

- 5 In his first letter of 22 November 2010 the examiner raised an objection under Article 3(d) of the Regulation and also the potential for an objection under Article 3(a).
- 6 It was common ground that paclitaxel, for example as Paxene (RTM) or Taxol (RTM), had previously been granted MAs for its medical use. The nub of the examiner's argument was that paclitaxel was the sole active ingredient and as this had already been authorised, the MA filed in support of this application was not the first authorization in the EU. A third party had filed observations in a letter dated 6 July 2010 that the application failed to comply with Article 3(d) with regard to Article 1(b).
- 7 The applicant argued against the examiner's objections. Several rounds of correspondence between the examiner and applicant ensued. The applicant filed particularly substantial submissions on 23 May 2013 along with 29 supporting documents and on 14 December 2015 with a further four supporting documents.
- 8 There were significant gaps in the time between correspondence as a result of mutually agreed stays in the proceedings to await pending judgments of the Court of Justice of the European Union ("CJEU") in *Neurim Pharmaceuticals (1991) Ltd v Comptroller-General of Patents (C-130/11)* ("Neurim"), *GlaxoSmithKline Biologicals SA v Comptroller General of Patents, Designs and Trade Marks (C-210/13)* ("GSK") which concerned, *inter alia*, the interpretation of Article 3(d) of the Regulation and in *Bayer CropScience AG v Deutsches Patent-und-Markenamt C-11/ 13* ("Bayer") which concerned the related Plant Protection Product Regulation 1610/96/EC (the plant protection Regulation is relevant to the medicinal products SPC Regulation by virtue of Recital 17 of 1610/96/EC).
- 9 As the examiner did not accept the applicant's submissions he offered a hearing in a letter dated 25 February 2016. He framed his objections in two questions which are detailed below in paragraph 12.
- 10 Before the hearing the applicant filed a 25 page skeleton argument and some additional supporting documents, bringing the number of supporting documents to 47 in total.
- 11 The hearing took place on 25 May 2016. Dr Hugh Goodfellow, assisted by Mr Matthew Georgiou and Dr Natalia Wegner-Cribbs, patent attorneys of Carpmaels & Ransford, represented the applicant company Abraxis Bioscience LLC, a wholly owned subsidiary of Celgene. Attending from Celgene were: Dr Neil Desai (VP of Strategic Platforms), Mr Peter Cicala (VP, Intellectual Property and Chief Patent Counsel) Jacqueline Bore (in-house counsel) and Dr Carla Kuhner (Senior Patent Agent). Mr Andrew Chalson (patent attorney at Quinn Emanuel) accompanied the Celgene delegation.

Issues to be addressed

- 12 In his letter of 25 February 2016 the examiner set out two questions to be addressed:
- (i) Does the product “paclitaxel formulated as albumin nanoparticles” constitute a new active ingredient as defined in Article 1(b) of the Regulation, as compared to paclitaxel solution formulations authorised before Abraxane (RTM) such as Paxene (RTM)?
 - (ii) If the answer to the first question is negative, should an SPC nonetheless be granted having regard, in particular, to the judgment in *Neurim Pharmaceuticals (1991) v Comptroller General of Patents C-130/11 (Neurim)*?
- 13 I will therefore address the issue of whether the application meets the requirements of Article 1(b) of the Regulation, having regard to the two questions put by the examiner, as above. It falls that if the answer to both these questions is in the negative then the application fails by virtue of Article 3(d) because paclitaxel is the active ingredient and therefore the submitted authorisation does not represent the first authorisation for paclitaxel in the EU.
- 14 The examiner had previously indicated that an objection may arise in respect of Article 3(a) and cited the CJEU case of *Medeva BV v Comptroller General of Patents, Designs and Trade Marks (C-322/10)* but subsequently withdrew this objection.

The law

- 15 The point at issue concerns Article 1(b) and Article 3(d) of the Regulation.
- 16 Article 1 reads, as far as is relevant:

Definitions

For the purposes of this Regulation, the following definitions shall apply:

(a) ‘medicinal product’ means any substance or combination of substances presented for treating or preventing disease in human beings or animals and any substance or combination of substances which may be administered to human beings or animals with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in humans or in animals;

(b) ‘product’ means the active ingredient or combination of active ingredients of a medicinal product;

(c) ‘basic patent’ means a patent which protects a product as such, a process to obtain a product or an application of a product, and which is designated by its holder for the purpose of the procedure for grant of a certificate;

(d).....

