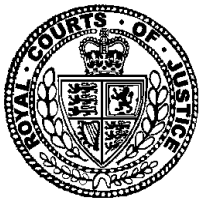

Neutral Citation Number: [2016] EWHC 1511 (Ch)

Case No: CH-2015-00022

Rolls Building
Fetter Lane, London, EC4A 1NL

Date: 26/07/2016

IN THE HIGH COURT OF JUSTICE
CHANCERY DIVISION
PATENTS COURT

ON APPEAL FROM

THE UNITED KINGDOM INTELLECTUAL PROPERTY OFFICE
IN THE MATTER OF THE PATENTS ACT 1977
AND IN THE MATTER OF PATENT APPLICATION NUMBERS
GB 1302651.3, GB 1302653.9, GB 1302654.7, GB 1302924.4, GB 1302925.1, GB 1302926.9, GB1302928.5, GB 1302929.3, GB 1303867.4, GB 1303868.2 and GB 1303983.9
ALL IN THE NAME OF OLEG ILIICH EPSHTEIN

Before :

MR ROGER WYAND QC SITTING AS A DEPUTY HIGH COURT JUDGE

- -

Between :

OLEG ILIICH EPSHTEIN	**Appellant**
- and -	
COMPTROLLER-GENERAL OF PATENTS DESIGNS AND TRADE MAKRS	**Respondent**

Dominic Hughes (instructed by **Gowling WLG (UK) LLP**) for the **Appellant**
Nicholas Saunders (instructed by **The Treasury Solicitor**) for the **Respondent**

Hearing dates: 21 June 2016

- -

Approved Judgment

I direct that pursuant to CPR PD 39A para 6.1 no official shorthand note shall be taken of this Judgment and that copies of this version as handed down may be treated as authentic.

MR ROGER WYAND QC SITTING AS A DEPUTY HIGH COURT JUDGE

1. This is an appeal from a decision of Dr L Cullen, Deputy Director acting for the Comptroller ("the Hearing Officer"), dated 29 October 2015. By his decision, the Hearing Officer rejected eleven patent applications in the name of Oleg Iliich Epshtein, on the grounds that they all lack industrial applicability under section 1(1)(c) and sufficiency under section 14(3) of the Patents Act 1977.

2. These eleven applications were originally filed and published under the provisions of the Patent Cooperation Treaty (PCT). On entering the national phase in the UK, they were each subsequently re-published as GB applications as listed below. All eleven applications relate to treatments for various medical conditions using oral and solid dosage forms prepared from mixtures of ultra-low dilutions of antibodies. These ultra-low dilutions of antibodies are referred to in the applications as 'activated-potentiated forms' or 'release-active forms' (RAF) of antibodies.

GB application number	**Shorthand label (based on some of the diseases or areas treated)**	**Uses ultra-dilute antibodies to**
1302924.4	Diabetes	• Insulin receptor • NO synthase
1302651.3	Genitourinary/ Prostate	• PSA • NO synthase
1302928.5	ADHD	• S-100 • NO synthase
1302925.1	Vertigo	• S-100 • NO synthase
1302653.9	Obesity / metabolic disorders / nicotine	• CB1 • S-100
1302654.7	Gastrointestinal / IBS	• S-100 • Histamine • TNF-α
1302926.9	Respiratory	• Bradykinin • Histamine • Morphine

1302929.3	Alzheimer's	• S-100 • NO synthase
1303868.2	HIV (1st)	• HIV
1303983.9	HIV (2nd)	• TNF-α • α-interferon • CD8.
1303867.4	Various infectious diseases	• CD4. • ϒ-interferon • α-interferon • CD8 • Histamine.

3. The history of the proceedings in the Intellectual Property Office in respect of the eleven applications is set out in the Hearing Officer's decision in paragraphs 7 to 21. Following two oral hearings, the Applicant filed a new set of amended claims and these are set out in paragraph 35 of the decision. These are the relevant claims for the purpose of this appeal.

