TÍTULO SOLICITADO: "PROTEÍNAS DE UNIÓN A ANTÍGENO DE FACTOR DE CRECIMIENTO TIPO FACTOR DE CRECIMIENTO EPIDÉRMICO DE UNIÓN A HEPARINA"

PUBLICACIÓN: Gaceta 633 del 20/10/2011, N° de publicación 1299.

SOLICITANTE: U3 PHARMA GMBH Y AMGEN INC.

APODERADO: LUZ CLEMENCIA DE PÁEZ.

TRÁMITE: Recurso de Reposición y en subsidio el de apelación en contra de la Resolución 23984 de abril 29 de 2013 por la cual se concede una patente de invención tramitada bajo el número de expediente PCT/10-048790.

TITO NOÉ PARRA MURILLO, mayor de edad, identificado como aparece al pie de mi firma, reconocido apoderado de la sociedad LAFRANCOL S.A.S. en el asunto de la referencia, de manera respetuosa, y dentro de los términos de ley, presento Recurso de Reposición y en subsidio de apelación contra la Resolución 23984 de abril 29 de 2013 por la cual se concedió a la solicitud PCT/10-048790 el privilegio de patente de invención.

I. PETICIÓN

Sírvase, Señor Superintendente, reponer íntegramente la Resolución 23984 de abril 29 de 2013, por la cual se declaró infundada la oposición presentada y se otorgó el privilegio de patente solicitado en el expediente de la referencia, y en su remplazo emitir otra que, con

fundamento en los argumentos expuestos en el escrito de observación y en el presente escrito, declare fundada dicha oposición y niegue el privilegio de patente mencionado, procediendo luego al definitivo archivo del expediente en cuestión.

II. ARGUMENTOS SOBRE LOS FUNDAMENTOS DE LA CONCESIÓN Y MOTIVOS DE INCONFORMIDAD

La Resolución 23984 de abril 29 de 2013, que concede el privilegio de patente de invención solicitado para el capítulo reivindicatorio del expediente 10-048790 titulado “**Proteínas de unión a antígeno de factor de crecimiento tipo factor de crecimiento epidérmico de unión a heparina**”, viola flagrantemente la Decisión 486 si se tiene en cuenta que existían motivos suficientes para afectar los requisitos de novedad y nivel inventivo de la solicitud en mención. Es evidente que el solicitante y la Resolución cometen un error cuando afirman que la oposición presentada por mi representada no muestra ningún tipo de argumento soportado técnicamente, ni desvirtúa la patentabilidad del objeto de estudio, declarándola infundada por cuanto, al momento de presentación del escrito de oposición se dejó en claro que para el presente caso nos encontramos frente a una combinación de compuestos, lo cual indudablemente afecta el requisito de nivel inventivo, éste mismo indispensable para acceder a cualquier beneficio patentario.

Así las cosas, me permito reiterar que la concesión de patente objeto del presente escrito se ve afectada por los documentos del estado del arte que fueron presentados inicialmente en el escrito de observación, por lo cual, basado en lo siguiente, solicito respetuosamente a ese Despacho dar análisis completo y a cabalidad sobre los siguientes documentos, los cuales sin lugar a dudas objetan la concesión en mención, toda vez que develan de manera expresa y sucinta lo que se pretende proteger en la presente solicitud.

Dicho así, me permito manifestar que agentes tales como Cisplatino, Bevacizumab, entre otros, han sido ampliamente divulgados en el sector químico-farmacéutico, y concretamente se han develado materias muy similares, las cuales ruego a ese Despacho analizar, en los siguientes documentos:

- **DE 2318020**
- **DE 2329485**
- **WO 9845331**

Así como resulta imprescindible manifestar que los anteriores documentos deben ser analizados a profundidad y cabalidad para así determinar finalmente si afectan o no la novedad y nivel inventivo de la presente solicitud, toda vez que en nuestra opinión se revelan materias muy similares, también es necesario reiterar que la solicitud de la referencia pretende proteger mediante el derecho patentario objetos que no son considerados invenciones. Es claro que una invención es toda creación humana que permita transformar la materia o energía que existe en la naturaleza, para su aprovechamiento por los seres humanos y satisfacer sus necesidades concretas. De igual modo, como ya se mencionó, según los parámetros de la Decisión 486 y normas concordantes, serán patentables las invenciones que cumplan con los requisitos de novedad, nivel inventivo y aplicación industrial. No obstante, puede observarse que la solicitud en comento pretende reivindicar combinaciones, las cuales no se consideran invenciones. En este sentido, la mezcla (Combinaciones) de productos (Moléculas) conocidos y su variación, bien sea en uso, forma, dimensión o de materia, NO se consideran invenciones por cuanto no son susceptibles de aplicación industrial, nivel inventivo y novedad, luego NO pueden acceder a beneficios patentarios. Por lo tanto, se suma una circunstancia más que imposibilita definitivamente la concesión de la solicitud en mención.

Y sobre el particular, es imprescindible señalar que un efecto sinérgico nuevo no se considera inventivo como tal, dado que puede ser obvio para una persona versada en la materia, cosa que sucede en el presente caso. En palabras del Doctor Carlos Correa, *“El efecto sinérgico entre dos o más drogas se puede considerar un “descubrimiento” y no una “invención”, dado que la sinergia ocurre en el cuerpo y se descubre a través de ensayos clínicos. Asimismo, cabe destacar que, en algunos casos, las reivindicaciones de combinaciones pueden equivaler, en términos prácticos, a reivindicaciones sobre tratamientos médicos (cuya patentabilidad está excluida en la mayoría de los países), cuando sólo brindan un método para administrar una combinación de drogas conocidas. Asimismo, la combinación de drogas para evitar la resistencia particular a una de ellas es una práctica normal en el desarrollo farmacéutico y, por lo general, es evidente para el hombre del oficio de nivel medio”* (Pautas para el examen de patentes farmacéuticas, CEIDIE, Pág. 8). En estos términos, está claro que nos encontramos frente a un tema totalmente sensible que merece toda la evaluación por cuanto las combinaciones deben considerarse excluidas de beneficios de patente.

Y en caso que ese Despacho decidiera insistir en el cabal cumplimiento de los requisitos exigidos para acceder al beneficio de patente, me permito allegar copia del International

Search Report y el respectivo Written Opinion Of The International Searching Authority, documentos en los cuales se resalta que la presente invención no cumple con los requisitos de novedad y nivel inventivo por cuanto existen documentos citados del estado del arte que afectan de manera definitiva tales exigencias. Lo anterior deja entrever, sin lugar a equívocos, que la presente solicitud no debió ser concedida, por lo cual es procedente la revocatoria de la Resolución objeto de este escrito.

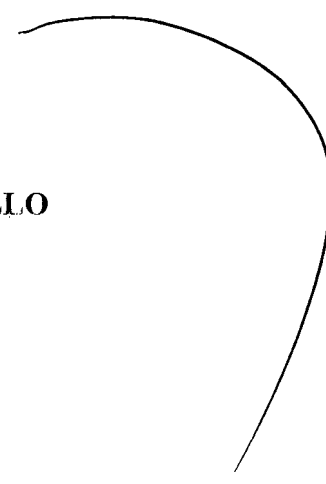
En este sentido, reitero con el debido respeto la necesidad de analizar a profundidad los requisitos de novedad y nivel inventivo para así determinar si la presente solicitud es merecedora de concesión de privilegio de patente.

ANEXOS

- 1- International Search Report y el Written Opinion Of The International Searching Authority de la equivalente internacional WO 2009/040134.

En subsidio apelo.

Señor Superintendente,



TITO NOÉ PARRA MURILLO

C.C. 79.579.680 de Bogotá

T.P. 71168 del C. S de la J.