(e).....

17 Article 3 reads:

Conditions for obtaining a certificate

A certificate shall be granted if, in the Member State in which the application referred to in Article 7 is submitted and at the date of that application:

(a) the product is protected by a basic patent in force;

(b) a valid authorisation to place the product on the market as a medicinal product has been granted in accordance with Directive 2001/83/EC or Directive 2001/82/EC, as appropriate;

(c) the product has not already been the subject of a certificate;

(d) the authorisation referred to in point (b) is the first authorisation to place the product on the market as a medicinal product.

18 The Recitals provide the underlying rationale for the Regulation. Recitals 2-6 were referred to in these proceedings. These read as follows:

(2) Pharmaceutical research plays a decisive role in the continuing improvement in public health.

(3) Medicinal products, especially those that are the result of long, costly research will not continue to be developed in the Community in Europe unless they are covered by favourable rules that provide for sufficient protection to encourage such research.

(4) At the moment, the period that elapses between the filing of an application for a patent for a new medicinal product and authorisation to place the medicinal product on the market makes the period of effective protection under the Patent insufficient to cover the investment put into the research.

(5) This situation leads to a lack of protection which penalises pharmaceutical research.

(6) There exists a risk of research centres situated in the Member States relocating to countries that offer greater protection.

The applicant's case

19 The applicant's skeleton argument summarised their arguments under five headers.

(i) Abraxane required substantial investments and suffered regulatory delays for which the Regulation intends to compensate; (ii) Abraxane is a unique and innovative nanomedicine in which the active ingredient is paclitaxel formulated as albumin bound nanoparticles - 'nab-paclitaxel'; (iii) Nab-paclitaxel is an active

ingredient that has superior therapeutic activities over previously authorised paclitaxel products; (iv) the albumin component of nab-paclitaxel is not a mere excipient or carrier, but rather has a therapeutic effect; (v) an SPC should be granted in accordance with the judgment in *Neurim*.

- 20 At the hearing Dr Goodfellow said he wanted to put the applicant's case in its entirety against the backdrop that their principal position is that nab-paclitaxel is a new active ingredient in its own right. In this context, he said he would then consider the technical details in light of the various items of case law that had been cited. I agreed with this approach. I will base this decision on the approach adopted by Dr Goodfellow in his verbal submissions and take account of his skeleton arguments as appropriate.
- 21 The fundamental question in my mind during the hearing and underlying this decision is whether the two different components - paclitaxel and albumin - create a single active ingredient - nab-paclitaxel; or whether nab-paclitaxel is a combination of its two constituent but separate substances. If I find it is a combination of two substances then it is necessary to consider that further in light of the case law. The question of whether nab-paclitaxel represents a new application, in light of *Neurim*, is dealt with separately.

The Patent

- 22 The Patent (EP0961612) lies in the field of an anti-cancer agents coated with proteins. It discloses a particular example of nanoparticles of paclitaxel contained within albumin nanoparticles. Claim 33 relates specifically to a paclitaxel–albumin nanoparticle composition. Claims 1, 32 and 33 read:
- 1. A composition comprising particles of a solid or liquid, substantially water insoluble pharmacologically active agent, coated with protein, wherein the average diameter of said particles is less than 200 nm, wherein said protein coating has free protein associated therewith, and wherein a portion of said pharmacologically active agent is contained within said protein coating and a portion of said pharmacologically active agent is associated with said free protein.*
- 32. A composition according to any one of claims 1 to 22 for use in eliminating cancer cells, wherein said composition is cremaphor free and said pharmacologically active agent is an antineoplastic.*
- 33. A composition according to claim 32, wherein said antineoplastic is paclitaxel and said protein is albumin.*
- 23 Dr Goodfellow began with an overview of the Patent. His first point was that it survived opposition in the EPO. I have no reason to doubt the validity of the claims in the Patent which are before me. I will therefore proceed on the basis that nab-paclitaxel is protected by the Patent.