4. The examiners dealing with the various applications all came to the same view as to the allowability of the applications and this was summarised by the Hearing Officer in paragraphs 36 to 39. The basic objection was that 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.

5. The Hearing Officer upheld the views of the examiners and refused the applications. It is that refusal that I am being asked to overturn.

Review not Re-hearing

6. I was reminded by Mr Saunders, who appeared for the Comptroller, that this appeal is a review and not a rehearing. He cited Robert Walker LJ in *Reef* [2003] RPC 5 at paragraph 26 where he said that an appellate court should have regard in particular to *"the nature of the evaluation required, the standing and experience of the fact-finding judge or tribunal, and the extent to which the judge or tribunal has to assess oral evidence"* and Lewison LJ in *Fine and Country v Okotoks* [2014] FSR 11 at paragraph 50: *"many of the points which the judge was called upon to decide were essentially value judgments, or what in the current jargon are called multi-factorial assessments. An appeal court must be especially cautious about interfering with a trial judge's decisions of this kind*".

7. I bear these strictures in mind in this appeal. The IPO Tribunal is a specialist forum with a technically qualified Hearing Officer and his views, particularly as to technical

matters, should be given due weight. There was no oral evidence before the Hearing Officer.

8. The Hearing Officer held that 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, he would consider the applications together. There was no objection to this course of action and I shall adopt the same approach. A further objection of novelty was raised by the examiners in respect of 10 of the 11 applications but the Hearing Officer did not find it necessary to consider that objection in the light of his findings on industrial application and sufficiency. There was a Respondent's Notice seeking to support the refusal on the ground that the applications lacked novelty, but it was withdrawn at the hearing before me. Accordingly, in the event that I allow Dr Epshtein's appeal, I am asked to remit the case to the UKIPO to consider the novelty objection in respect of the 10 relevant applications.

Subject Matter of the Applications

9. In order to understand the objections raised and the Appellant's grounds of appeal against the decision, it is necessary to explain in general terms the subject matter of the applications. The applications are all related to pharmaceutical compositions which are prepared in the same way and are to be used in the treatment of various diseases. It is the method of preparation which, effectively, gives rise to the objections.

10. Mr Hughes, who appeared for the Appellant, took me to three of the applications and Mr Saunders took me to one of those three. I shall refer to that one application, GB 1302928.5 (WO 2012/010970 A2), entitled "A Method of Treating Attention Deficit Hyperactivity Disorder".

11. In the background section of the specification it explains that:

> Neurotropic drugs having antiserum to brain-specific protein S-100 are known. (RU 2156621 C1, A61K39/395, 9/27/2000). However, these medicines do not provide sufficient therapeutic efficiency for treatment of neurobehavioral diseases, including attention deficit hyperactivity disorder. Thus, there is a continuing need for new drug products with the desired therapeutic efficacy for the treatment of attention deficit hyperactivity disorder.

12. It goes on to explain:

> The S-100 protein is a cytoplasmic acidic calcium binding protein found predominantly in the gray matter of the brain, primarily in glia and Schwann cells. The protein exists in several homo-or heterodimeric isoforms consisting of two immunologically distinct subunits, alpha and beta. The S-100 protein has been suggested for use as an aid in the diagnosis and assessment of brain lesions and neurological damage due to brain injury, as in stroke. Yardan et al., *Usefulness of S100B Protein in Neurological Disorders*, J Pak Med Assoc Vol. 61, No. 3, March 2011, which is incorporated herein by reference.
>
> Ultra-low doses of antibodies to S-100 protein have been shown to have anxiolytic, anti-asthenic, anti-aggressive, stress-protective, anti-hypoxic, anti-ischemic, neuroprotective and nootropic activity. *See* Castagne V. et al., *Antibodies to S100 proteins have anxiolytic-like activity at ultra-low doses in the adult rat*, J Pharm Pharmacol. 2008, 60(3):309-16; Epstein O. I., *Antibodies to calcium-binding S100B protein block the conditioning of long-term sensitization in the terrestrial snail*, Pharmacol Biochem Behav., 2009, 94(1):37-42; Voronina T.A. et al., Chapter 8. *Antibodies to S-100 protein in anxiety-depressive disorders in experimental and clinical conditions. In "Animal models in biological psychiatry"*, Ed. Kalueff A. V. NY, "Nova Science Publishers, Inc.", 2006, pp. 137-152, all of which are incorporated herein by reference.