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION See paragraph 2 below

International application No.
PCT/EP2008/008233

International filing date (day/month/year)
26.09.2008

Priority date (day/month/year)
26.09.2007

International Patent Classification (IPC) or both national classification and IPC
INV. C07K16/22 A61K39/395 A61K33/24 A61P35/00
ADD. C07K16/28

Applicant
U3 PHARMA AG

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



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Date of completion of
this opinion

see form
PCT/ISA/210

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WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2008/008233

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).
2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))
3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☒ on paper
 - ☒ in electronic form
 - c. time of filing/furnishing:
 - ☒ contained in the international application as filed.
 - ☐ filed together with the international application in electronic form.
 - ☒ furnished subsequently to this Authority for the purposes of search.
4. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
5. Additional comments:

see separate sheet

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2008/008233

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

- ☐ the entire international application
- ☒ claims Nos. 1-5, 12, 15-18, 20-74 (all in part)

because:

- ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international search (*specify*):
- ☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 15-18, 20-74 (all in part) are so unclear that no meaningful opinion could be formed (*specify*):

see separate sheet

- ☒ the claims, or said claims Nos. 1-5, 15-18, 20-74 (all in part) are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):

see separate sheet

- ☐ no international search report has been established for the whole application or for said claims Nos.
- ☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:
- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13ter (a) or (b).
- ☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-bis of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.
- ☐ See Supplemental Box for further details

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2008/008233

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	<u>1, 5-16, 20-32, 38-41, 43-54, 56-64, 67-74</u>
	No: Claims	<u>2-4, 17-19, 33-37, 42, 55, 65-66</u>
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-74</u>
Industrial applicability (IA)	Yes: Claims	<u>1-74</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43bis.1 and 70.10)
and / or

2. Non-written disclosures (Rules 43bis.1 and 70.9)

see form 210

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/EP2008/008233

Reference is made to the following documents:

- D1:** MIYAMOTO S ET AL: "Heparin-binding epidermal growth factor-like growth factor as a novel targeting molecule for cancer therapy" CANCER SCIENCE, JAPANESE CANCER ASSOCIATION, TOKYO, JP, vol. 97, 1 May 2006 (2006-05-01), pages 341-347, XP003020176 ISSN: 1347-9032
- D2:** WO 2005/100403 A (ABBOTT LAB [US]; REILLY EDWARD B [US]; LACY SUSAN E [US]; FUNG EMMA [U]) 27 October 2005 (2005-10-27)
- D3:** WO 2005/010151 A (ABGENIX INC [US]; WEBER RICHARD [US]; FENG XIAO [US]; FOORD ORIT [US];) 3 February 2005 (2005-02-03)
- D4:** ITOH Y ET AL: "IL-8 promotes cell proliferation and migration through metalloproteinase-cleavage proHB-EGF in human colon carcinoma cells" CYTOKINE, ACADEMIC PRESS LTD, PHILADELPHIA, PA, US, vol. 29, no. 6, 21 March 2005 (2005-03-21), pages 275-282, XP004769509 ISSN: 1043-4666
- D5:** MISHIMA KAZUHIKO ET AL: "Heparin-binding epidermal growth factor-like growth factor stimulates mitogenic signaling and is highly expressed in human malignant gliomas" ACTA NEUROPATHOLOGICA, vol. 96, no. 4, October 1998 (1998-10), pages 322-328, XP002510490 ISSN: 0001-6322

Re Item I

Basid of the Report

- I.1** (i) Pages 4-12, 23-25, 32-40, 43-48, 56-57, 61, 75, 88-89, 106-107, (ii) claims 1-74 and (iii) Figs. 3H, 8A-8H, 9A-9F, 13-13V, 14A-14Z, 14AA, 14AB, 14AC, 15A-15M, 16A-16L, 17A, 17B, 18A-18F, 19A-19G, 20-20K and 21A-21K as filed together with the electronic sequence listings for the purposes of search merely renumber the sequences previously provided and bring the description into accordance with said renumbering. The following opinion takes said pages (i), claims (ii) and Figs. (iii) into account.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

III.1 Underlying claims 1(A)(iv), 1(B)(iv), 5(A)(iv), 5(B)(iv), 15(A)(ii), 15(B)(ii), 16(A)(ii), 16(B)(ii) (and those parts of claims 2-10, 20-30, 44-74 which relate thereto) relate to a very large number of amino acid sequences, wherein said sequences are defined in terms of one of 184 possible reference sequences, wherein said reference sequences may be 5-17 aa in length, and wherein the amino acid sequences claimed may have up to (i) two or (ii) four amino acid modifications, with respect to said reference sequences, and wherein said modifications may be a substitution, deletion or insertion.