- 24 Dr Goodfellow said the Patent relates to *“methods for the production of particulate vehicles for the intravenous administration of pharmacologically active agents, as well as novel compositions produced thereby”*. He went on to say it describes how the invention *“provides both immediately bioavailable drug molecules (i.e., drug molecules which are molecularly bound to a protein), and pure drug particles coated with a protein”*.
- 25 Dr Goodfellow submitted that the Patent neatly solves a problem that relates to intravenous drug delivery, referring to passages in paragraphs 2 and 3 which read *“Intravenous drug delivery permits rapid and direct equilibration with the blood stream which carries the medication to the rest of the body....Injectable controlled-release nanoparticles can provide a pre-programmed duration of action, ranging from days to weeks to months from a single injection.”*
- 26 At the hearing Dr Goodfellow particularly emphasised the size of the nanoparticles as critical to their effectiveness in drug delivery. This was a significant new element of the applicant’s case which had not been made in previous correspondence.
- 27 He referred to passages in paragraph 4 which reads: *“Microparticles and foreign bodies present in the blood are generally cleared from the circulation by the ‘blood filtering organs’, namely, the spleen, lungs and liver. The particulate matter contained in normal whole blood comprises red blood cells (typically 8 microns in diameter), white blood cells (typically 6 -8 microns in diameter), and platelets (typically 1-3 microns in diameter). The microcirculation in most organs and tissues allows the free passage of these blood cells. When microthrombi (blood clots) of size greater than 10-15 microns are present in circulation, a risk of infarction or blockage of the capillaries results, leading to ischemia or oxygen deprivation and possible tissue death. Injection into the circulation of particles greater than 10-15 microns in diameter, therefore, must be avoided. A suspension of particles less than 7-8 microns, is however, relatively safe and has been used for the delivery of pharmacologically active agents in the form of liposomes and emulsions, nutritional agents, and contrast media for imaging applications.”*
- 28 At paragraph 5 the Patent says *“The size of particles and their mode of delivery determines their biological behaviour....Particles in the size range of a few nanometers to 100 nm enter the lymphatic capillaries following interstitial injection, and phagocytosis may occur within the lymph nodes. After intravenous/intraarterial injection, particles less than about 2 microns will be rapidly cleared from the blood stream by the reticuloendothelial (RES) system, also known as the mononuclear phagocyte system (MPS). Particles larger than about 7 microns will, after intravenous injection, be trapped in the lung capillaries. After intraarterial injection, particles are trapped in the first capillary bed reached. Inhaled particles are trapped by the alveolar macrophages”*.
- 29 Dr Goodfellow’s point was that these passages in the Patent make it clear that particles which are too big, e.g. 10-15 microns, must be avoided as they get stuck in the circulation with serious consequences while particles that are too small, (e.g. a few nanometres to 100nm) are engulfed by phagocytes in the lymphatic system and consequently are cleared before they reach their intended destination at the site of a tumour. He emphasised that nab-paclitaxel particles have a size “sweet spot” (of approximately 130nm) which he says allows them *“greater access to deep within the*

tumour microenvironment'. He pointed out that the microvasculature of tumours has leaky junctions bigger than 100nm which allow the nanoparticles in.

- 30 Dr Goodfellow made submissions in relation to the solubility of paclitaxel and how this is improved by forming paclitaxel in albumin coated particles over conventional oil in water, e.g. cremaphor, solubilising agents. He referred to a passage in paragraph 8 of the Patent which reads "*The poor aqueous solubility of taxol, however, presents a problem for human administration. Indeed, the delivery of drugs that are inherently insoluble or poorly soluble in an aqueous medium can be seriously impaired if oral delivery is not effective. Accordingly, currently used taxol formulations require a cremophor to solubilize the drug*". It goes on to say "*taxol itself did not show excessive toxic effects, but severe allergic reactions were caused by the emulsifiers employed to solubilize the drug. The current regimen of administration involves treatment of the patient with antihistamines and steroids prior to injection of the drug to reduce the allergic side effects of the cremaphor*".
- 31 The Patent then goes on to say that various attempts to improve the solubility of paclitaxel without creating problems of toxicity have been tried such as modifying its functional groups, for example by sulphonation or by forming amino acid ester derivatives. The Patent says these failed to yield a clinically successful product. Moreover, says the Patent, modifications of functional groups increases the cost of drug preparation and may induce unwanted side effects such as allergic reactions.
- 32 Following this background, the Patent says at paragraph 21 "*Thus it is an object of this invention to deliver pharmacologically active agents (e.g., paclitaxel, taxane, Taxotere, and the like) in unmodified form in a composition that does not cause allergic reactions due to the presence of added emulsifiers and solubilizing agents, as are currently employed in drug delivery.*"
- 33 Paragraph 22 goes on to say "*It is a further object of the present invention to deliver pharmacologically active agents in a composition of microparticles or nanoparticles, optionally suspended in a suitable biocompatible liquid*".
- 34 Having read the Patent and listened to Dr Goodfellow's submissions, I consider it provides at least a theoretical rationale for nab-paclitaxel particles in gaining access to tumour cells *in vivo* and that the protein component offers advantages over cremaphor for improving the solubility of paclitaxel. Later, Dr Goodfellow submitted several scientific papers as evidence to support this rationale.

