

Table 1: UK Patent applications in name of Oleg Ilich Epshtein at issue in this case and their corresponding UK and PCT publication numbers

#	UK Application No.	UK Publication No.	PCT Publication No.
1	GB1302651.3	GB 2495885	WO 2012/007849
2	GB1302653.9	GB 2496076	WO 2012/007847
3	GB1302654.7	GB 2496794	WO 2012/007839
4	GB1302924.4	GB 2496799	WO 2012/010966
5	GB1302925.1	GB 2496342	WO 2012/010974
6	GB1302926.9	GB 2496800	WO 2012/010973
7	GB1302928.5	GB 2496343	WO 2012/010970
8	GB1302929.3	GB 2496801	WO 2012/010978
9	GB1303867.4	GB 2503066	WO 2012/017328
10	GB1303868.2	GB 2497453	WO 2012/017323
11	GB1303983.9	GB 2498276	WO 2012/018284

- 4 Before looking at the individual applications, I consider below the general approach to ultra-low dilutions outlined in these eleven applications.

Activated-Potentiated Forms of Antibodies

- 5 All these patent applications relate to the preparation of mixtures of activated-potentiated forms of antibodies, and the use of those mixtures in the treatment of various diseases. The term “activated-potentiated” is disclosed in the applications to mean that a series of dilutions are performed, either with water or with a water/alcohol mixture, which gives rise to a therapeutic activity. Typically in the applications, mixtures of the centesimal dilutions C12 (dilution factor of 1×10^{24}), C30 (1×10^{60}), C50 (1×10^{100}), and C200 (1×10^{400}) are used. The “activated-potentiated” terminology and the methodology of centesimal dilutions are described as being borrowed from the field of homeopathy. However, the applicant has been keen to point out that the present applications do not pertain to homeopathy in as much as they are concerned not with treating “like-with-like”, as in homeopathy, but are concerned with the treatment of diseases with antibodies that have been subjected to the serial centesimal dilutions. In this respect, the approach outlined in the current applications has been described as *chimeric* – a combination of homeopathic methodology and the principles of conventional medicine. The term *chimeric* to describe this approach was, so far as I can determine, first used in an EPO decision concerning an EP patent application by the Applicant (see EPO Technical Board of Appeal decision, T-1273/09 Homeopathic mixture/EPSTEIN).
- 6 It is noted that such ultra-high dilutions (or ultra-low doses) statistically speaking are highly unlikely to contain even one molecule of starting antibody. The C12 centesimal dilution (dilution factor 1×10^{24}) on its own would result in a dilution below the Avogadro limit (6.022×10^{23}). Indeed, starting with one *mole* of substance and subjecting it to the C12 dilution would result in a solution in which there is approximately a 60% chance of there being one *molecule* of substance present. The dilutions described in the present applications are significantly more dilute than this.

Nevertheless, each application describes the preparation of at least one composition comprising a mixture of ultra-high dilutions of antibodies, and in each application evidence is presented in support of the therapeutic activity of the mixtures of ultra-dilute antibodies.

The Applications

- 7 Application GB1302651.3 "*Combination pharmaceutical composition and methods of treating genitourinary system disorders*" was filed on 15 July 2011, claiming an earliest priority date of 15 July 2010. It was published as GB 2495885 A on 24 April 2013. The Section 20 compliance period (as extended) expires on 15 November 2015. A first examination report was issued on 13 March 2013 that adopted sections I, V, VII, and VIII of the International Preliminary Report on Patentability that was issued on this application in the international phase of the PCT procedure. Amendments were filed on 16 September 2013, and a subsequent examination report was issued on 12 August 2014 in which issues of novelty, sufficiency of disclosure, and industrial application were raised. After a telephone conversation on 13 January 2015, a request for an oral hearing was submitted on 11 February 2015. A pre-hearing report was issued on 03 March 2015 that set out the outstanding issues to be considered at the requested hearing. A hearing was appointed for 18 June 2015.
- 8 Application GB1302653.9 "*Pharmaceutical compositions and methods of treatment*" was filed on 15 July 2011, claiming an earliest priority date of 15 July 2010. It was published as GB 2496076 A on 01 May 2013. The Section 20 compliance period (as extended) expires on 15 November 2015. A first examination report was issued on 19 March 2013 that adopted sections I, V, VII, and VIII of the International Preliminary Report on Patentability that was issued on this application in the international phase of the PCT procedure. Amendments were filed on 19 September 2013, and a subsequent examination report was issued on 11 December 2014 in which issues of added matter, sufficiency, industrial application, and novelty/inventive step were raised. After a telephone conversation on 13 January 2015, a request for an oral hearing was submitted on 11 February 2015. A pre-hearing report was issued on 03 March 2015 that set out the outstanding issues to be considered at the requested hearing. A hearing was appointed for 18 June 2015.
- 9 Application GB1302654.7 "*Combination pharmaceutical composition and methods of treating and methods of treating functional diseases or conditions of gastrointestinal tract*" was filed on 15 July 2011, claiming an earliest priority date of 15 July 2010. It was published as GB 2496794 A on 22 May 2013. The Section 20 compliance period (as extended) expires on 15 November 2015. A first examination report was issued on 12 April 2013 that adopted sections V, VII, and VIII of the International Preliminary Report on Patentability that was issued on this application in the international phase of the PCT procedure. Amendments were filed on 09 October 2013, and a subsequent examination report was issued on 14 August 2014 in which issues of novelty, sufficiency, and industrial application were raised. After a telephone conversation on 13 January 2015, a request for an oral hearing was submitted on 11 February 2015. A pre-hearing report was issued on 03 March 2015 that set out the outstanding issues to be considered at the requested hearing. A hearing was appointed for 02 July 2015.

- 10 Application GB1302924.4 "*A combination pharmaceutical composition and methods of treating diabetes and metabolic disorders*" was filed on 15 July 2011, claiming an earliest priority date of 21 July 2010. It was published as GB 2496799 A on 22 May 2013. The Section 20 compliance period (as extended) expires on 21 July 2015. A first examination report was issued on 16 April 2013 that adopted sections V, VII, and VIII of the International Preliminary Report on Patentability that was issued on this application in the international phase of the PCT procedure. Amendments were filed on 16 October 2013, and a subsequent examination report was issued in which the issues of novelty, sufficiency, and industrial application were raised. After a telephone conversation on 13 January 2015, a request for an oral hearing was submitted on 11 February 2015. A pre-hearing report was issued on 03 March 2015 that set out the outstanding issues to be considered at the requested hearing. A hearing was appointed for 18 June 2015.
- 11 Application GB1302925.1 "*Combination pharmaceutical compositions and method of treatment of vertigo, kinetosis and vegetative-vascular dystonia*" was filed on 15 July 2011, claiming an earliest priority date of 21 July 2010. It was published as GB 2496342 A on 08 May 2013. The Section 20 compliance period (as extended) expires on 21 November 2015. Amended claims were filed on 07 May 2013, and a first examination report was issued on 04 July 2013 that adopted sections V, VII, and VIII of the International Preliminary Report on Patentability that was issued on this application in the international phase of the PCT procedure. Subsequent amendments were filed on 06 January 2014, and a subsequent examination report was issued on 18 August 2014 in which issues of novelty, sufficiency of disclosure, and industrial application were raised. After a telephone conversation on 13 January 2015, a request for an oral hearing was submitted on 11 February 2015. A pre-hearing report was issued on 03 March 2015 that set out the outstanding issues to be considered at the requested hearing. A hearing was appointed for 18 June 2015.
- 12 Application GB1302926.9 "*Combination pharmaceutical composition and methods of treating diseases or conditions associated with respiratory disease or condition*" was filed on 15 July 2011, claiming an earliest priority date of 21 July 2010. It was published as GB 2496800 A on 22 May 2013. The Section 20 compliance period (as extended) expires on 21 November 2015. Amended claims were filed on 7 May 2013, and a first examination report was issued on 4 July 2013 that adopted sections V, VII, and VIII of the International Preliminary Report on Patentability that was issued on this application in the international phase of the PCT procedure. Subsequent amendments were filed on 06 January 2014, and a subsequent examination report was issued on 13 August 2014 in which issues of novelty, sufficiency of disclosure, and industrial application were raised. After a telephone conversation on 13 January 2015, a request for an oral hearing was submitted on 11 February 2015. A pre-hearing report was issued on 03 March 2015 that set out the outstanding issues to be considered at the requested hearing. A hearing was appointed for 02 July 2015.
- 13 Application GB1302928.5 "*A method of treating attention deficit hyperactivity disorder*" was filed on 15 July 2011, claiming an earliest priority date of 21 July 2010. It was published as GB 2496343 A on 08 May 2013. The Section 20 compliance period (as extended) expires on 21 November 2015. A first examination report was issued on 28 March 2013 that adopted sections V, VII, and VIII of the International

Preliminary Report on Patentability that was issued on this application in the international phase of the PCT procedure. Amendments were filed on 26 September 2013, and a subsequent examination report was issued on 14 August 2014 in which issues of sufficiency, novelty, and industrial application were raised. After a telephone conversation on 13 January 2015, a request for an oral hearing was submitted on 11 February 2015. A pre-hearing report was issued on 03 March 2015 that set out the outstanding issues to be considered at the requested hearing. A hearing was appointed for 18 June 2015.