For a 5 aa reference sequence (i.e. SEQ ID NO: 348) the first modification may be performed at any of 5 positions, the second modification at any of 4 positions. There are three types of possible modifications, thus leading to a total of $5^3 \times 4^3 = 8 \times 10^3$ types of modification-combinations for this one reference sequence, which is the simplest (doubly modified) and shortest (5 aa) variant.

For a quadruply modified, 17 aa sequence (see i.e. claim 1(A)(iv) and reference SEQ ID NO: 197) this leads to 1.8×10^{14} possible modification combinations.

Support and disclosure in the application is only provided for a very small number of the antibodies claimed, namely those which explicitly comprise the abovementioned 184 reference SEQ ID NOs: 189-372.

III.2 Underlying claims 15(A)(iii), 15(B)(iii), 16(A)(iii)-(vi), 16(B)(iii)-(vi) refers to a very large number of possible CDRH3 amino acid sequences of the formulae $X_1X_2X_3 \dots$ etc. (SEQ ID Nos: 1095-1116, 1033-1041, 1089-1094), encompassing up to 4.6×10^{14} possible permutations.

The initial phase of the structure search revealed a very large number ($> 5 \times 10^6$) of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of claim 15 may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT).

III.3 For the above reasons, the search was performed taking into consideration the

non-compliance in determining the extent of the search of claims 1, 5, 15 and 16 (and those parts of the dependent claims which relate thereto).

The search of claims 1, 5, 15 and 16 (and the dependent claims) was restricted to those embodiments comprising the technical features of claims 1(A)(i)-(iii), 1(B)(i)-(iii), 5(A)(i)-(iii), 5(B)(i)-(iii), 15(A)(i), 15(B)(i), 16(A)(i), 16(B)(i), namely those which comprise one of SEQ ID Nos: 189-372.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

V.1 Patentability

- 1.1 Claims 50, 65-69 relate to a subject-matter considered by this Authority to be covered by the provision of Rule 39.1(iv)/67.1(iv) PCT. The patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognise as patentable claims to the use of a compound in medical treatment, but may allow claims to a product, in particular substances or compositions for in a first or further medical treatment.

V.2 Novelty

- 2.1 Claim 1 refers to (i) an antigen-binding protein that (ii) binds HB-EGF. Claim 1 does not speak of specific (i.e. immunospecific) binding. Consequently the functional feature of "binding HB-EGF" does not provide a clear limitation and any generic antigen-binding protein, that i.e. aspecifically, transiently binds/interacts with HB-EGF is encompassed.

The only clearly discernible technical features in underlying claims 1-10, 13-19 are thus the particular structural features.

- 2.2 D2 discloses a germline VL-region which is 100% homologous to present SEQ

ID NO: 6 (see D2; SEQ ID No: 16). D3 discloses a VH-domain of an anti-EGFRvIII-antibody which is 98.3% identical to present SEQ ID NO: 164 (see D3; SEQ ID NO: 131). Both of these sequences from D2 and D3 constitute subunits of generic antigen-binding proteins.

Hence, the subject-matter of claims 1, 5-10, 13-16 is not novel (Article 33(2) PCT).

The combinations of structural features as per claims 2-4, 17-19 have not been previously reported and are novel (Article 33(2) PCT).

2.3 D3 discloses the following additional technical features:

Fab, Fab', etc. (see D3; p. 28, ll. 9-17), human, monoclonal Abs (see D3; p. 8, ll. 9-11), IgG1-IgG4 isotypes (see D3; p. 38, ll. 22-24, p. 49, ll. 11-12), labelling groups, effector groups, biotinylation, toxin (i.e. auristatin, maytansinoid) - conjugated antibodies (see D3; p. 31 ll. 9-18, p. 43, l. 4 to p. 44, l. 18), corresponding nucleic acid, vectors, host-cells and methods of producing antibodies (see D3; p. 48, l. 34 to p. 49, l. 34), methods of treatment for cancer (see D3; claims 15-22), specifically for the treatment of cancers in which EGFRvIII is overexpressed (see D3; p. 2, ll. 8-14).