The marketing authorisation for Abraxane

- 35 The original SmPC accompanied a Commission Decision for the authorisation of "abraxane paclitaxel" as a medicinal product (under Regulation 726/2004) dated 14 January 2008. The SmPC gives the name of the medicinal product as "*Abraxane 5mg/ml powder for suspension for infusion*".
- 36 As mentioned above, this MA was amended and submitted on 14 December 2015. The amended version appears on the EMEA webpages concerning Abraxane. The definition of the medicinal product remains the same but the details of the qualitative

and quantitative compositions and therapeutic indications and discussion of pharmacodynamic properties have been amended. Two new therapeutic indications and new data were also included. The passages I refer to below are from the amended SmPC.

37 Under the header of “2. Qualitative and quantitative composition” the SmPC reads: *“Each vial contains [100/250] mg of paclitaxel formulated as albumin bound nanoparticles”*.

38 Under the heading of “therapeutic indications” the SmPC reads:

“Abraxane monotherapy is indicated for the treatment of metastatic breast cancer in adult patients who have failed first-line treatment for metastatic disease and for whom standard, anthracycline containing therapy is not indicated”.

“Abraxane in combination with gemcitabine is indicated for the first-line treatment of adult patients with metastatic adenocarcinoma of the pancreas”.

“Abraxane in combination with carboplatin is indicated for the first-line treatment of non-small cell lung cancer in adult patients who are not candidates for potentially curative surgery and/or radiation therapy”.

39 Under the header of “5.1 Pharmacodynamic properties” the SmPC includes a passage which reads *“Paclitaxel is an antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilises microtubules by preventing depolymerisation. This stability results in the inhibition of the normal dynamic reorganisation of the microtubule network that is essential for vital interphase and mitotic cellular functions...”*.

40 In relation to albumin the SmPC says at 5.1: *“Abraxane contains human serum albumin-paclitaxel nanoparticles of approximately 130 nm in size, where the paclitaxel is present in a non-crystalline, amorphous state. Upon intravenous administration, the nanoparticles dissociate rapidly into soluble, albumin bound paclitaxel complexes of approximately 10 nm in size. Albumin is known to mediate endothelial caveolar transcytosis of plasma constituents, and in vitro studies demonstrated that the presence of albumin in Abraxane enhances transport of paclitaxel across endothelial cells. It is hypothesised that this enhanced transendothelial caveolar transport is mediated by the gp-60 albumin receptor, and that there is enhanced accumulation of paclitaxel in the area of tumour due to the albumin-binding protein Secreted Protein Acidic Rich in Cysteine (SPARC)”*.

41 Under the header of “pharmaceutical particulars - 6.1 list of excipients” the SmPC reads *“Human albumin solution (containing sodium, sodium caprylate and N-acetyl DL tryptophanate)”*.

42 Nab-paclitaxel and Abraxane were used interchangeably during the hearing and sometimes in the literature (Abraxane is also referred to in some papers as ‘ABI-007’). I wish to make it clear that in this decision where I refer to Abraxane that I am content to accept that the effects of Abraxane are due to nab-paclitaxel, the active

substance. Paclitaxel is sometimes referred to in the literature by its trade mark "Taxol".