- 14 Application GB1302929.3 "*A method of treating Alzheimer's disease*" was filed on 15 July 2011, claiming an earliest priority date of 21 July 2010. It was published as GB 2496801 A on 22 May 2013. The Section 20 compliance period (as extended) expires on 21 November 2015. Amended claims were filed on 14 May 2013, and a first examination report was issued on 04 July 2013 that adopted sections I, V, VII, and VIII of the International Preliminary Report on Patentability that was issued on this application in the international phase of the PCT procedure. Subsequent amendments were filed on 06 January 2014, and a subsequent examination report was issued on 13 August 2014 in which issues of sufficiency of disclosure, novelty, and industrial application were raised. After a telephone conversation on 13 January 2015, a request for an oral hearing was submitted on 11 February 2015. A pre-hearing report was issued on 03 March 2015 that set out the outstanding issues to be considered at the requested hearing. A hearing was appointed for 02 July 2015.
- 15 Application GB1303867.4 "*Combination pharmaceutical composition and methods of treating and preventing the infectious diseases*" was filed on 15 July 2011, claiming an earliest priority date of 06 August 2010. It was published as GB 2503066 A on 18 December 2013. The Section 20 compliance period (as extended) expires on 06 December 2015. A first examination report was issued on 28 March 2013 that adopted sections V, VII, and VIII of the International Preliminary Report on Patentability that was issued on this application in the international phase of the PCT procedure. Amendments were filed on 31 October 2013, and a subsequent examination report was issued on 05 September 2014 in which issues of novelty, sufficiency, and industrial application were raised. After a telephone conversation on 13 January 2015, a request for an oral hearing was submitted on 11 February 2015. A pre-hearing report was issued on 03 March 2015 that set out the outstanding issues to be considered at the requested hearing. A hearing was appointed for 02 July 2015.
- 16 Application GB1303868.2 "*Pharmaceutical composition and methods of treating and preventing the diseases caused by HIV or associated with HIV*" was filed on 15 July 2011, claiming an earliest priority date of 06 August 2010. It was published as GB 2497453 A on 12 June 2013. The Section 20 compliance period (as extended) expires on 06 December 2015. A first examination report was issued on 01 May 2013 that adopted sections V, VII, and VIII of the International Preliminary Report on Patentability that was issued on this application in the international phase of the PCT procedure. Amendments were filed on 02 December 2013, and a subsequent examination report was issued on 01 September 2014 in which issues of novelty, sufficiency, and industrial application were raised. After a telephone conversation on 13 January 2015, a request for an oral hearing was submitted on 11 February 2015. A pre-hearing report was issued on 03 March 2015 that set out the outstanding

issues to be considered at the requested hearing. A hearing was appointed for 02 July 2015.

- 17 Application GB1303983.9 "*Drug and method for the prophylaxis of HIV infection and for the prophylaxis and treatment of diseases caused by or associated with HIV, including AIDS*" was filed on 15 July 2011, claiming an earliest priority date of 06 August 2010. It was published as GB 2498276 A on 10 July 2013. The Section 20 compliance period (as extended) expires on 06 December 2015. A first examination report was issued on 17 April 2013 that adopted sections I and V of the International Preliminary Report on Patentability that was issued on this application in the international phase of the PCT procedure. Amendments were filed on 21 October 2013, and a subsequent examination report was issued on 13 August 2014 in which issues of sufficiency and industrial application were raised. After a telephone conversation on 13 January 2015, a request for an oral hearing was submitted on 11 February 2015. A pre-hearing report was issued on 03 March 2015 that set out the outstanding issues to be considered at the requested hearing. A hearing was appointed for 02 July 2015.
- 18 A first oral hearing was held on 18 June 2015. In attendance at the hearing were the agent representing the Applicant (Mr. Thomas Leonard of Kilburn & Strode LLP, hereinafter "the Agent") and his technical assistant (Dr. Rosemary Lees of Kilburn & Strode LLP). Also in attendance were Mr. Christopher Freeth (Solicitor) of Wragge Lawrence Graham & Co. LLP, Mr. Edward D. Pergament (Counsellor at Law) of Pergament Gilman & Cepeda LLP, Dr. Michael P. Kenney (Counsellor at Law) of Pergament Gilman & Cepeda LLP, Mr. Sergey Tarasov of OOO "NPF" Materia Medica Holdings, and Ms. Darya Reznichenko of OOO "NPF" Materia Medica Holdings. The Hearing Officer was assisted by Dr. Richard Wood. This hearing dealt with applications GB1302651.3; GB1302653.9; GB1302924.4; GB1302925.1; and GB1302928.5. The applicant filed a skeleton argument accompanied by 36 exhibits, as well as 8 witness statements with a total of 53 associated exhibits, relating to these applications one week before the hearing on 11 June 2015.
- 19 A second oral hearing was held on 02 July 2015. The attendees, with the exception of Mr. Edward D. Pergament, were the same as for the first oral hearing; the Hearing Officer was assisted by Dr. Simon Grand. This hearing dealt with applications GB1302654.7; GB1302926.9; GB1302929.3; GB1303867.4; GB1303868.2 and GB1303983.9. The Applicant filed a skeleton argument accompanied by 19 exhibits, as well as 5 witness statements with a total of 70 associated exhibits 4 days before the hearing on 29 June 2015.
- 20 Before the first hearing, the Hearing Officer requested that the Agent provide submissions in respect of the points raised in the pre-hearing report(s) especially with respect to sufficiency and industrial application. Furthermore, the Hearing Officer requested that he be addressed on the nature of the active compound/agent in the claimed compositions, and the relevance of the EPO Boards of Appeal decision in T-1273/09. Additionally, the Hearing Officer requested that the Agent provide submissions regarding the theory of ultra-low doses of antibodies, specifically: its level of acceptance by the community of scientists working in the relevant discipline; its consistency with existing generally accepted theories; and testable predictions made by the theory. The Hearing Officer especially asked the

Agent to consider the decision in *Blacklight Power v The Comptroller-General of Patents* [2008] EWHC 2763 (Pat).

- 21 In light of the submissions and arguments presented at the first hearing, the Hearing Officer asked the Agent to provide submissions at the second hearing pertaining to the decisions in *Biogen Inc v Medeva plc* [1997] RPC 1, *Novartis AG v Johnson & Johnson* [2009] EWHC (Pat) 1671; [2010] EWCA Civ 1039, and *American Home Products Corp. v Novartis Pharmaceuticals UK Ltd* [2001] RPC 8.

Claims

Version of claims on file at the hearing

- 22 The independent claims on file at the time of the oral hearings for each application are detailed below. These claims were submitted ahead of each respective oral hearing and were the version of the claims considered at each hearing.

- 23 GB1302651.3

Claim 1:

A pharmaceutical composition comprising a) a mixture of one or more repeated consecutive dilutions of an antibody to prostate-specific antigen, and b) a mixture of one or more repeated consecutive dilutions of an antibody to endothelial NO-synthase.

- 24 GB1302653.9

Claim 1:

A combination pharmaceutical composition comprising a) a mixture of activated-potentiated forms of an antibody to S-100 protein, b) a mixture of activated-potentiated forms of an antibody to histamine, and c) a mixture of activated-potentiated forms of an antibody to TNF-alpha.

Claim 41:

A method of obtaining a pharmaceutical composition comprising a mixture of activated-potentiated forms of an antibody to histamine, a mixture of activated-potentiated forms of an antibody to S-100 protein and a mixture of activated-potentiated forms of an antibody to TNF-alpha, the method comprising the steps of preparing consecutive repeated dilutions of the antibodies and multiple shaking of each obtained solution in accordance with homeopathic technology, and then either combining the potentiated solutions by mixing them, or, alternatively, impregnating a earner [sic] mass with said combined solution or with the solutions separately.

- 25 GB1302654.7

Claim 1:

A combination pharmaceutical composition comprising a) a mixture of activated potentiated forms of an antibody to S-100 protein, b) a mixture of activated-potentiated forms of an antibody to histamine, and c) a mixture of activated-potentiated forms of an antibody to TNF-alpha.

Claim 41:

A method of obtaining a pharmaceutical composition comprising a mixture of activated-potentiated forms of an antibody to histamine, a mixture of activated-potentiated forms of an antibody to S-100 protein and a mixture of activated-potentiated forms of an antibody to TNF-alpha, the method comprising the steps of preparing consecutive repeated dilutions of the antibodies and multiple shaking of each obtained solution in accordance with homeopathic technology, and then either combining the potentiated solutions by mixing them, or, alternatively, impregnating a earner [sic] mass with said combined solution or with the solutions separately.

26 GB1302924.4

Claim 1:

A pharmaceutical composition comprising a) a mixture of activated-potentiated forms of an antibody to a C-terminal fragment of the beta subunit of human insulin receptor, and b) a mixture of activated-potentiated forms of an antibody to endothelial NO synthase.

Claim 36:

A method of making a pharmaceutical composition for treating a patient suffering from diabetes comprising a) a mixture of activated-potentiated forms of an antibody to a C25 terminal fragment of human insulin receptor and b) a mixture of activated-potentiated forms of an antibody to endothelial NO-synthase, the method comprising preparing consecutive repeated dilutions of each antibody and multiple shaking of each obtained solution in accordance with homeopathic technology, and then either combining the potentiated solutions by mixing them, or, alternatively, impregnating a carrier mass with said combined solution or with the solutions separately.

27 GB1302925.1

Claim 1:

A combination pharmaceutical composition comprising a) a mixture of activated potentiated forms of an antibody to brain-specific protein S-100 and b) a mixture of activated potentiated forms of an antibody to endothelial NO synthase.

Claim 21:

A method of preparing a pharmaceutical composition comprising a mixture of activated-potentiated forms of an antibody to brain-specific protein S-100 and b) a mixture of activated-potentiated forms of an antibody to endothelial NO

synthase, the method comprising the steps of preparing consecutive repeated dilutions of each of the antibodies and multiple shaking of each obtained solution, and then either combining the potentiated solutions by mixing them, or, alternatively, impregnating a carrier mass with said combined solution or with the solutions separately.

28 GB1302926.9

Claim 1:

A combination pharmaceutical composition comprising a) a mixture of activated-potentiated forms of an antibody to bradykinin, b) a mixture of activated-potentiated forms of an antibody to histamine and c) a mixture of activated-potentiated forms of an antibody to morphine.

Claim 14:

A method of obtaining a pharmaceutical composition comprising a mixture of activated-potentiated forms of an antibody to bradykinin, a mixture of activated-potentiated forms of an antibody to histamine and a mixture of activated-potentiated forms of an antibody to morphine, the method comprising preparing consecutive repeated dilutions of each of the antibodies and multiple shaking of each obtained solution in accordance with homeopathic technology, and then either combining the potentiated solutions by mixing them, or, alternatively, impregnating a carrier mass with said combined solution or with the solutions separately.

29 GB1302928.5

Claim 1:

A combination pharmaceutical composition comprising a mixture of activated-potentiated forms of an antibody to brain-specific protein S-100 and a mixture of activated-potentiated forms of antibodies to endothelial NO synthase for use in treating attention deficit hyperactivity disorder, or for use in treating attention deficit disorder.

Claim 19:

A pharmaceutical composition comprising a mixture of activated-potentiated forms of an antibody to brain-specific protein S-100 and a mixture of activated-potentiated forms of an antibody to endothelial NO synthase, wherein the pharmaceutical composition is obtained by method comprising preparing consecutive repeated dilutions of each of the antibodies and multiple shaking of each obtained solution in accordance with homeopathic technology, and then either combining the solutions by mixing them, or, alternatively, impregnating a carrier mass with said combined solution or with the solutions separately.