The subject-matter of claims 20-30, 44-50, 51, 57-64, 67-70, 74 is not novel (Article 33(2) PCT).

The term "active agent" is meaningless as it is not clear what type of activity is envisaged. It thus does not form any clear, distinguishing technical feature. Hence, the same argumentation as for claims 51 & 70 also applies to claims 52 & 71 (Article 33(2) PCT).

Furthermore, the anti-EGFRvIII antibody of D3 itself already fulfills the criteria of claims 52-54, 56, 72, seeing as it is an active, anti-neoplastic, anti-EGFR antibody. The subject-matter of claims 52-54, 56, 72 is not novel (Article 33(2) PCT).

PCT).

- 2.4 The antigen-binding protein of claim 11 is characterized in that it specifically recognizes either (i) an IHGE-containing epitope or (ii) an EGF-like domain of HB-EGF.

Polyclonal antibodies are known in the art (see D4, D5) which bind and block epitopes within the "EGF-like domain" of HB-EGF which is responsible for EGFR-interaction. The manner in which these polyclonal antibodies were manufactured does not differ substantially from the one used to generate the primary polyclonal immuneresponse from which the underlying monoclonal antibodies were ultimately retrieved. The prior art pAb thus must comprise antibody-subpopulations which are functionally equivalent (i.e. with respect to the binding of neutralizing epitopes) to the mAbs of the underlying application.

The subject-matter of claims 11-12, 31-32, 43 therefore is not novel (Article 33(2) PCT).

Furthermore, the IHGE-sequence is located in a region of HB-EGF which is relevant to both EGFR and diphtheria toxin (DT) binding. EGFR and DT thus also fall within the functional definitions of claims 11-12, 31.

Naturally occurring Fc-domains of the aforementioned prior art pAb fulfill the criteria of providing a detectable label, a predetermined polypeptide group, an effector group and a therapeutically effective, ADCC-mediating group. The subject-matter of claims 38-41 thus does not introduce any novel technical feature over D4-D5 or claim 31 and equally is not novel (Article 33(2) PCT).

The combinations of technical features as per claims 33-37 & 42 have not been previously reported and are novel (Article 33(2) PCT).

- 2.5 The combinations of technical features as per claims 55, 65-66, 73 have not been previously reported and are novel (Article 33(2) PCT).

V.3 Inventive Step

- 3.1 D1 discloses inhibition of tumour growth in vivo by means of anti-HB-EGF siRNA or DT-analogue CRM197 (see D1; p. 344, left column). D1 itself already suggests that antiHB-EGF neutralizing antibodies are potentially hopeful therapeutic molecules (see D1; p. 346, right column). D1 also already reports of previously known neutralizing anti-HB-EGF polyclonal antibodies (see D1; p. 344, both columns), which are capable of inhibiting HB-EGF stimulated glioblastoma cell proliferation by up to 40% at a concentration of 10 ug/ml. Such neutralizing anti-HB-EGF antibodies are considered the closest prior art to the underlying application.
- 3.2 The subject-matter of underlying claims 2-4, 17-19 differs from D1 in that the compound claimed is a polyclonal antibody comprising at least one CDRL and at least one CDRH selected from SEQ ID Nos: 189-274 and 275-372, respectively, which are derived from antibodies U2-1 through U2-65.
- 3.3 (i) Figs. 22A and 22B demonstrate that not all of the antibodies U2-1 through U2-65 are inhibitors of HB-EGF/EGFR signalling. I.e. U2-32 and U2-13 etc. are completely ineffective. The technical effect shared by all of U2-1 through U2-65 is thus mere HB-EGF binding. The provision of mere binding-molecules to the known antigen HB-EGF, however, may routinely be achieved through routine antibody-engineering techniques. Hence, the subject-matter of claims 2-4, 17-19 does not involve an inventive step over the entire scope claimed (Article 33(3) PCT).
- (ii) Certain anti-HB-EGF antibodies, i.e. U2-39 and U2-42, are shown to be effective inhibitors of EGFR-phosphorylation/signalling. However, neutralizing antibodies per se are already known in the art (see D1; see above). The provision of alternative neutralizing antibodies per se does not involve an inventive step.
- (iii) Particularly effective neutralizing antibodies could be considered to involve

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)

International application No.