The purpose of the Regulation

43 Before looking closely at the characteristics of nab-paclitaxel, I think it is appropriate to consider Dr Goodfellow's submissions that an SPC for nab-paclitaxel is in line with the general purpose the Regulation. He referred to Recitals 2-6 of the Regulation and also drew my attention to several authorities which elaborate on the purpose of the Regulation.

44 Dr Goodfellow emphasised that over ten years of various clinical trials had been conducted to support the authorisation for nab-paclitaxel under Article 3 (2) of Regulation 726/2004,¹ the EU Regulation for the authorization of medicinal products which reads as follows:

Any medicinal product not appearing in the Annex may be granted a marketing authorisation by the Community in accordance with the provisions of this Regulation, if:

(a)...

(b)... the applicant shows that the medicinal product constitutes a significant therapeutic, scientific or technical innovation or that the granting of authorisation in accordance with this Regulation is in the interests of patients or animal health at Community² level".

45 I took Dr Goodfellow's submission on this point to be that as nab-paclitaxel had met the requirements of 726/2004, especially in light of several trials over a ten year period, that its pharmacological action is proven and that it represents a significant therapeutic innovation. I am happy to accept this.

46 Dr Goodfellow had referred extensively to the Advocate General's Opinion in *Neurim* both in correspondence and at the hearing. In paragraph 41 of her Opinion, the Advocate General discusses the complexity of balancing the interests of different stakeholder groups, namely the pharmaceutical sector, generic companies and state health systems in relation to SPC protection. In the following paragraph, 42, she makes the point "*In view of the complexity of that balance of interests, it is necessary*

¹ REGULATION (EC) No 726/2004 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 31 March 2004 laying down EU procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency

² The "European Community" is referred to in some of the legislation which pre-dates the Lisbon Treaty. Article 1 of the Lisbon Treaty establishing the European Union in 2007 says "the Union shall replace and succeed the European Community". In this decision the terms "Community" and "European Union" are used interchangeably. <http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A12012M%2FTXT>

to proceed with great caution when making teleological interpretation of the individual provisions of the regulation”.

- 47 I am also minded of the comments of Jacob J (as he then was) in *Draco AB’s SPC Application* (RPC 14) [2006] which the applicant had referred to in their skeleton. Jacob J said that the SPC scheme :

“It is not for the general protection of the fruits of research. It is to compensate for lost time in the exploitation of inventions which are patented”.

- 48 The Explanatory Memorandum³ lays out the rationale for the Regulation and can be helpful in informing the interpretation of it. Dr Goodfellow referred to paragraph 12 which reads:

“However, the proposal is not confined to new products only. A new process for obtaining the product or a new application of the product may also be protected by a certificate. All research, whatever the strategy or final result, must be given sufficient protection.”

- 49 However, it is important to take in this in the context of the paragraph which precedes it. Paragraph 11 reads (my emphasis is underlined):

“The proposal for a Regulation therefore concerns only new medicinal products. It does not involve granting a certificate for all medicinal products that are authorized to be placed on the market. Only one certificate may be granted for any one product, a product being understood to mean an active substance in the strict sense. Minor changes to the medicinal product such as a new dose, the use of a different salt or ester or a different pharmaceutical form will not lead to the Issue of a new certificate”.

- 50 Overall, I consider that the general situation that arises in the case of nab-paclitaxel is not inconsistent with the general purpose of the Regulation. Clearly however, the specific provisions of the Regulation were established to provide a framework of key parameters to ensure that the extension of protection provided by the SPC scheme was appropriate, having regard to the various stakeholder interests. It is one these fundamental parameters that is at issue here, namely Article 1(b).
- 51 Dr Goodfellow then made significant submissions on the basis of a Court of Appeal case, *Generics UK Ltd v Daiichi Pharmaceutical Co Ltd; Daiichi Sankyo Co Ltd EWCA Civ 646 [2009] (Daiichi)*. I found Dr Goodfellow’s submissions in relation to *Daiichi* to be relevant. It is therefore important that I consider *Daiichi* and the related documentation in some detail. Firstly, I will briefly outline the facts in *Daiichi*.
- 52 *Daiichi’s* patent (‘283) relates to levofloxacin, an enantiomer of an antibiotic called ofloxacin. Levofloxacin, was novel and inventive (the inventiveness being confirmed by the Court of Appeal in *Daiichi* itself). The ‘283 patent was filed on 20 June 1986. A patent existed for ofloxacin - ‘005, filed in 1981 (and therefore expired in 2001). *Daiichi* obtained an MA for ofloxacin in Germany in May 1985 and in the UK in March

³ Proposal for a Council Regulation (EEC) concerning the creation of a supplementary protection certificate for medicinal products” Brussels 11 April 1990.