13. It then has a section about nitric oxide (NO), its synthesis by the endothelium by NO synthase and its role within the body. The summary of the invention is as follows:

> In one aspect, the present invention provides pharmaceutical composition for treatment of attention deficit hyperactivity disorder, comprising activated-potentiated form of antibodies to brain-specific protein S-100 and activated-potentiated form of antibodies to endothelial NO synthase as an additional strengthening component.
>
> In another aspect, the present invention provides pharmaceutical composition for treatment of attention deficit disorder, comprising activated-potentiated form of antibodies to brain-specific protein S-100 and activated-potentiated form of antibodies to endothelial NO synthase as an additional strengthening component.

14. The "Detailed Description" explains the meaning of "activated-potentiated form" and how it is produced:

> The term "antibody" as used herein shall mean an immunoglobulin that specifically binds to, and is thereby defined as complementary with, a particular spatial and polar organization of another molecule. Antibodies as recited in the claims may include a complete immunoglobulin or fragment thereof, may be natural, polyclonal or monoclonal, and may include various classes and isotypes, such as IgA, IgD, IgE, IgG1, IgG2a, IgG2b and IgG3, IgM, etc. Fragments thereof may include Fab, Fv and $F(ab')_2$, Fab', and the like. The singular "antibody" includes plural "antibodies".
>
> 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). Examples of homeopathic potentization are described in U.S. Patent. Nos. 7,572,441 and 7,582,294, which are incorporated herein by reference in their entirety and for the purpose stated. While the term "activated-potentiated form" is used in the claims, the term "ultra-low doses" is used in the examples. The term "ultra-low doses" became a term of art in the field of art created by study and use of homeopathically diluted and potentized form of substance. The term "ultra-low dose" or "ultra-low doses" is meant as fully supportive and primarily synonymous with the term 'activated-potentiated" form used in the claims.

In other words, an antibody is in the "activated-potentiated" or "potentiated" form when three factors are present. First, the "activated-potentiated" form of the antibody is a product of a preparation process well accepted in the homeopathic art. Second, the "activated-potentiated" form of antibody must have biological activity determined by methods well accepted in modern pharmacology. And third, the biological activity exhibited by the "activated potentiated" form of the antibody cannot be explained by the presence of the molecular form of the antibody in the final product of the homeopathic process.

15. The specification contains an example of a clinical trial: Example 2.

Group 1 - the active drug group was given 300 mg tablets impregnated with an aqueous-alcohol solutions (6 mg/tab) of activated-potentiated form of polyclonal rabbit antibodies to brain specific S-100 protein (anti-S-100), and to endothelial NO-synthase (anti-eNOS) in ultra low dose (ULD anti-S-100 + ULD anti-eNOS), purified on antigen, obtained by super dilution of initial solution (with concentration of 2.5 mg/ml) in 100^{12}, 100^{30}, 100^{200} time, equivalent to mixture of centesimal homeopathic dilutions C12, C30, C200;

Group 2 - the comparison group was given 300 mg tablets impregnated with an aqueous-alcohol solution (3 mg/tab) of activated-potentiated forms of polyclonal rabbit antibodies to brain-specific S-100 protein purified on antigen in ultra low dose (ULD anti-S100) obtained by super dilution of initial solution in 100^{12}, 100^{30}, 100^{50} times, of equivalent mixture homeopathic dilutions C12, C30, C50.