30 GB1302929.3

Claim 1:

A combination pharmaceutical composition comprising a) a mixture of activated-potentiated forms of an antibody to brain-specific protein S-5 100 and b) a mixture of activated-potentiated forms of an antibody to endothelial NO synthase, for use in treating Alzheimer's disease.

Claim 18:

A method of preparing a combination pharmaceutical composition comprising a mixture of activated-potentiated forms of an antibody to brain-specific protein S-100 and a mixture of activated-potentiated forms of an antibody to endothelial NO synthase, the method comprising preparing consecutive repeated dilutions of the antibodies and multiple shaking of each obtained solution, and then either combining the potentiated solutions by mixing them, or, alternatively, impregnating a carrier mass with said combined solution or with the solutions separately.

31 GB1303867.4

Claim 1:

A combination pharmaceutical composition comprising a) a mixture of activated-potentiated forms of an antibody to CD4 and b) a mixture of activated-potentiated forms of an antibody to gamma interferon.

Claim 14:

A method of making pharmaceutical composition comprising a mixture of activated potentiated forms of an antibody to CD4 and a mixture of activated-potentiated forms of an antibody to gamma interferon, the method comprising preparing consecutive repeated dilutions of each of the antibodies and multiple shaking of each obtained solution in accordance with homeopathic technology, and then either combining the potentiated solutions by mixing them, or, alternatively, impregnating a carrier mass with said combined solution or with the solutions separately.

Claim 15:

A method of making pharmaceutical composition comprising a mixture of activated-potentiated forms of an antibody to CD4, a mixture of activated-potentiated forms of an antibody to gamma interferon and a mixture of activated-potentiated forms of an antibody to histamine, the method comprising preparing consecutive repeated dilutions of each of the antibodies and multiple shaking of each obtained solution in accordance with homeopathic technology, and then either combining the potentiated solutions by mixing them, or, alternatively, impregnating a carrier mass with said combined solution or with the solutions separately.

Claim 16:

A method of making pharmaceutical composition comprising a mixture of activated-potentiated forms of an antibody to CD4, a mixture of activated-potentiated forms of an antibody to gamma interferon, a mixture of activated-

potentiated forms of an antibody to CD8 and a mixture of activated-potentiated forms of an antibody to alpha interferon, the method comprising preparing consecutive repeated dilutions of each of the antibodies and multiple shaking of each obtained solution in accordance with homeopathic technology, and then either combining the potentiated solutions by mixing them, or, alternatively, impregnating a carrier mass with said combined solution or with the solutions separately.

32 GB1303868.2

Claim 1:

A pharmaceutical composition comprising a mixture of activated-potentiated forms of an antibody to HIV protein, wherein the HIV protein is selected from the group consisting of HIV protease and HIV capsid protein P24.

33 GB1303983.9

Claim 1:

A medicinal agent for the treatment of HIV and AIDS, the medicinal agent comprising a mixture of activated-potentiated forms of antibodies to a protein or a peptide of the immune system that interacts with HIV or whose content and/or functional activity changes thanks to the HIV contamination, wherein the protein or peptide is selected from the group consisting of tumor necrosis factor alpha, alpha interferon and CD8.

Amended Claims Filed After Hearing & Currently On-File

34 Following the two oral hearings, on 10 July 2015, the Applicant filed a new set of amended claims for each of these 11 applications. The amendments proposed limit each of the independent composition claims to the specific dilutions disclosed in each application, i.e. the mixture of activated-potentiated forms of an antibody was either in the form of a mixture of “C12, C30 and C200 dilutions” or a mixture of “C12, C30 and C50 dilutions”. In addition, the independent method claims (as identified above) were deleted or made dependent on the independent composition claim leaving only an independent composition claim for each application (see below). One independent composition claim was amended to refer to “a mixture of activated-potentiated forms of an antibody” rather than “to a mixture of one or more repeated consecutive dilutions of an antibody”.

35 The amended claims for each application are listed below:

GB1302651.3

Claim 1:

A pharmaceutical composition comprising a) a mixture of activated-potentiated forms of an antibody to prostate-specific antigen, and b) a mixture of activated-potentiated forms of an antibody to endothelial NO-synthase, wherein each of said mixtures of activated-potentiated forms of the antibodies is in the form of a mixture of C12, C30 and C200 dilutions.

GB1302653.9

Claim 1:

A pharmaceutical composition comprising a mixture of activated-potentiated forms of an antibody to human cannabinoid receptor 1 (CB1), wherein said mixture of activated-potentiated forms of an antibody to human CB1 is in the form of a mixture of C12, C30 and C200 dilutions.

GB1302654.7

Claim 1:

A combination pharmaceutical composition comprising a) a mixture of activated potentiated forms of an antibody to S-100 protein, b) a mixture of activated-potentiated forms of an antibody to histamine, and c) a mixture of activated-potentiated forms of an antibody to TNF-alpha, wherein each of said mixtures of activated-potentiated forms of the antibodies is in the form of a mixture of C12, C30 and C200 dilutions.

GB1302924.4

Claim 1:

A pharmaceutical composition comprising a) a mixture of activated-potentiated forms of an antibody to a C-terminal fragment of the beta subunit of human insulin receptor, and b) a mixture of activated-potentiated forms of an antibody to endothelial NO synthase, wherein each of said mixtures of activated-potentiated forms of the antibodies is in the form of a mixture of C12, C30 and C200 dilutions.

GB1302925.1

Claim 1:

A combination pharmaceutical composition comprising a) a mixture of activated potentiated forms of an antibody to brain-specific protein S-100 and b) a mixture of activated potentiated forms of an antibody to endothelial NO synthase., wherein each of said mixtures of activated-potentiated forms of the antibodies is in the form of a mixture of C12, C30 and C200 dilutions.

GB1302926.9

Claim 1:

A combination pharmaceutical composition comprising a) a mixture of activated-potentiated forms of an antibody to bradykinin, b) a mixture of activated-potentiated forms of an antibody to histamine and c) a mixture of activated-potentiated forms of an antibody to morphine wherein each of said mixtures of activated-potentiated forms of the antibodies is in the form of a mixture of C12, C30 and C50 dilutions.

GB1302928.5

Claim 1:

A combination pharmaceutical composition comprising a mixture of activated-potentiated forms of an antibody to brain-specific protein S-100 and a mixture

of activated-potentiated forms of antibodies to endothelial NO synthase for use in treating attention deficit hyperactivity disorder, or for use in treating attention deficit disorder, wherein each of said mixtures of activated-potentiated forms of the antibodies is in the form of a mixture of C12, C30 and C200 dilutions.

GB1302929.3

Claim 1:

A combination pharmaceutical composition comprising a) a mixture of activated-potentiated forms of an antibody to brain-specific protein S-100 and b) a mixture of activated-potentiated forms of an antibody to endothelial NO synthase, for use in treating Alzheimer's disease, wherein each of said mixtures of activated-potentiated forms of the antibodies is in the form of a mixture of C12, C30 and C200 dilutions.

GB1303867.4

Claim 1:

A combination pharmaceutical composition comprising a) a mixture of activated-potentiated forms of an antibody to CD4 and b) a mixture of activated-potentiated forms of an antibody to gamma interferon, wherein each of said mixtures of activated-potentiated forms of the antibodies is in the form of a mixture of C12, C30 and C50 dilutions.

GB1303868.2

Claim 1:

A pharmaceutical composition comprising a mixture of activated-potentiated forms of an antibody to HIV protein, wherein the HIV protein is selected from the group consisting of HIV protease and HIV capsid protein P24, wherein said mixtures of activated-potentiated forms of the antibodies is in the form of a mixture of C12, C30 and C50 dilutions.

GB1303983.9

Claim 1:

A medicinal agent for the treatment of HIV and AIDS, the medicinal agent comprising a mixture of activated-potentiated forms of antibodies to a protein or a peptide of the immune system that interacts with HIV or whose content and/or functional activity changes thanks to the HIV contamination, wherein the protein or peptide is selected from the group consisting of tumour necrosis factor alpha, alpha interferon and CD8, wherein each of said mixtures of activated-potentiated forms of the antibodies is in the form of a mixture of C12, C30 and C50 dilutions.

The Examiners' Arguments

- 36 The views of the respective examiners dealing with these applications can be summarised succinctly and simply, i.e., the compositions and medical uses claimed

in each of the applications go against the current opinion of the scientific community as a whole, because, statistically speaking, the compositions claimed do not contain a single molecule of the starting antibody and so there is no active agent present to exert a therapeutic effect.

- 37 In consequence, for each of the applications, the Examiner raised objection under section 1(1)(c) of the Act that the invention as claimed was not capable of industrial application because it was not considered plausible that ultra-low doses of antibodies had any effect beyond the placebo effect. The claimed inventions operate in a manner that is contrary to well-established physical and chemical laws because the ultra-high dilutions of antibodies result in solutions that, statistically speaking, do not contain a single molecule of the starting antibody.
- 38 Related to this, for each of the applications, the Examiner raised objection under section 14(3) of the Act that the invention as claimed was not disclosed in sufficient detail to enable the skilled person to work the invention. In particular, the Examiner argued that the applications did not give sufficient evidence of what was responsible for the claimed therapeutic effects and therefore that the effects could not be reliably repeated by the skilled person. Furthermore, the Examiners argued that there is insufficient evidence in the applications to overcome existing scientific opinion about the effectiveness of the claimed ultra-low doses of antibodies.
- 39 In addition, the objections raised by the Examiner under Section 1(1)(a) that the applications concerned lacked novelty was based on the argument that, as the preparations disclosed were all prepared in the same manner, the ingredients that remain after the dilution process are solvent and any inactive excipients associated with the solution because no molecules of antibody would be expected to be present. Hence, any preparation made in the same way, discloses the same preparation.

The Applicant's Arguments

- 40 The thrust of the Applicant's arguments are that each of the applications at issue discloses tests that demonstrate the efficacy of the compositions of the inventions. The applications each teach how to prepare the compositions, and the therapeutic effect of the compositions has been demonstrated in a repeatable manner.
- 41 The plausibility of the invention is demonstrated by the effective therapeutic response, obtained from compositions prepared according to the invention. The data on efficacy of the compositions is supported by various witness statements. If the invention leads to an effective therapeutic response, then compositions prepared according to the method of the invention are more than just solvent.
- 42 It is not necessary to demonstrate how these inventions work. Nonetheless evidence has been provided in support of a new scientific discovery that compositions of this type are more than simply solvent (see JKS document discussion later).
- 43 The Applicant argues that not only have these compositions been shown to be effective, but also in view of the supporting witness statements (and additional data),

the observed effects of these compositions are not counter to the prevailing view of the scientific community.