1990. In June 1997 MAs were granted for levofloxacin. In Oct 1997 *Daiichi* filed an application for an SPC for levofloxacin.

53 *Daiichi's* opponent Generics UK contended that levofloxacin was not entitled to an SPC because, as levofloxacin is the active component of ofloxacin, the 1985 MA for ofloxacin represented the first MA for levofloxacin in the EU.

54 I am particularly struck by two passages in *Daiichi J* which Dr Goodfellow pointed to where Jacob LJ said in paragraphs 53 and 54 :

For one thing is clear, those earlier authorisations did not entitle Daiichi to market levofloxacin as such. Moreover the kind of research which led to levofloxacin was research which led to what for all practical purposes was a new medicine – the very kind of research referred to in recital (2). Moreover levofloxacin had to get marketing authorisation on the basis it was a new drug. The case is wholly within the policy reasons for the grant of SPCs as set out in the recitals” [53].

“.....once '005 ran out anyone could market ofloxacin. They could not market levofloxacin because of the patent in suit. And prior to the patent in suit they could not market levofloxacin for the simple reason invention was needed to make it. In reality there is no unwarranted extension of protection. It must be remembered here that an earlier patent may include within its claims things which are the subject of later inventions – improvement inventions are a major feature of the patent system. No one could reasonably contend that the grant of a patent for an improvement to an earlier invention extends the life of a patent for that earlier invention.”[54]

55 Dr Goodfellow submitted that *Daiichi* was “absolutely on all fours” with the applicant’s case. He said *“We are not seeking a monopoly on paclitaxel. We seek an SPC on nab-paclitaxel. Before we made the invention, nobody could make it. It was only after the invention could people make it and we were able to apply for marketing authorisation for it. The scope of this SPC, should you grant it, would be limited to that medicine. Generic companies, anybody, is free to market paclitaxel. They can't market nab-paclitaxel for the same reasons as are set out there. Firstly, it is because of the patent in suit, invention was required to make it. In reality, as Jacob LJ said, there is no unwarranted extension of protection. It is all based on the innovation”* .

56 To strengthen this line of argument, Dr Goodfellow referred to the corresponding Plant Protection Product Regulation and Jacob LJ’s reference to it in *Daiichi*. Recital 14 of that Regulation, which as I have said above applies to the Medicinal Products SPC Regulation, reads:

“Whereas the issue of a certificate for a product consisting of an active substance does not prejudice the issue of other certificates for derivatives (salts and esters) of the substance provided that the derivatives are the subject of patents specifically covering them”.

57 Jacob LJ in *Daiichi* comments on this at paragraph 75, where he says:

“Any rational or purposive reading of Recital 14 would not limit its use for construction of the Regulation only to derivatives in the strict chemical sense. The Recital is clearly using “derivatives (salts and esters)” by way of example only. The important point is that the product is sufficiently novel and inventive to justify a patent”

- 58 While there might be strong parallels on circumstantial grounds between the present case and *Daiichi* I consider the factual context of *Daiichi* differs considerably from the present case. *Daiichi* concerned two different forms, stereoisomers, of what was accepted as a single molecule. Two different enantiomers have the same atoms, and same structure - it is their molecular geometry that is different. Also it is known that different enantiomers in a racemic composition can be active and non-active. That is very different to what we have in the case of nab-paclitaxel - two clearly different molecules present in a single particle.
- 59 In all, I found Dr Goodfellow’s submissions in relation to *Daiichi* in terms of the purpose of the Regulation, persuasive. I agree that the situation in *Daiichi*, in terms of patent protection and the coverage provided by the MA and the consequences of both the protection afforded by the patent and the MA in *Daiichi*, has strong similarities to the situation which would arise from an SPC were it to be granted on the basis of the application for nab-paclitaxel in the present case.
- 60 Overall, I consider that the present situation is not inconsistent with the rationale underlying the Regulation. Also at a general level the applicant’s case has some support from the judgment in *Daiichi*. Together, these create a favourable policy backdrop which I should be mindful of in forming my decision. Clearly then the particular facts surrounding the present case, the characteristics of nab-paclitaxel, need to be looked at in fine detail.