Group 3 - the control group (placebo) was given of 300 mg tablets having excipients (lactose monohydrate – 267 mg, microcrystal cellulose – 30 mg, magnesium stearate – 3 mg).

16. This was a double blind placebo-controlled study in 146 children, with the syndrome of attention deficit and hyperactivity disorder, in the 6 to 12 year old range who were randomised into the three groups. All of the children had clinically marked presentations of ADHD. The results were described as follows:

> The analysis of the effectiveness of 12 weeks of therapy in the three groups showed a decrease of more than 25% from the initial total score on a scale ADHDRS-IV-Home Version in 75% (n = 36) of children treated with the composition ULD anti-S100 + anti-eNOS; in 66% (n = 33) of patients treated with ULD anti-S100 and in 56% (n = 28) of children receiving placebo. Differences of efficiency between the groups showing a more detailed assessment, taking into account the three-level grading of improvement of condition (reduction of total score on a scale ADHDRS-IV for <25%, 25-49.9% or ≥ 50% from the baseline), are presented in Table 2. Significant improvement with a reduction in total score on 50% or more from the baseline was noted in 52% of children in group 9 who were taking ULD anti-S100 + anti-eNOS, and in 34% of children in group 2 who were taking ULD anti-S100 (vs. 8% of patients in group 3 with placebo).

17. The results were presented in tabular form:

Table 2. The dynamics of total score by the scale ADHDRS-IV-Home Version by the end of 12 weeks of therapy

Groups of patients	**The proportion of patients with decrease of total score by the scale ADHDRS-IV-Home Version**		
	Less than 25.0% from baseline	on 25.0 – 49.9% from baseline	on 50.0% and more from baseline
ULD anti-S100 + anti-eNOS, n=48	12 (25%)	11 (23%)	25 (52%) ##
ULD anti - S100, n=50	17 (34%)	16 (32%)	17 (34%) ##
Placebo, n=50	22 (44%)	24 (48%)	4 (8%)

The difference is significant in comparison with the placebo group: ## p<0.01.

The Law

18. The relevant sections of the Patents Act 1977 ("the 1977 Act") are:

> *Section 1(1)(c)*
> *"A patent may be granted only for an invention in respect of which the following conditions are satisfied, that is to say –*

> *...*
> *(c) it is capable of industrial application;*
> *...*
> *and references in this Act to a patentable invention shall be construed accordingly."*
> Section 4(1)
> *"An invention shall be taken to be capable of industrial application if it can be made or used in any industry, including agriculture."*
> and Section 14(2) and (3)
> *(2) Every application for a patent shall contain –*
> *...*
> *(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."*

19. The Hearing Officer referred to the case of *Human Genome Sciences v Eli Lilly* [2011] UKSC 51 and extracted from Lord Neuberger's Opinion the following four principles to be applied when considering whether the requirement of industrial applicability was satisfied:

> *(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", of having to carry out "a research programme".*

20. There is no challenge in this appeal to that summary of the principles to be applied.

21. The Hearing Officer referred to the case of *Blacklight Power Inc. v The Comptroller-General of Patents* [2008] EWHC 2763 which, he said, "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".

22. He then set out the following quote from the judgment of Floyd J (as he then was):

> *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.

23. The Hearing Officer went on:

> 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*."

24. In *Blacklight*, the case was remitted to the IPO and the Hearing Officer in that case reviewed the applications in the light of the test identified in that judgment. He concluded that the court had 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 the 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. He used the same approach that he had outlined in his original decision where he had proposed that theories that are generally accepted as valid descriptions of nature have three main criteria which are 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."

25. The test from *Blacklight* was applied in *Robinson's Application* where the Hearing Officer 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.

The Decision under appeal

26. The Hearing Officer in this case set out the arguments of the Agent for the Applicant and then summarised as follows:

69 …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.

27. The Hearing Officer then set out the arguments of the examiner in rejecting the applications:

> 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 applicatiosn *(sic)* 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.