- 44 Therefore the inventions are plausible and fulfil the requirements for industrial application, sufficiency and novelty.
- 45 In addition, the Intellectual Property Office has exceeded its remit by laying an undue burden on the Applicant.

The issues to be decided

- 46 As noted above, the issues to be decided are whether the applications at issue comply with sections 1(1)(a), 1(1)(c), and 14(3) of the Act, that is whether the claimed inventions are novel, are capable of industrial application, and are disclosed in sufficient detail to enable the skilled addressee to work them.
- 47 I will first consider the issue whether these applications relate to inventions that are capable of industrial application under Section 1(1)(c) and are disclosed in a manner which is clear enough and complete enough for the invention to be performed by a person skilled in the art sufficiency as required under Section 14(3).
- 48 If I find that the application meets the requirements under Section 1(1)(c) and under Section 14(3), I will then go on to consider the issue of novelty under Section 1(1)(a).
- 49 Should I find that the applications are capable of industrial application, are sufficiently disclosed and are novel, I will remit the cases back to the Examiners dealing with the respective cases for completion of the examination process.
- 50 Further, as the issues of industrial application and sufficiency are the same for each of the 11 applications in question, rather than considering each application individually, I will consider these applications all together.
- 51 Similarly, for each application with the exception of GB1303983.9, the issue of novelty was raised. If it is necessary for me to consider novelty, as the issue raised on all the cases was substantially similar, I propose to consider the 10 applications together as a group rather than individually.
- 52 In assessing the issues of industrial application, sufficiency, and novelty for these applications, I will take account of the submissions and arguments presented at both of the oral hearings.

The Law and Relevant Case Law

- 53 Section 1(1)(c) of the Act sets out the criteria for industrial application as follows:

“A patent may be granted only for an invention in respect of which the following conditions are satisfied, that is to say -

(a) ...;

(b) ...;

(c) *it is capable of industrial application;*

(d) ...;

and references in this Act to a patentable invention shall be construed accordingly."

54 Section 4(1) of the Act further defines industrial application:

"An invention shall be taken to be capable of industrial application if it can be made or used in any industry, including agriculture."

The test set out in section 1(1)(c) and further elaborated in section 4 of the Act are framed to have, as nearly as practicable, as section 130(7) of the Act makes clear, the same effects in the UK as the corresponding provisions of the EPC; in this instance Article 52(1) and Article 57. Thus, although not binding on the IPO, decisions on patentability given by EPO Boards of Appeal have persuasive value in interpreting sections 1 and 4 of the Act.

55 Section 14 deals with the requirement for sufficiency of the specification at the application stage:

"(2) Every application for a patent shall contain –

(a) ...;

(b) a specification containing a description of the invention,

(3) The specification of an application shall disclose the invention in a manner which is clear enough and complete enough for the invention to be performed by a person skilled in the art."

56 It is established practice that Section 14(3) of the Act means the applicant must ensure that, at the time of filing, the specification discloses the essential features of the invention in sufficient detail for the skilled person to be able to put the invention into practice. If the disclosure of the invention claimed is not clear and complete enough, then either the application must be refused or the claims restricted to matter that is adequately disclosed. Any deficiencies in the specification cannot be rectified by adding technical matter after filing as this would contravene section 76 of the Act.

Relevant Case Law – UK Courts

57 In *Chiron Corp v Murex Diagnostics Ltd and other* [1996] RPC 535 (page 607), hereafter *Chiron*, the Court of Appeal held that the requirement that the invention can be made or used "*in any kind of industry*" so as to be "*capable of industrial application*" carries the connotation of trade or manufacture in its widest sense, whether or not for commercial profit. "*Industry*" in this context is understood in its broad sense as including any useful and practical, as distinct from intellectual or

aesthetic, activity. The Court went on to hold that industry does not “*exist in that sense to make or use that which is useless for any known purpose*”.

58 In *Human Genome Sciences v Eli Lilly* [2011] UKSC 51, [2012] RPC 6, hereafter *Human Genome Sciences*, the question of industrial application (Articles 52 and 57 EPC equivalent to Section 1(1)(c) and Section 4, respectively, of the Act) and its application to patents for biological material was considered in some detail. The invention concerned a gene, Neutrokin- β , which had been found by data mining techniques, and a function was assigned to this gene based upon its homology to other members of the Tumour Necrosis Factor (TNF) ligand superfamily, but without any data obtained from *in vivo* or *in vitro* studies. The UK Supreme Court, having considered UK case law and European jurisprudence, overturned the decision of the Patents Court (previously upheld at appeal), because the basis upon which the judge in the lower court had decided the issue was not consistent with the approach adopted by the EPO Technical Board of Appeal in decision T-0018/09. Lord Neuberger summarized the Board’s approach regarding the requirements of Article 57 EPC in relation to biological material in a set of fifteen points, and concluded that in light of these points the patent in suit satisfied the requirement of Article 57 i.e. was industrially applicable. The majority of the fifteen points relate specifically to the biomedical fields; however the principles set out in points 1-4 can be applied broadly when considering the industrial application of a patent¹. The first four points for consideration are as follows:

- (i) The patent must disclose “a practical application” and “some profitable use” for the claimed substance, so that the ensuing monopoly “can be expected [to lead to] some ... commercial benefit”;
- (ii) A “concrete benefit”, namely the invention’s “use ... in industrial practice” must be “derivable directly from the description”, coupled with common general knowledge;
- (iii) A merely “speculative” use will not suffice, so “a vague and speculative indication of possible objectives that might or might not be achievable” will not do;
- (iv) The patent and common general knowledge must enable the skilled person “to reproduce” or “exploit” the claimed invention without “undue burden”, or having to carry out “a research programme”;

59 In *Blacklight Power Inc. v The Comptroller-General of Patents*, [2008] EWHC 2763; [2009] RPC 6, hereafter referred to as *Blacklight Power*, the Patents Court determined that the correct test to apply when considering whether or not an application based on a new scientific theory is patentable under Section 1(1)(c) of the Act is one based on the balance of probabilities. The judgment, referring to various authorities which considered exclusion to patentability under section 1(2) rather than requirements for patentability under section 1(1), at paras 33 and 34 states:

¹ Points (v)-(x) relate to situations where a patent discloses a new protein and its encoding gene, while points (xi) – (xv) relate to situations where the protein is said to be a member of a family or superfamily.

“33. Although all these cases are concerned with exclusions to patentability, I cannot think that the same does not apply to objections to patentability such as we are concerned with here. **The Office, at the application stage, is necessarily an imperfect tribunal of fact. For example if there is a genuine dispute as to whether a particular technical fact is part of the common general knowledge, the Office may or may not be able to resolve it. There may be substantial doubt about it. It may be critical to whether the application is allowed or refused. In those circumstances an application should not be refused, because an incorrect refusal cannot be remedied at a later stage.**

34. I think that the effect of these authorities is as follows. **It is not the law that any doubt, however small, on an issue of fact would force the Comptroller to allow the application to proceed to grant. Rather he should examine the material before him and attempt to come to a conclusion on the balance of probabilities. If he considers that there is a substantial doubt about an issue of fact which could lead to patentability at that stage, he should consider whether there is a reasonable prospect that matters will turn out differently if the matter is fully investigated at a trial. If so he should allow the application to proceed.**

- 60 The judge make clear, at para 35, that “*If there is such a reasonable prospect he [the examiner] should allow the matter to proceed to grant.* In addition, he indicated that “*The reasonable prospect must be based on credible material before the Office. Macawberism, here as elsewhere, does not provide any basis for supposing that anything helpful will turn up.*” The judge also commented that “*It goes without saying that mere optimism and a reasonable prospect of matters turning out differently are not the same thing.*”
- 61 The judgement states that this is the test to apply if there is a “*substantial doubt*” about an issue of fact which is relevant to determining the patentability of an invention under section 1(1)(c) of the Act. As pointed out by the judge at para 37, if there is no such “*substantial doubt*”, as in the case of a claim to a perpetual motion machine, then there “*is no reasonable prospect that matters will turn out differently on a fuller investigation*”. Such an application should be refused.
- 62 The judge also made the point that “*the greater has been the opportunity for the applicant to produce such material at the application stage, the smaller scope there is for supposing that giving him the benefit of the doubt will lead to a different conclusion before the courts.*”
- 63 In this case, the judge was not able to go on and decide whether, if the Hearing Officer had applied the correct test (i.e. the balance of probabilities test that the court had identified), he should have allowed the application in question to proceed to grant. As a result, the case was remitted back to the Hearing Officer for him to reconsider the evidence based on the correct test identified by the court and determine whether or not the two applications in question could be granted.

Relevant IPO decisions

- 64 The Hearing Officer in BL O/170/09 (*Blacklight Power Inc.’s Applications*), dealing with the two remitted patent applications following the outcome of the appeal to the Patents Court discussed above, reviewed the applications in light of the test

identified in that judgement. He concluded that the court had already made clear in the terms of the remittal that it had taken the view that there was a substantial doubt about the validity of the scientific theory on which these applications were based, and so he could proceed directly to consider if there was a reasonable prospect that this conclusion would turn out differently if the matter was fully investigated at a trial. The Hearing Officer used the same approach he outlined in his original decision (see para 22 of BL O/114/08) wherein he proposed that theories that are generally accepted as valid descriptions of nature have three main criteria which he summarised as follows:

“a) the explanation provided by the theory is consistent with existing generally accepted theories. If it is not, it should provide a better explanation of physical phenomena than do current theories, and should be consistent with any accepted theories that it does not displace;

b) the theory should make testable predictions, and experimental evidence should show rival theories to be false and should match the predictions of the new theory;

c) the theory should be accepted as a valid explanation of physical phenomena by the community of scientists who work in the relevant discipline.

It may be that other criteria can be identified, for example that a successful theory should also be intellectually satisfying and economical in its explanation, but I think that for any theory to be accepted as “true” it must satisfy at least a), b) and c) above.”

- 65 In BL O/336/08 (*Robinson’s Application*), the claimed invention related to a more accurate way of determining the velocity of a remote object in space using a relativistic effect. The examiner considered that this application failed section 1(1)(c) and 14(3) of the Act because it contravened Einstein’s theory of special relativity. In applying the test from *Blacklight Power*, the Hearing Officer found that there was a substantial doubt and used the same criteria as the Hearing Officer in BL O/170/09 to assess the reasonable prospect. He found that there was a substantial doubt about the validity of the underlying theory on which the invention was based and there was no reasonable prospect that a full investigation with the benefit of expert evidence would find it to be valid.