The nab-paclitaxel nanoparticle and the albumin-paclitaxel interaction

- 61 A key element of the applicant’s case is that the combination of albumin and paclitaxel in nab-paclitaxel creates a new product. In earlier correspondence (letter of 28 May 2013, page 12, paragraph 5) the applicant had submitted that “*the new structure (of albumin) thus changes the characterisation of the product (nab-paclitaxel)*”.
- 62 There has been no suggestion by the applicant that albumin is not a molecule in its own right - it clearly is. Albumin is specifically referred to as an excipient in section 6.1 of the SmPC. However, Mr Georgiou and Dr Goodfellow sought to distinguish the albumin in the nab-paclitaxel nanoparticles as *processed* albumin from albumin in solution, “free albumin”. They emphasised that the binding between paclitaxel and processed albumin is stronger than between paclitaxel and free albumin and this creates a different entity from paclitaxel bound to free albumin in the blood.
- 63 It is clear from the applicant’s submissions both in correspondence and at the hearing that they considered this relatively tight binding between paclitaxel and albumin in nab-paclitaxel is critical to enabling the particle to be transported into tumour tissue where it produces its therapeutic effects. Before I look at the

applicant's submissions on the nature of the nab-paclitaxel particle, I will consider what the Patent says about it.

- 64 Paragraph 29 of the Patent explains the make-up of the particle and reads: "*The invention further provides a drug delivery system in which part of the molecules of pharmacologically active agent are bound to the protein (e.g., human serum albumin), and are therefore immediately bioavailable upon administration to a mammal. The other portion of the pharmacologically active agent is contained within nanoparticles coated by protein. The nanoparticles containing the pharmacologically active agent are present as a pure active component, without dilution by any polymeric matrix.*"
- 65 The Patent goes on to say at paragraph 31 "*A large number of conventional pharmacologically active agents circulate in the blood stream bound to carrier proteins (through hydrophobic or ionic interactions) of which the most common example is serum albumin (my emphasis). Invention methods and compositions produced thereby provide for a pharmacologically active agent that is "pre-bound" to a protein (through hydrophobic or ionic interactions) prior to administration*".
- 66 The Patent describes how the nanoparticles may be prepared in paragraph 27 which reads "*described herein are methods for the formation of nanoparticles of pharmacologically active agents by a solvent evaporation technique from an oil-in-water emulsion prepared under conditions of high shear forces (e.g., sonication, high pressure homogenization, or the like) without the use of any conventional surfactants, and without the use of any polymeric core material to form the matrix of the nanoparticle. Instead, proteins (e.g., human serum albumin) are employed as a stabilizing agent*".
- 67 Examples 1, 5, 6 of the Patent describe the preparation of the nanoparticles by emulsification and high pressure homogenization, followed by filtration. It says these techniques yielded particles of 160-220m or 140-160nm in size.
- 68 The Patent discusses the differences between prior art nanoparticles and the nanoparticles of the invention. It says that chemical crosslinking (e.g. with glutaraldehyde) is not suitable for water-insoluble drugs such as paclitaxel (paragraphs 12 and 13).
- 69 In their written correspondence of 14 December 2015 the applicant submitted that the albumin in nab-paclitaxel was crosslinked. Support for this can be found in the Patent at paragraph 46 which reads "*High shear is used to disperse a dispersing agent containing dissolved or suspended pharmacologically active agent into an aqueous solution of a biocompatible polymer, optionally bearing sulfhydryl or disulfide groups (e.g., albumin) whereby a shell of crosslinked polymer is formed around fine droplets of nonaqueous medium. The high shear conditions produce cavitation in the liquid that causes tremendous local heating and results in the formation of superoxide ions that are capable of cross linking the polymer, for example, by oxidizing the sulfhydryl residues (and/or disrupting existing disulfide bonds) to form new, cross linking disulfide bonds*".
- 70 I note, in particular, that the Patent refers to albumin as a carrier and as a structural support. In paragraph 32 the Patent says "*The high concentration of albumin in*

invention particles, compared to Taxol, provides a significant amount of the drug in the form of molecules bound to albumin, which is also the natural carrier of the drug in the blood stream.” Paragraph 34 goes on to say “Human serum albumin serves as the structural component of invention nanoparticles, and also as a cryoprotectant and reconstitution aid”.