28. In paragraph 74 of his decision, the Hearing Officer set out his understanding of the standard of proof that was required to be satisfied by the Applicant:

> 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.

29. This was criticised by counsel for the Applicant, however, I reject that criticism. It is a correct statement of the standard of proof as laid down by Floyd J in the *Blacklight* case.

30. Under a heading "What is it that must be assessed?" the Hearing Officer sets out what he proposes are the issues he must assess:

> 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?

31. Two criticisms are made of this statement, namely: (1) the statement "as these applications all relate to compositions *per se* and not solely to therapeutic use" is inaccurate, and; (2) in any event, if (a) is established, there is no requirement for (b) also to be satisfied.

32. I do not believe that the first criticism is justified. Although, as Mr Hughes points out, some of the claims in the applications do relate to therapeutic uses, all of the applications do not relate solely to therapeutic uses as stated by the Hearing Officer.

33. There is, however, more force to the second criticism. It appears from the Hearing Officer's subsequent analysis that the second limb of the assessment proposed involves an evaluation of a theory to explain how the therapeutic effect, which is assessed as plausible under the first limb, is achieved. Thus, in paragraph 79 of the decision the Hearing Officer says: *"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."*

34. The Hearing Officer goes on in paragraph 80 to say:

> 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.

35. I do not accept that this is a correct application of the principles enunciated in the *Blacklight* case. As the Hearing Officer accepted, it is not necessary to disclose or describe the mechanism of action for an invention to be patentable. In the *Blacklight* case, the claimed inventions depended on the existence of a lower-energy state hydrogen species. If it did exist then the objections on grounds of lack of industrial applicability and sufficiency would fall away. The Hearing Officer there held that the existence of the lower-energy hydrogen species depended on a theory of atomic

structure contrary to standard quantum mechanics. It was argued on behalf of Blacklight that the theory explained a number of phenomena observed in experiments performed by Blacklight. At the end of the day, the Hearing Officer decided that the evidence did not establish the existence of a material not generally accepted to exist in nature and therefore the inventions were not capable of industrial application and would not be capable of being performed by the skilled person.

36. In the present case, if the results of the trials and experiments set out in the applications show that a therapeutic effect is plausible, then it cannot be said that the alleged invention is not capable of industrial application and is not capable of being performed by the skilled person. It is not necessary for the Applicant to go on to explain the mechanism for the therapeutic effect, if a therapeutic effect is demonstrated to be plausible by trials and experiments. I do not accept, as submitted by Mr Saunders for the Comptroller, that it is necessary to consider the plausibility of the claimed invention being able to elicit a therapeutic effect even if the evidence establishes that the trials and experiments showed that a therapeutic effect was plausible. The issue therefore for this appeal is whether the Hearing Officer found that the evidence did establish that the trials and experiments showed that a therapeutic effect was plausible and whether he was correct to dismiss the therapeutic effect.

37. I was taken through a number of recent cases by Mr Hughes to show that the concept of 'plausibility' had developed since the Hearing Officer's decision. In particular, I was referred to *Human Genome Sciences v Eli Lilly* [2011] UKSC 51, a case decided before the decision in this case but not referred to on this point, and the further cases, *Idenix v Gilead* [2014] EWHC 3916 (Pat), *Merck v Ono* [2015] EWHC 2973 (Pat) and *Actavis v Lilly* [2015] 3294 (Pat), the latter having been decided after the decision in this case. It was suggested that the Hearing Officer had failed to take into account the low plausibility thresholds for sufficiency and industrial applicability. I do not consider it necessary to consider more than the statement by Lord Hope in the *Human Genome Case*:

"I would not quarrel with Jacob L.J.'s comment, after consulting the Shorter Oxford English Dictionary, that the sense [the word 'plausibly'] conveys is that there must be some real reason for supposing that the statement is true: para. 111. The important point, however, is that the standard is not any higher than that.
The same sense is conveyed by some of the other expressions which can be found in the case law on industrial applicability, and which are mentioned by Lord Neuberger in his judgment in that case, such as "reasonably credible".