Analysis

- 66 In the discussion below, I will use the term ‘active agent’ in its conventional sense, i.e. to refer to an entity that has a chemical or biological interaction with other entities, e.g. an antibody is the active agent that has a biological or chemical interaction with an antigen, a chemical compound is the active agent that has a chemical or biological interaction with a receptor or another chemical compound. To contrast with the term active agent, I will use the term ‘active principle’ to refer to that feature or phenomenon that gives a unique nature to the ultra-low dose (ULD) compositions in these applications such that they have a therapeutic effect over and above that of solvent alone.

- 67 In both sets of skeleton arguments filed in advance of the hearings, the Agent stated, “[t]he plausibility of the data in each application appears to underlie the objections raised by the Examiner. Since the Examiner has not acknowledged the effects demonstrated in each application, novelty, sufficiency and industrial applicability have not been acknowledged”.
- 68 The Agent states that the applications at issue are all based “on a new scientific discovery, specifically a previously unidentified mechanism for modulating confirmation and biological functioning of receptors using antibodies that are diluted to ultra-low concentrations”. He goes on to state that the “data contained within each application demonstrates a real, useful effect of the claimed pharmaceutical compositions. The effects are plausible based on the data in the applications. Moreover, the stated effects of the claimed compositions are supported by the scientific community.” The witness statements and supporting exhibits provided with the skeleton arguments provide additional support and evidence regarding the plausibility of the data in the applications.
- 69 At the hearing and in the skeleton arguments, ‘plausibility’ was the term used to refer to the need to show that the disclosure in each application meets the requirements of the Act and, on the balance of probabilities, relates to an invention that does not contravene well established scientific theory and that is described in sufficient detail to be worked by a person skilled in the art. Also as the Applicant considers that the novelty objections raised by the examiner on these applications are also based on an incorrect analysis of the significance of the therapeutic results and of the disclosure in each applications, they consider that all of the outstanding objections on these applications can be overcome by demonstrating that the compositions of the inventions do have a therapeutic effect and therefore are not just solvent and excipients. If the Applicant can demonstrate that the invention as claimed in each instance is plausible then this will overcome the objections to industrial application, sufficiency and novelty given that these objections all flow from the same argument – that the inventions as claimed relate to compositions that do not contain any therapeutic molecule i.e. antibody. Consequently, the Applicant has provided a great deal of evidence and argument with respect to the use of the compositions of the 11 applications before me, in an attempt to establish that the inventions are all indeed plausible.
- 70 I consider that this is a helpful way to approach the key issue in this case.
- 71 The invention put forward in all the applications is that of ultra low dilutions of antibodies which (statistically speaking) no longer contain any molecules of antibody and can be used to prepare solid and liquid dosage forms which have measurable therapeutic effects using appropriate methods accepted in the prior art. These inventions have been termed *chimeric* in nature, i.e. they are obtained by dilution of an antibody (rather than an antigen as would be the case in homeopathy) with external treatment, usually vertical mechanical shaking, - a preparative technique from homeopathy – and are used to produce compositions in solid and/or liquid form that have a therapeutic effect. This therapeutic effect is measured using appropriate techniques e.g. tests in various animal models, such as rats, mice and guinea pigs. Thus the process of dilution and external treatment of an antibody to obtain a mixture of ultra low dilutions of antibody produces an activated-potentiated form (or release-

active form) of the antibody which, although there is no molecule of antibody present (as disclosed in each application), is still able to exert a therapeutic effect.

- 72 The examiner considers that the inventions disclosed in the applications at issue are contrary to well established theories of medicine and how molecules such as antibodies exert their therapeutic effects. Such therapeutic effects are understood in terms of well established principles of medicine and are based on an interaction between an agent that has a therapeutic effect such as an antibody or a small chemical entity and a target for this therapeutic activity such as an antigen or a receptor. Such an interaction takes place where the antibody binds to the antigen and leads to a measurable change in some property of the antigen and antibody, e.g. light properties, conformational properties, binding properties, reactivity etc. The effect may be to increase activity (agonism) or reduce activity (antagonism) and various physical and chemical techniques are available in the art for measuring therapeutic effects, e.g., assays, spectroscopy. The applications as filed do not offer any explanation as to how the compositions claimed achieve the therapeutic effects disclosed in each application.
- 73 The examiner argues, in relation to each application that, as it is admitted in the description, there is no antibody molecule present in the mixtures of ultra low dilutions of antibody, and so any therapeutic effect observed is not dependent on the presence of an active agent. The mixtures of ultra low dilutions of an antibody will comprise molecules of solvent – either water or water & alcohol – and, possibly any excipients or impurities from the solvent. Thus any effects observed for these compositions cannot be understood on the basis of an understanding of conventional antibody-antigen interactions based on a molecule of antibody binding to a molecule of antigen. There is no active agent involved in the sense that is normally understood. Hence the examiners conclusion that these applications disclose a placebo effect and lack industrial application and sufficiency. Although the Applicant names the mixtures of ultra low dilutions of an antibody as activated-potentiated forms of the antibody, in the applications as filed there is no explanation of how these activated potentiated forms of the antibody exert their therapeutic effect.
- 74 In a case such as the present in which the requirements for industrial application and sufficiency of description turn on the validity of the underlying theory, the question arises as to what standard of proof should be applied by the examiner. Guidance on this was given in *Blacklight Power*. Following the approach outlined in *Blacklight Power*, based on the material before me in relation to these applications, I must decide if there is a substantial doubt about an issue of fact which could lead to patentability and if, on the balance of probabilities, there is a reasonable prospect that matters will turn out differently if this issue is fully investigated at trial with the benefit of expert evidence. If I consider there is a reasonable prospect, then I should allow these applications to proceed.
- 75 To assist my assessment, I will take the same approach as adopted by the respective Hearing Officers in BL O/114/08 & BL O/170/09 (*Blacklight Power*) and BL O/338/08 (*Robinson*). I consider this approach was endorsed by the Patents Court in *Blacklight Power* (see para 47). To consider whether the theory espoused in the patent applications at issue could be “*generally accepted as a valid theory of nature*” I will consider the plausibility of the applications under the following criteria:

a) *the explanation provided by the theory is consistent with existing generally accepted theories. If it is not, it should provide a better explanation of physical phenomena than do current theories, and should be consistent with any accepted theories that it does not displace;*

b) *the theory should make testable predictions, and experimental evidence should show rival theories to be false and should match the predictions of the new theory;*

c) *the theory should be accepted as a valid explanation of physical phenomena by the community of scientists who work in the relevant discipline. It may be that other criteria can be identified, for example that a successful theory should also be intellectually satisfying and economical in its explanation, but I think that for any theory to be accepted as “true” it must satisfy at least a), b) and c) above. Where I refer to the “truth” or “validity” of a scientific theory in this decision it is in that sense.”*

What is it that must be assessed?

76 It seems to me that the issue of the plausibility of the data in each application goes beyond merely whether the “*therapeutic effects demonstrated*” should be acknowledged (as the skeleton argument for the first hearing states). I consider that, as these applications all relate to compositions *per se* and not solely to therapeutic use, it is necessary to assess both:

a) The plausibility of the therapeutic data provided

b) The plausibility of the claimed compositions being able to elicit such a therapeutic effect?

77 As mentioned above, the present applications relate to the preparation of ultra-low doses (ULDs) of antibodies and their use in therapy. These ULD compositions are water or water-alcohol compositions containing no antibody/antibodies, but which are instead to said to have “release activity” (or to be “activated-potentiated”).

78 In assessing these compositions, I need to exercise care in my analysis of the inventions. The Agent was correct to point out that a disclosure or a description of the mechanism of action is not necessary for an invention to be patentable, and that I must be careful not to put a higher barrier in the way of these applications to demonstrate patentability than on others; the Agent in the skeleton arguments argues that already “*a burden of proof has been laid on the applicant that is disproportionate to that necessary for meeting the requirements of patentability*”.

79 However, as in *Blacklight Power*, where there is genuine doubt about the extent to which an invention relies on theory which is clearly contrary to well established physical laws, there is a burden on the Applicant to demonstrate that the prevailing view is not correct. I would not characterise this as a higher burden of proof than is necessary to meet any of the requirements under section 1(1) of the Act or, as the court reviewed in *Blacklight Power*, to show that the applications are not excluded under section 1(2) of the Act. I believe, therefore, that the burden of proof laid upon the Applicant is proportionate. I will return to this point later.

- 80 In light of the extremely high dilution factors involved in preparing the compositions of these applications, even if any antibodies were present in the compositions as described, their concentrations would be so vanishingly small that they would not be present in any biologically relevant amount. Consequently the claimed activities cannot be ascribed to a conventional chemical or biological interaction (such as drug/receptor or antibody/antigen interactions), and therefore the inventions as claimed would appear to operate in a way that is clearly contrary to the accepted principles of chemistry and medicine. It is therefore appropriate to ask what support is provided not only for the therapeutic activity of the compositions, but to ask also what evidence is provided in support of those compositions being able to act in such a fashion.
- 81 At this point, I note the Agent's reference to granted patent GB 2414670. This patent relates to homeopathic subject matter. The skeleton arguments for the first hearing state "*It is notable that there is a granted UK patent for homeopathic subject matter, GB2414670, further demonstrating the patentability of homeopathic subject matter*". However, I do not think that this assists me in determining the plausibility of these inventions. Firstly because the Applicant has been quick to assert that the current applications are not homeopathic, and, secondly, because the decision to grant a patent must be made on the basis of the law and the facts relating to the applications in question.