PCT/EP2008/008233

an inventive step. While the assays used in D1 and Fig. 22 are not directly comparable, it is apparent that many of the antibodies currently claimed (i.e. U2-5 and U2-15) do not achieve 40% inhibition of EGFR-tyrosine phosphorylation, thus do not provide an inhibition of tumour-cell proliferation of up to 40% and thus do not provide for any particular or unexpected degree of HB-EGF neutralization. Consequently, the subject-matter of claims 2-4, 17-19 does not involve an inventive step over the entire scope claimed (Article 33(3) PCT).

(iv) mAbs U2-39 and U2-42 are shown in example 18 to be therapeutically effective in vivo. Therapeutic effectiveness of anti-HB-EGF antibodies in vivo per se was already predicted in D1. However, as the underlying application is the first report of such an in vivo therapy to be actually put into practice, the particular effectiveness of these two particular antibodies was not to be expected. U2-39 and U2-42 involve an inventive step.

(v) However, the subject-matter of claims 2-4, 17-19 is defined in only partial structural features of U2-39 and U2-42. The particular efficacy of a classical antibody resides in the precise three-dimensional structure of its antigen-binding region which is determined by three CDRs and four FR-domains per VH- and per VL-domain. It logically follows that an antibody comprising only parts of this three-dimensional structure will only be capable of reproducing part of the abovementioned efficacy. The subject-matter of claims 2-4, 17-19 thus does not provide the abovementioned particular technical effect over the entire scope claimed (even if it were limited to only partial structural features derived from U2-39 or U2-42) and thus does not involve an inventive step (Article 33(3) PCT).

(vi) From the above it also follows that technical support in the underlying application is only provided for the specific U2-39 and U2-42 derived structural features but not i.e. for such structural features which are then further modified by means of generic/unspecified amino acid permutations (see i.e. claim 1(A)(iv) or claim 1(A)(iii)). Such permutations thus do not provide the abovementioned particular technical efficacy over the entire scope claimed and thus do not involve an inventive step.

- 3.4 It has been established above that not all anti-HB-EGF antibodies of claims 2-4, 17-19 provide a therapeutic effect. The technical effect achieved by the subject-matter of claims 55 & 73 thus is indistinguishable from anti-receptor tyrosine kinase, Avastin or cisplatin monotherapy and is neither unexpected or non-obvious. The subject-matter of claims 55 & 73 does not involve an inventive step (Article 33(3) PCT).
- 3.5 It has been established above that not all anti-HB-EGF antibodies of claims 2-4, 17-19 provide a therapeutic effect, and that said claims thus in their broadest interpretation relate to mere HB-EGF binders. HB-EGF has previously been used to correlate HB-EGF expression to cancer-pathology (see D1; Fig. 3). The subject-matter of claims 65-66 thus does not provide for any unexpected or non-obvious technical effect and does not involve an inventive step (Article 33(3) PCT).
- 3.6 With respect to the non-novel subject-matter of claims 31-32 (see above), claims 33-37 do not introduce any technical feature that alone or in combination with said non-novel subject-matter go beyond the application of routine antibody-engineering techniques. The subject-matter of claims 33-37 does not involve an inventive step (Article 33(3) PCT).
- 3.7 The subject-matter of claim 42 further differs from D1 in that the claimed antigen binding protein is coupled to calicheamicin, auristatin-PE, geldanamycin, maytanasine, or derivatives thereof.

The technical effect resulting from this difference is the targeted drug-delivery of said chemotherapeutics to either shed/soluble/mature HB-EGF. Delivery to cell-bound proHB-EGF has not been demonstrated. It is not clear what delivery to a soluble factor is supposed to achieve since an antibody/HB-EGF complex will no longer bind to EGFR-positive cancer cells, and thus no drug-delivery to cancer cells takes place.

In absence of any particular technical effect that can be attributed to the

WRITTEN OPINION OF THE
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International application No.