38. Counsel for the Comptroller referred to paragraphs 149 to 178 of the judgment of Carr J in *Actavis v Lilly* [2015] EWHC 3294 where he was dealing with the standard of plausibility for obviousness as compared to the standard for sufficiency. In particular, he relied on the passage where Carr J cited T609/02 *Salk* §9 in §153 of his judgment which emphasises that what is required is that:

"*…the patent provides some information in the form of, for example, experimental tests, to the avail that the claimed compound has a direct effect on a metabolic mechanism specifically involved in the disease, this mechanism being either known from the prior art or demonstrated in the patent per se…*"

and paragraph 175 where he stated:

"If a claim that a particular drug is useful in the treatment of a particular disease is incredible, then the same consequences should follow as for an implausible claim of wide scope. However, whether an invention is plausible is fact sensitive and will depend upon the nature of the invention, the scope of the claim, the disclosure of the specification and the common general knowledge."

39. The Hearing Officer referred to the "numerous papers and trials" submitted by the Applicant to substantiate the claim to plausibility and the witness statements provided in regard to the plausibility of the therapeutic data in the applications as filed. He set out his conclusions on this material in paragraph 86 of his decision:

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.

40. Mr Hughes submitted that the Hearing Officer was incorrect in holding that more was required than plausibility of a therapeutic effect. I agree. It is relevant that there is no explanation for a therapeutic effect according to scientific orthodoxy but, provided that the evidence of an actual therapeutic effect is established by evidence to be plausible, that satisfies the requirement from *Salk*, that the effect is "*demonstrated in the patent per se …"*. Thus, once the Hearing Officer accepted that the data provided indicates that a therapeutic effect is plausible, the objection to patentability on grounds of lack of sufficiency and industrial applicability fall away. The Applicant has taught how to make the products, the subject of the claims, and has provided evidence of the plausibility of the therapeutic effect of them. It is not necessary for the Applicant to go on to explain how or why the therapeutic effect is produced, even though the effect cannot be explained by well-established theories of medicine. The invention claimed is not to a theory but to a product producing a therapeutic effect which has been demonstrated to be plausibly effective. To require anything more than that is to put too high a requirement for plausibility.

41. The Hearing Officer, however, went on to consider "The plausibility of the claimed compositions being able to elicit such a therapeutic effect?" He recited the fact, admitted in the applications, that the biological activity cannot be explained by the presence of the molecular form of the antibody because of the very high dilution carried out in accordance with homeopathic dilution practices.

42. The Hearing Officer then stated:

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.

43. The Hearing Officer considered evidence produced by the Applicant to support a theory that samples of the "activated-potentiated" antibodies prepared according to the methods described in the patent applications caused changes in the conformation of the interferon gamma protein when added to them. The evidence was in the form of a declaration describing a study carried out by Dr Judith Klein-Seetharaman then of the University of Pittsburgh who used nuclear magnetic resonance spectroscopy (NMR) and dynamic light scattering (DLS) to detect these changes and the results were

compared to a placebo consisting of distilled water that has undergone the same process as the test samples without any antibody in the starting solution.

44. The NMR results reported by Dr Klein-Seetharaman indicate a change of conformation in the presence of the samples with the antibody in the starting solution as compared to in the presence of the placebo. The DLS results suggested that the antibody solution has no appreciable effect on the protein size confirming that no antibodies are actually present in solution. The Hearing Officer concluded from this that the only evidence of a physical difference between the sample and the placebo are the NMR studies.

45. The Hearing Officer pointed out that Dr Klein-Seetharaman did not prepare her own samples (they were prepared by the Applicant) 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 GB 1302925.1))."

46. The Hearing Officer set out an extract from Dr Klein-Seetharaman's evidence and commented:

> 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.

47. The Hearing Officer summarised the evidence suggesting the reasons for 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.