Plausibility – the view of the Applicant

- 82 At the oral hearings, the Agent presented a large body of material in order to address the issue of the plausibility of the inventions. These submissions can be summarised as follows:
- a) Evidence in support of a new scientific discovery comprising the expert evidence of Dr. Judith Klein-Seetharaman, who performed studies including NMR and light scattering studies that appear to show that ultra-dilute solutions of a single antibody (an antibody raised against IFN γ) have an effect on the conformation of IFN γ protein; an "activated-potentiated" distilled water placebo did not show the same effects;
 - b) For each of the applications as-filed, examples are included which demonstrate the effectiveness of the claimed pharmaceutical compositions, for example *in vivo* rat model studies, open-label clinical studies, and double-blind placebo controlled studies;
 - c) The fact that commercial products exist (that are marketed in Russia and elsewhere), and that those commercial products correspond to the claimed inventions; and sales figures relating to those commercial products;
 - d) Witness statements from a number of experts who attest to the plausibility of the inventions in light of the rat etc models and clinical trials and the data that was obtained from those trials; and witness statements from a number of experts who attest to the efficacy of the commercial products.
- 83 Based on these submissions, the arguments presented by the Agent can be summarised as follows:

- a) for each of the claimed combinations of ultra-high dilutions of antibodies, evidence is presented that plausibly suggests that the claimed combinations of mixtures of ultra-low doses of antibodies are effective in the various treatments that are claimed;
- b) in light of the testimony of the various experts, the stated effects of the claimed compositions “do not contradict the scientific community as a whole. In fact, the scientific community supports our position”;
- c) the inventions are capable of industrial application by virtue of the fact that products corresponding to the claimed inventions are being manufactured and sold, and the evidence provided to demonstrate their effectiveness.

The plausibility of the therapeutic data

84 The Applicant has provided numerous papers and trials in order to substantiate the assertion that the inventions are plausible. In addition, and more importantly (for consideration of sufficiency at least), witness statements have been provided in regard to the plausibility of the therapeutic data in the applications as filed. That provided by Dr Benjamin Buehrer’s statement (statement BMB) regarding patent applications GB1302924.4 and GB1202653.9 is typical.

85 In relation to the evidence filed in support of GB1202653.9, he states:

“I am unable to provide an explanation of the mechanism of action of the ultra-low dose of antibodies to CB1. Nevertheless, the data I have reviewed suggest to me that administration of activated-potentiated forms of an antibody to CB1 ... could plausibly be used in the treatment of obesity.”

In relation to the evidence filed in support of GB1302924.4 he states:

“Although it is difficult to understand why the activated-potentiated antibodies have the effect they do, there is clearly a difference between treatment with distilled water and treatment with ultra-low concentrations of antibodies, suggesting an effect on plasma glucose levels.

and:

“Taking into account the methodology used, the controls present, the sample sizes, and assuming the description of how the assay was performed is accurate (I have no reason to believe that it is not), the data in Study 1 of Example 1 ... certainly render it plausible that the combination of a mixture of activated-potentiated forms of an antibody to is an effective treatment for ... diabetes”

86 I am not in a position to critically evaluate the tests undertaken and certainly not to disregard the statements of the witnesses that the Applicant has collected. Thus I accept that the data provided indicates that a therapeutic effect is plausible, noting merely that none of the witnesses commenting on the examples within the applications appear to provide an explanation for how the ultra-low dose (ULD) compositions might work. Thus, I consider that what is being affirmed by the witness statements is the plausibility of the results on the basis of the information provided and not that of the “new scientific discovery” as such.

The plausibility of the claimed compositions being able to elicit such a therapeutic effect?

- 87 The applications as filed, the Applicant's statement in the skeleton arguments, and the Agent's arguments at the hearings all made it very clear that all of the compositions under consideration are diluted beyond the Avogadro limit and thus statistically contain none of the starting antibodies. Thus the composition is not acting in a conventionally understood chemical/pharmaceutical fashion. Furthermore, all of the submissions and arguments were equally clear that the compositions are not homeopathic; that is although they rely on homeopathic dilution techniques, they do not rely on homeopathic theory (like cures the like) for their efficacy.
- 88 As summarised above the examiners' view of the compositions in the various applications was that each composition comprises a solution of antibodies diluted below the Avogadro limit and that as a consequence they are merely water or water-ethanol. They also note that the consensus of the scientific and medical community is that homeopathic treatments based on the dilutions disclosed in these applications have not been proven to provide effects beyond placebo.
- 89 The Applicant quite rightly notes that the compositions in the applications at issue are not homeopathic; they are instead '*chimeric*'. They are posited to be both effective across the population and testable in 'conventional' medical fashion.
- 90 However, whilst it seems reasonable to distinguish these compositions from homeopathy as such, it is acknowledged that the preparation of the ULDs and the dilutions used relies on homeopathic methodology. The description of GB1302651.3 is typical of the applications when it states:

"The term 'activated-potentiated form' or 'potentiated form' respectively, with respect to antibodies recited herein is used to denote a product of homeopathic potentization of any initial solution of antibodies. 'Homeopathic potentization' denotes the use of methods of homeopathy to impart homeopathic potency to an initial solution of relevant substance. Although not so limited, 'homeopathic potentization' may involve, for example, repeated consecutive dilutions combined with external treatment, particularly vertical (mechanical) shaking. In other words, an initial solution of antibody is subjected to consecutive repeated dilution and multiple vertical shaking of each obtained solution in accordance with homeopathic technology. The preferred concentration of the initial solution of antibody in the solvent, preferably water or a water-ethyl alcohol mixture, ranges from about 0.5 to about 5.0 mg/ml. The preferred procedure for preparing each component, i.e. antibody solution, is the use of the mixture of three aqueous or aqueous-alcohol dilutions of the primary matrix solution (mother tincture) of antibodies diluted 100^{12} , 100^{30} and 100^{200} times, respectively, which is equivalent to centesimal homeopathic dilutions (C12, C30, and C200) or the use of the mixture of three aqueous or aqueous-alcohol dilutions of the primary matrix solution of antibodies diluted 100^{12} , 100^{30} and 100^{50} times, respectively, which is equivalent to centesimal homeopathic dilutions (C12, C30, and C50)".

- 91 Thus the generation of the active principle utilises ‘homeopathic potentization’. The nature of the initial solution does not conform to homeopathic theory, but the means by which antibodies are diluted beyond the Avogadro limit is still utilised. It is appropriate here to draw attention to the documents regarding homeopathy cited by the examiner against the various applications. These demonstrate the scepticism in the scientific community regarding the efficacy of homeopathic medicine. This scepticism derives not simply from the treatment of like with like (from which these applications clearly differ), but also from the doubts that an active principle can both be generated, and made more potent, by increasing levels of dilution. Mere statements that the current invention is not homeopathy do not overcome this hurdle to plausibility.
- 92 Hence if the methods used are understood to be homeopathic potentization in a strict sense then they rely on disputed science rejected by the conventional scientific view. However the point that seemed to be put before me by the Agent at the hearings was that, although the same dilution processes are gone through as in homeopathy, the starting solutions contain antibodies, and not allergens etc, so the similarity with homeopathy ends there – the starting material is the key feature and key difference.
- 93 Therefore I cannot rely on ‘homeopathic potency’ as it is usually understood and so how am I (in the place of the skilled worker) to understand how in physical or chemical terms an active principle is generated with confidence to disregard the conventional view that these ultra-dilute compositions are not merely solvent?
- 94 The Applicant postulates that the dilution process results in compositions which have “release activity” (to use the phrase used by Dr Epshtein in his statement) or are “activated-potentiated”. The Agent informed me at the hearing that studies are ongoing and referred me to Dr Epshtein’s statement saying *‘In addition to our work in clinical development of products containing RAF [release active form] antibodies and on exploring their mechanisms of action, we also developed evidence as to the existence of there being some form of a discreet physical factor’ – some physical entity – ‘the nature of which is yet unknown, present in such products and which produces the biological effects we observed’*”.
- 95 No further details of how this release activation works in chemical or physical terms are given in either the applications or the supporting evidence. The Agent argues that an explanation of how the compositions work is not necessary; the therapeutic evidence is enough and to ask for a mechanism of action is to place an undue burden on the Applicant. I shall return to this point later, but for now note only that no alternative scientific framework by which I might understand the generation of these active principles has been put before me.

Plausibility of the compositions: NMR and DLS studies

- 96 Thus, whilst the Applicant has provided much evidence which is intended to demonstrate that the compositions of the inventions have a technical effect, much less evidence has been presented that elucidates what is the active principle or the actual mode of action.

- 97 This evidence, provided in support of the theory that a discrete “physical factor” (to use the wording of Dr Epshtein’s statement) or other unknown active principle is present in the compositions, takes the form of a declaration and study by Dr Judith Klein-Seetharaman of the University of Pittsburgh (Exhibits JKS and JKS1)². In particular, this study investigated changes in conformation of the interferon gamma (IFNg) protein in the presence of activated-potentiated antibodies raised against IFNg. The “activated-potentiated” antibodies used in the study were prepared according to the methods described in the patent applications by the Applicant and supplied to Dr Klein-Seetharaman. They are referred to as “release active forms” or “RAF” antibodies in Exhibit JKS1. The study used nuclear magnetic resonance spectroscopy (NMR) and dynamic light scattering (DLS) to detect these changes and the results were compared to placebo (addition of “activated-potentiated” distilled water, i.e. distilled water that has undergone the same process as the test samples, without antibody in the starting solution).
- 98 According to Dr Klein-Seetharaman the NMR results indicate a change of conformation in the presence of the RAF antibodies solution, whilst no change was observed with the placebo. For the DLS results, it was suggested that the RAF antibody solution has no appreciable effect on the IFNg complex size.
- 99 The lack of an effect in the DLS experiments is of no direct assistance here; only confirming that no antibodies are actually present in solution. Therefore the only evidence of a physical difference between the RAF water placebo and the RAF antibodies are the NMR studies.
- 100 I note that Dr Klein-Seetharaman did not prepare her own samples in these experiments and thus it is not possible to quantify the likelihood of these results being as a result of sample contamination (for example, as suggested by the examiner of the International Preliminary Report on Patentability of 15 October 2012 on PCT/IB2011/002378 (corresponding to GB1302925.1)).
- 101 Dr Klein-Seetharaman states (my emphasis added) that:

*“The results of My Study **demonstrate** an effect of activated-potentiated forms of polyclonal antibodies to IFNg on the structure of IFNg. I also predict that these structural changes may lead to a modulation of receptor activity in the presence of the activated-potentiated forms of the antibodies when compared with the structural and functional characteristics of the IFNg in the absence of such antibodies. This is despite the fact the concentration of the antibodies is sufficiently low that the likelihood of an antibody molecule being present and being able to exert a direct effect via a “conventional” mechanism is almost zero. In addition, the noted effects for the RAF antibodies are not consistent with the expected effects of administration of conventional antibodies to IFNg. The use of the distilled water placebo further confirms that **the observed effects must be due to the RAF antibodies**, rather than as a result of the administration of any solvent or excipient present in the samples. For these reasons **it is my opinion that the activated-potentiated forms of IFNg have the ability to modulate the structural or conformational arrangement of IFNg,***

² Dr Klein-Seetharaman is currently working at the University of Warwick in UK.

and furthermore these changes may affect the functioning of IFNg in a biological system. The RAF antibodies could therefore represent a new method for modulation of biological systems.”