PCT/EP2008/008233

proposed antibody-drug conjugates, such a construct must be deemed arbitrary.
The subject-matter of claim 42 does not involve an inventive step (Article 33(3)
PCT)..

Re Item VI

Certain documents cited

Certain published documents

Application No Patent No	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
WO2008047914	24.04.2008	19.10.2007	20.10.2006
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WO2007142276	13.12.2007	06.06.2007	06.06.2006
WO2007142277	13.12.2007	06.06.2007	06.06.2006

Re Item VIII

Certain observations on the international application

VIII.1 Present Fig. 7 is fundamentally unclear (Article 84 EPC) as it provides two different "names" for each VHCDR amino acid sequence, and uses the same name for more than one amino acid sequence (i.e CDRH1-10 for SEQ ID Nos: 275 and 280).

VIII.2 The following terminology is unclear and leaves the reader in doubt as to the technical features referred to (Article 6 PCT):

"antigen binding protein" in combination with "CDRL1" or "VH" or "VL" (claims 1-10, 13-19) - the term antigen-binding protein describes a product exclusively in terms of its desired functional properties without providing any information of what type of protein is envisaged, the terms CDR, VH and VL, on the other hand, as used by i.e. Chothia or Kabath, only makes sense in context of clearly

immunoglobulin-like structures. The antibody-like character of the claimed product does not become apparent.

"antigen binding protein" (claims 11-12) - see above

"competes for binding" (claim 12) - as long as it is not specified for which target competitiveness is determined this statement is meaningless

"said first ... said second amino acid sequence" (claims 17-19) - claim 16 does not speak of or define which amino acid sequence is considered to be the "first" or the "second". This formulation is inconsistent with the reference-signs (A), (B), (i), (ii), etc. as previously used.

"covalently bonded" (claim 18) - implies that an isolated CDR is supposed to be directly covalently linked to a further CDR, thus describing a non-functional construct

"first amino acid sequence comprises ... CDRL3, CDRL2, CDRL1", dito for "second amino acid comprises ... CDRH3, CDRH2, CDRH1" (claim 19) - the "amino acid sequences" (SEQ ID NOs) as defined in claim 16 are a single CDR, they do not comprise multiple such CDRs. Inconsistent use of the expression "amino acid sequence".

"predetermined polypeptide group" (claims 27, 39) - can refer to any portion of the protein of claim 1.

"effector group" (claims 28, 40) - does not specify what type of effect

"therapeutic group" (claim 29, 41) - does not specify what type of therapeutic effect, i.e. the one that is allegedly already inherent to the binding protein of claim 1

"derivatives" (claim 30, 42) - does not provide any type of functional or structural

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)

International application No.

PCT/EP2008/008233

limitation, does not specify how many modifications are envisaged

"active agent" (claim 52, 71) - does not specify what type of activity

"hyperproliferative disease" (claims 57-59, 63-64, 66-68) - does not specify which cell-type is proliferating, and thus does not specify the therapeutic target. Amounts to the definition of a disorder in terms of the underlying molecular mechanism. Also, technical support is only provided for tumours/cancer.

"associated with/accompanied by" (claims 58-60, 65, 67) - does not specify in what way associated/accompanied, "disturbed" HB-EGF expression must not necessarily be the cause, but may instead be the consequence of the disorder

"disturbed" (claim 59) - subjective terminology

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2008/008233

A. CLASSIFICATION OF SUBJECT MATTER INV. C07K16/22 A61K39/395 A61K33/24 A61P35/00 ADD. C07K16/28		
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 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, 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.
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☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.		
* Special categories of cited documents: *A* document defining the general state of the art which is not considered to be of particular relevance *E* earlier 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. *Z* document member of the same patent family		
Date of the actual completion of the international search 15 January 2009		Date of mailing of the international search report 28/01/2009
Name and mailing address of the ISA/ European Patent Office, P.B. 5618 Patentlaan 2 NL - 2280 HV Rijswijk Tel: (+31-70) 340-2040 Fax: (+31-70) 340-3016		Authorized officer Bumb, Peter

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International application No
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International application No
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