48. The Hearing Officer went through these nine observations, identifying the problems associated with them on a conventional scientific basis and concluded:

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*?

49. The Hearing Officer then went through the three criteria summarised by the Hearing Officer in the *Blacklight Power* case for the acceptance of theories as valid descriptions of nature. Under the first criterion he stated:

119 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-potentiation, preparation of solutions or solid dosage forms) does not.

50. Under the second criterion he concluded:

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.

51. Under the third criterion he commented that he had been presented with very little evidence in relation to ultra low dose compositions in general that is not reliant on the Applicant or his company and he had been presented with no documents in relation to ULD antibody compositions which do not rely on compositions made by the Applicant or his company. He then concluded:

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 it's 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.

52. Having reached that conclusion, the Hearing Officer then turned to the Applicant's objection that "a burden of proof has been laid on the Applicant that is disproportionate to that necessary for meeting the requirements of patentability". He referred to the "Examination Guidelines for Patent Applications relating to Medical Inventions in the Intellectual Property Office" and the dicta in *Prendergast's Applications* [2002] RPC 446 that "*Relatively rudimentary tests would suffice*" and accepted that the test data provided in relation to these applications goes beyond rudimentary tests. However, he distinguished the inventions under consideration in this case from the conventional therapeutic compositions in *Prendergast's Applications*. This, he said, means that "*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.*" (Paragraph 128)

53. The Hearing Officer has made two errors of law in his analysis of the plausibility of the invention in this case.

54. First, he has decided that it is not enough that the therapeutic effect is plausibly established but that the scientific or medical theory behind the therapeutic effect must be explained and be established as plausible. This is to misunderstand the *Blacklight Power* case. If the claimed effect can be established to be plausible, there is no need to establish a plausible theory to explain it. It is only if there is no claimed effect, or if the claimed effect cannot be tested in a way that would establish it as being plausible, that it is necessary for the Applicant for a patent to establish the plausibility of the scientific theory behind the claim. In *Blacklight Power* there were two applications. The first was directed to a plasma reactor to generate power and new forms of hydrogen. The second was to a laser comprising a laser medium comprising the new form of hydrogen. Experiments had been conducted to seek to show that this new form of hydrogen existed. These were inconclusive in the view of the Hearing Officer and he held that the existence of the new form of hydrogen was not plausible. This is fundamental to the plausibility of the claimed inventions.

55. In the present case, the Hearing Officer has held that the data provided indicated that a therapeutic effect is plausible. If the therapeutic effect is plausible then the claim is plausible, even though the reason for the therapeutic effect cannot be explained.

56. This brings me to the second error by the Hearing Officer. He held that the data indicated that a therapeutic effect was plausible and 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 have a therapeutic effect are appropriate and performed in the appropriate manner. He nevertheless comes to the conclusion that in the absence of a satisfactory explanation of the mechanism involved he "*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*".

57. I can find no basis for this conclusion. The data resulted from double-blind placebo controlled studies which were appropriately performed, as the Hearing Officer accepted was established by the evidence. It is therefore not open to the Hearing Officer to reject the data on the basis of placebo effect and experimental anomalies without some basis for this criticism. It is a criticism that is inconsistent with his findings on the evidence.

58. There is no doubt that the claimed effects are difficult to believe and, without the data showing a plausible therapeutic effect, the Hearing Officer would have been correct to reject the applications on the basis that the invention as claimed could not plausibly produce a therapeutic effect. However, once the plausibility of the therapeutic effect is shown to be established by data, the sufficiency objection cannot be maintained.

59. The Hearing Officer also rejected the Applications on the ground of lack of industrial applicability with the same statement that the data is "a mixture of the placebo effect and a series of experimental anomalies". He held that this meant that he should ignore that commercial exploitation of the patented products. As I have held that there was no basis for the Hearing Officer to reject the data in the Applications, this objection too cannot be maintained.

60. In the premises, I will remit these Applications back to the United Kingdom IPO for further consideration.