“I do not see a reason why the observed changes for RAF antibodies to IFNg would be limited to this protein alone, and it is plausible that similar results may be observed for other RAF antibodies and the corresponding antigen”.

102 These are very strong statements on the basis of limited evidence and seem rather more strident than might be expected of one study on one antibody given the apparent potential for experimental error (or the potential for other influences on protein conformation, e.g. perhaps including solvent effects etc). Nonetheless, this evidence cannot be lightly dismissed, and I shall have to give it due weight alongside the other evidence provided.

What am I taught about the nature of the compositions?

103 In addition to this evidence, the applications each state that the invention involves ultra-low doses (ULD) of antibodies, in the claims they are referred to as “activated-potentiated forms of antibodies” and in some of the supporting evidence they are referred to as “release-active forms” of antibodies. I find this plurality of terms confusing. I am working on the assumption that all three terms refer to the same thing. All of these terms describe water or water-alcohol compositions containing no antibody/antibodies, but which are said to have “release activity”.

104 The compositions of the applications are generated by multiple serial dilutions of an initial solution of particular antibodies. The point at which these diluted solutions

Table 2: Summary of dosage form type used in Examples disclosed in each application.

#	Application no.	Solution, in vitro	Solution, animal (non-human)	Tablet, human
1	GB1302651.3	-	Exs.1 and 3	Ex.2
2	GB1302653.9	Ex.1	Exs.2-3 and 10	Exs.4-9
3	GB1302925.1	Ex.1	Ex.3	Ex.2
4	GB1302928.5	Ex.1	-	Ex.2
5	GB1302654.7	-	Ex.1	Ex.2
6	GB1302924.4	-	Ex.1	Exs.2-4
7	GB1302926.9	-	Ex.1	Exs.2-4
8	GB1302929.3	Ex.1	Ex.3	Ex.2
9	GB1303868.2	Exs.1-4	-	-
10	GB1303983.9	Exs.1-3	-	-
11	GB1303867.4	Exs.1-5	Ex.6-7	Exs.8-12

become activated-potentiated (or release-active) is not defined, but I assume that this is at some point below the Avogadro limit.

105 The applications also indicate that solid carriers such as isomalt or lactose can also be impregnated with these ULD compositions. The exact nature of the solid unit dosage form does not appear to be important provided that granules of carrier previously saturated with the ULD solution form of antibodies are used. The described solid dosage form preparation involves saturation, irrigation in a fluidised boiling bed and subsequent drying via heated air flow at a temperature below 40 °C. Such solid dosage forms provide a very different chemical and physical environment than an oral solution dosage form. Table 2 below shows the distribution of examples using solid and liquid dosage forms in each of the 11 applications.

106 Thus to summarise, I am presented with evidence or other statements suggesting to me that the effects in the therapeutic data are:

- (i) determined by choice of initial antibodies according to conventional chemical/pharmaceutical criteria i.e. antibodies known to have an influence in pathways of the disease to be treated;
- (ii) attributed to the exposure of the initial solutions to the antibodies and dependent on the nature of the antibodies to which the solutions are exposed (i.e. different effects for the water control, single antibody ULD and multi-antibody ULD compositions are observed);
- (iii) produced using solutions prepared by homeopathic-type dilutions
- (iv) tested using conventional medical assays and studies (i.e. cell, macrophage, murine etc and human studies are all expected to give relevant results);
- (v) not attributed to the presence of antibodies in the final ULD (all dilutions used are below the Avogadro limit);
- (vi) caused by some difference in terms of possibly allosteric interaction, nature unknown, with cell proteins in water/alcohol (JKS document)
- (vii) not attributed to a conventional response i.e. modulation of activity at a receptor active site or antigen-antibody (DLS experiment in JKS document)
- (viii) not affected by environment of final dosage form (solution or impregnated isomalt solid dosage forms used)
- (ix) effective through gastric administration (all human tests in the applications appear to be conducted by oral administration of ULD-impregnated tablets).

107 What framework do I have to understand these observations within? As already noted, I am asked to accept as plausible the inventions of these applications without an underlying explanation of how these ULD antibodies actually act. Whilst it is true that a mechanism or explanation is not required for a grantable patent, the Applicant has proposed no viable theory that would account for the observations. If a conventional understanding of what is occurring is not relevant, some disclosure of a

framework for understanding – in terms of what the patent is claiming - is still necessary

- 108 In the absence of such a framework, I have to look carefully at what is described in these patent applications and I have to make an assessment of what is described in each application on the basis of the tools that are available to me i.e. the current state of the art comprising known and accepted theories supported by a very large body of evidence.
- 109 The picture that all of observations (i)-(ix) paint together is critical. The Applicant is well aware of the doubts in the conventional medicine community with regard to homeopathy and thus has sought to demonstrate how these inventions differ from homeopathy in that they are conventionally testable and not subject to the problems apparently inherent in homeopathy treatments for demonstrating efficacy across a patient group (as opposed to demonstrating efficacy for an individual patient). However, the subject of these applications appears to be a significant departure from 'conventional' medicine as this chimeric approach cannot itself rely on conventional pharmacology and pharmacokinetics (i.e. normal chemical-chemical interactions) to explain how the treatment works. In particular, there is no drug/receptor interaction and no antibody/antigen interaction.
- 110 Despite this, several of the listed points above relate to a conventional chemical understanding of cell and human biology. Chief among those is the initial selection of antibodies (point (i)). This is straightforward; the antibodies have been selected according to conventional theories of cell-protein interactions and thus the selection presents no problem in terms of plausibility. The testability of the compositions using conventional assays (point (iv)) also relies on a conventional understanding. However, whereas these assays would normally be understood to function via chemical-chemical interaction, here the active principle interacting with the chemicals of the assay is unknown other than by its generation (it is accepted that solvent, but no active molecules are present). Thus whilst at first sight the assay results seem conventional and consistent with a chemical-chemical interaction, in fact they are unexplained if they cannot be understood in these terms because no active principle is present in the composition.
- 111 The initial exposure of antibodies to solutions appears to be critical to the effect observed (point (ii) above) and yet later exposure to a similarly complex environment (point (viii)) (the hydrogen bond donors and acceptors of the saccharides in the isomalt tablet) would appear to have no effect (in that solution and solid forms are disclosed as acting on the same targets). The skilled worker cannot rely on a homeopathic understanding of this, in terms of potency increasing as dilution increases so that environment is unimportant (notwithstanding the point made earlier that this explanation would not of itself be inherently considered plausible given how homeopathy is regarded within the scientific community). Furthermore, in solution it is the ULD composition that brings about an environmental effect (point (vi)).
- 112 Moreover as all the human trials in the applications relate to administration of pills the skilled worker must also accept that the unidentified active principle persists not only in solution, and in a saccharide framework, but also in the gut (including stomach acid) prior to movement unchanged to the target cell site (antigen) of interest (point (ix)).

- 113 Thus the skilled worker is presented with a number of problems for which no explanation has been provided. What in the simple dilution (and shaking etc) process actually results in the creation of an active principle that is robust enough (in chemical or physical terms) to persist despite extreme changes of environment, that if experienced at the preparation stage would, one assumes, result in a very different active principle? This goes against current understanding of physical laws. Conventional science requires that in order to persist in those different environments the active principle must be a chemical entity (i.e. an active agent) which apparently is ruled out here as no non-solvent molecules are present. Alternatively, the active principle must be physical in nature and generated and used concomitantly e.g. X-rays, ultrasound etc.
- 114 The data provided in each application relates primarily to one or at most two combinations of dilution mixtures, i.e. either a mixture of C12+C30+C200 or a mixture of C12+C30+C50. No information is provided in terms of dosage response or intensity response in the applications as filed. Having reviewed the information provided, specifically those documents purported or purporting to illustrate some dosage dependence (Exhibits OE10-12 and *Bulletin of Experimental Biology and Medicine*, Vol.148, Suppl.1, 2009, Larentsova et al., pages 88-90, "The Use of Tenoten and Tenoten (Pediatric Formulation) as a Drug for premedication in Adults and Children during Outpatients Dentist Visit"), I find these documents inconclusive and that none of them help me to understand the nature of the active principle. They do not appear to offer any clear guidance in terms of analogy with conventional chemical concentration dependence or physical intensity variance.
- 115 Therefore in trying to reach a conclusion on the balance of probabilities as to whether these inventions are plausible I have the conventional view that the putative active agent is in fact merely water (or water/alcohol) given the simple dilution process on one hand. On the other, I have an assertion of difference from mere water (or water/alcohol), that the active principle is not reliant on homeopathy, but with supporting evidence for the nature of the active principle limited to one piece of NMR data. Alongside this there is much data suggesting a therapeutic effect that witnesses agree is plausible.
- 116 Is the information provided enough to argue either that the invention is plausible or, failing that, that there is the "substantial doubt" required in *Blacklight Power*?

Plausibility – applying the test

- 117 I will now consider where the above discussion leaves me in terms of the three criteria in BL O/114/08 (*Blacklight Power*) in relation to whether the theory espoused in the patent application under consideration could be "*generally accepted as a valid theory of nature*".
- 118 As noted above, I will adopt the Hearing Officer's general approach to these criteria in seeking to determine the extent to which the theory of ultra low dose antibodies may be considered generally accepted (bearing in mind the Court's conclusions about how the actual test should actually be applied (see earlier)).

a) *the explanation provided by the theory is consistent with existing generally accepted theories.*

- 119 The Applicant's arguments with regard to the first criterion relate primarily to the evidence of the test data supported by the witness statements, and the statement by the Applicant of the general principle of the invention relating to the "phenomenon of 'release activity'". The skeleton arguments for the first hearing further state:

"Note also that it is a generally accepted theory that administration of a composition can exert, for example, a conformational change in a protein, can lead to chemical and physiological changes in the biological system to which the composition is administered. Indeed, administration of 'normal' antibody compositions would usually lead to sequestering of the target antigen (or other effects) that alter the downstream biological effects of that antigen in biological system[s]."

"Exhibit JKS demonstrates that the activated-potentiated antibodies are able to exert an effect on their target antigen, notably an effect that is not seen for placebo samples that are prepared in the same way but have no antibody in the starting solution. Nor is the effect seen for proteins that are not the target antigen."

Whilst the mechanism of action of the claimed composition remains unknown, this is not relevant to patentability."

However, the phenomenon of release activity underpinning these inventions does not conform to generally accepted theories. As discussed above, the therapeutic results appear plausible on the basis of the data, but the chimeric nature of the compositions immediately puts them outside of accepted theories before giving any consideration to the problems of how an active principle could even be generated let alone persist without recourse to either conventional scientific understanding or the homeopathic alternative. While the start (selection of antibody) and end points (assay to show therapeutic effect) relate to generally accepted theories, everything in between (dilutions, release-activity or activation-potential, preparation of solutions or solid dosage forms) does not.

b) *The theory should make testable predictions, and experimental evidence should show rival theories to be false and should match the predictions of the new theory*

- 120 In BL O/114/08 the Hearing Officer was unable to reach a final conclusion in terms of criterion b) due to a lack of the relevant technical knowledge. I have already noted that I am not in a position to critically evaluate the therapeutic tests put forward and thus I must do likewise.

- 121 I would only comment that the various witness statements and associated exhibits provided by the Applicant indicate that the tests used in each of the applications to show that the compositions based on ultra-low dilutions of antibodies have a therapeutic effect are appropriate and performed in the appropriate manner. However, such an assessment is based on applying well established principles of chemistry and physics and the results are understood in that context, i.e., such tests usually involve an active agent interaction which causes a measurable effect.

However, as discussed earlier, given the ultra low dilutions used to prepare the composition, it is accepted that the active principle in these compositions is not an active agent so the tests cannot be understood or explained in this manner. This is a contradictory result. If the effects observed in the therapeutic data are based on some physical phenomenon derived from how the ULD compositions are prepared, this appears to be independent of environment – solid, liquid or acidic. Again this is a contradictory result.

c) The theory should be accepted as a valid explanation of physical phenomena by the community of scientists who work in the relevant discipline.

- 122 In BL O/114/08 the Hearing Officer took the evidence presented to him in support of the theory and divided it in terms of that evidence produced by, and related to, the Applicant on the one hand and on the other that produced by unrelated parties.
- 123 The situation in relation to these applications is not on a par with that in *Blacklight Power*, as in the latter case a theory as such was being looked at whereas here the journal and test data stick very much too reviewing therapeutic results. There is no analysis of the nature of the active principle that would cause such results. I consider that it is appropriate to look at the information provided to me and to establish to what extent this points to a view of an active principle supported by the scientific community. Therefore taking this approach, I note that of the documents presented to me at the hearing, 50 related to ultra low dose antibody compositions: of these 13 were co-authored by the Applicant (including his witness statement); of the remaining 37, 36 are either co-authored by workers at Materia Medica Holdings (MMH), sponsored directly by MMH, utilise MMH originating products in their studies, or are witness statements obtained for the oral hearings; only 1 document uses compositions not produced by MMH (Exhibit OE6). Of the aforementioned 50 documents, 1 document has been presented postulating how the active principle works/is generated (the Applicant's witness statement) and 1 has been provided suggesting what is the unique nature of these compositions other than by surmising the presence of an active agent from the results of therapeutic testing (Exhibit JKS1). Neither of these documents relates to preparation of compositions independent of either the Applicant or MMH.
- 124 Thus I have been presented with very little evidence in relation to ultra low dose compositions in general that is not reliant on the Applicant (or MMH). I have been presented with no documents in relation to ULD antibody compositions which do not rely on compositions made by the Applicant or his company.
- 125 In the absence of a body of material not associated with the Applicant supporting ULD compositions, I come to the conclusion that the inventions of these applications do not pass the test of the final criterion. I note that the Applicant has argued that the acceptance of the therapeutic test results in the application by the witnesses providing statements and the testimony of Dr Klein-Seetharaman demonstrates acceptance. However, the acceptance of the witness statements is in general qualified, it relates only to the plausibility of the results not the phenomenon of release activity, and I conclude on the basis of the studies conducted by Dr Klein-Seetharaman that her statement of acceptance goes way beyond that which seems reasonable in its generality given the limited tests conducted with one set of ULD antibody compositions. Therefore I do not think that ULD antibody compositions can

be stated to be “*accepted as a valid explanation of physical phenomena by the community of scientists who work in the relevant discipline*”.

- 126 As a consequence, I return to the teachings of the applications themselves. I am presented with therapeutic data which the witness statements assure me are plausible. Is this information sufficient to render all of the inventions plausible given the plausibility gap noted above in terms of the nature of the active principle? I do not believe it is. I conclude that I have been asked to accept as plausible a conglomeration of conventional chemical and homeopathic principles with an unexplained means of communication (i.e. transfer from solution to pill to body) of an unexplained active agent. In the absence of at least one of these I must come to the conclusion that the data provided, its quantity notwithstanding, is a mixture of the placebo effect and a series of experimental anomalies rather than a coherent theory and, more importantly, coherent inventions. I am content that there is a substantial doubt about the plausibility of an active principle of this nature, and thus its actual existence, and furthermore that there is not a reasonable prospect that the Applicant’s ‘theory’ (by which I mean the phenomenon of release activity and the reality of the ULD antibody compositions as actual active principles) might turn out to be valid if it were to be fully investigated at trial with the benefit of expert evidence.
- 127 Having reached a conclusion I shall now return to the argument that the IPO has exceeded its remit and that “*a burden of proof has been laid on the Applicant that is disproportionate to that necessary for meeting the requirements of patentability*”. In considering this I note the Agent’s arguments in relation to the requirement for support of medical use claims. In particular my attention was drawn to the *Examination Guidelines for Patent Applications relating to Medical Inventions in the Intellectual Property Office*, May 2013 edition, which summarises the situation regarding evidence in support of a therapeutic effect as follows: “*The form of evidence is not critical; the application may provide in vivo or in vitro data, and in silico modelling data may be sufficient if it is considered to provide a credible basis for support*” and also the requirement in *Prendergast’s Applications* [2000] RPC 446 that “*relatively rudimentary tests would suffice*”. In relation to these applications I agree that the test data provided goes beyond rudimentary tests. However the inventions under consideration in this case do not appear to be conventional therapeutic compositions as was the case in *Prendergast’s Applications*.
- 128 Instead I am considering inventions stated neither to be conventional medicine nor homeopathic medicine. For the reasons already laid out above, the methods of generation and activity of the active principle lack any framework for understanding. To define the invention by what it is not does not create a plausible invention, i.e., it is not homeopathic, it is not conventionally chemical, it is not within the scope of the invention if it does not, in fact, work when tested therapeutically - as asserted by the Agent at the oral hearing. Thus the burden of proof must necessarily be different for these inventions than was required in *Prendergast’s Applications* or those concerning other conventional medical applications. This difference lies in the fact that some evidence is required to show that the conventional scientific view or framework for understanding therapeutic effects should be ignored. It remains my view that the evidence provided in the form of the JKS statement (and its associated exhibits) does not do this, with or without the accompanying therapeutic data.

- 129 I will also address the issue of the commercial success of a number of the marketed forms of the inventions in relation to industrial applicability.
- 130 As noted above, *Human Genome Sciences* gives four generally applicable points regarding industrial application. At the hearing the Agent argued that the claimed inventions meet these four points, placing greater importance on the first point giving the commercial success of a number of marketed forms of these inventions in Russia and a number of other neighbouring countries such as Ukraine, Uzbekistan, Kazakhstan, Moldova & Kyrgyzstan. In his view the combined gross sales figures of several million Pounds for period 2010-2014 for three commercial products derived from activated-potentiated antibody compositions in combination with the fact that each of the applications describe in clear terms the intended purpose of the composition to treat specific conditions (described therein) and each application provides evidence that these compositions have a measurable effect, demonstrated that points (i), (ii), (iii) and (iv) from *Human Genome Sciences* is met. Hence the applications are all industrially applicable.
- 131 I do not agree with this argument. The fact that someone can be convinced to buy a product is not of itself evidence of the “practical application” or “profitable use” required of point (i) from *Human Genome Sciences*. Precedent cases over a number of years have held that systems which operate in a manner contrary to well-established laws are not capable of industrial application. One could still market a product purporting to be e.g. a perpetual motion machine and the mere fact that people were prepared to buy them would not make the device any more capable of practical application in fact (as *Chiron* indicates industry does not exist in that sense to make or use that which is useless for any known purpose). As I have already discussed, the inventions as claimed disclose a conglomeration of conventional chemical and homeopathic principles with an unexplained means of communication (i.e. transfer from solution to pill to body) of an unexplained active principle and the data provided in relation to the use of the invention, its quantity notwithstanding, is a mixture of the placebo effect and a series of experimental anomalies. Thus, I do not see how this meets points (i), (ii), (iii) and (iv) from *Human Genome Sciences*.
- 132 I disagree with the Agent’s assertion that *Chiron* has been superseded by *Human Genome Sciences*. The requirements for industrial applicability set out in *Chiron* are generally applicable: the invention must be capable of being made or used in any kind of industry; and that industry does not exist in that sense to make or use that which is useless for any known purpose. *Human Genome Sciences* relates to industrial applicability and its specific application to patents claiming biological material. It identified a number of points to take into account when assessing the industrial application of such patents including some that are more generally applicable, as discussed above. Thus both decisions are relevant to the assessment of industrial applicability

Conclusion

- 133 Taking into account all of the above, I conclude that on the basis of the evidence provided there is a substantial doubt that each of the applications disclose an invention that will work in the manner described. Thus there is a substantial doubt about an issue of fact concerning patentability of these applications. Having

considered the question of whether there is a reasonable prospect that the Applicant's theory might turn out to be valid if it were to be investigated at trial with the benefit of expert evidence, on the balance of probabilities, I do not think so. Therefore, I consider that the applications all lack industrial applicability under section 1(1)(c) and sufficiency under section 14(3) of the Act.

134 Given my conclusion in relation to industrial applicability and sufficiency, I do not need to go on and consider novelty under section 1(1)(a) of the Act.

135 As noted above, after the oral hearings, the Applicant filed amended claims for each of the applications. While these proposed amendments appear to simplify and make clear the mixture of ultra low dilutions of each antibody used to prepare the composition, they would not in my view alter my conclusion in relation to industrial applicability and sufficiency under sections 1(1)(c) and 14(3) of the Act.

136 Thus, I refuse these applications under Section 18(3) of the Act.

Appeal

137 Any appeal must be lodged within 28 days after the date of this decision.

Dr L CULLEN

Deputy Director, acting for the Comptroller