- 71 Dr Goodfellow pointed to a paper by *Paal et.al.*⁴ which discusses the interaction of paclitaxel and albumin. In the background section it outlines the common general knowledge that albumin is the most common human protein and that its main physiological function is to transport proteins, and also to maintain osmotic pressure and the pH of blood. The paper goes on to say that the binding of albumin to paclitaxel had previously been thought of as non-specific but it provides evidence for a specific high-affinity and several intermediate affinity binding sites on albumin for paclitaxel.
- 72 Dr Goodfellow then referred to *Gardner et.al.*⁵ which shows that following administration of nab-paclitaxel to a patient over 95% of paclitaxel remained bound to albumin over time (in serum). He went on to say that during the production process of nab-paclitaxel it had been found that the binding affinity between processed albumin and paclitaxel found in nab-paclitaxel is three fold higher than that between native albumin and paclitaxel. This point was elaborated in the applicant’s skeleton (paragraph 4.16) which said that “ $K_D=42\mu\text{m}$ for processed albumin in Abraxane, whereas it is only $K_D=134\mu\text{m}$ for native albumin”. The higher the dissociation constant, the lower the affinity.
- 73 An Abraxis Science study report⁶ submitted as evidence says that (page 9) “*ABI-007-flutax exhibited 2.3 fold higher binding to HSA than Taxol-flutax. Since paclitaxel is primarily transported by albumin in vivo, this increase in binding may have clinical implications (flutax is a fluorescence marker).* This report also refers to human serum albumin as “*the carrier for paclitaxel in vivo*” (page 7, lines 4-5).
- 74 The issue of covalent bonding was a significant point in these proceedings. Covalent bonds are often regarded as being an important characteristic in defining a molecule as a single entity, given that electron pairs are shared.
- 75 Dr Goodfellow discussed the CJEU case of *Arne Forsgren v Osterreichisches Patentamt* (C-631/13) (“Forsgren”) to support his argument that the presence of a covalent bond is not crucial to determining whether a substance that comprises two parts are to be considered as a single ingredient. He pointed to paragraph 25 in this judgment which reads:

⁴ Paal et. al., High affinity binding of paclitaxel to human serum albumin, Eur J Biochem 2001; 268(7): 2187-2191

⁵ Gardner E et al., Quantitative determination of total and unbound paclitaxel in human plasma following Abraxane treatment, J Chromatogr B Analyt Technol Biomed Life Sci. 2008 February 1; 862(1-2): 213–218.

⁶ American BioScience Inc., Study N21660, Binding of Paclitaxel to Albumin, Microtubules, and Cells. Inhibition of binding by Cremophor-EL and Comparative analysis of ABI-007 versus Taxol. BIO-EL-1

“since Regulation No 469/2009 does not draw any distinction according to whether an active ingredient is covalently bound with other substances, it is not appropriate to exclude, on that ground, the grant of an SPC for such an active ingredient”.

76 I note, however, that in a preceding paragraph, 21, the CJEU sets the context in which the statement is made. Paragraph 21 reads:

“By its first question, the referring court asks, in essence, whether Articles 1(b) and 3(a) of Regulation No 469/2009 must be interpreted as precluding the possibility that an active ingredient can give rise to the grant of an SPC on the sole ground that the active ingredient is covalently bound to other active ingredients forming part of a medicinal product”.

77 I should point out that the situation in *Forsgren* was different to what we have in this case. In *Forsgren* the applicant was arguing that a molecule (protein D) was not precluded from being considered as an active in its own right despite the fact that it was covalently bonded to another molecule which was deemed to be an “active ingredient”.

78 Dr Goodfellow also suggested, quite reasonably in the circumstances, that the interaction between processed albumin and paclitaxel is functionally comparable in some ways to a covalent bond. He added that if the applicant had simply covalently bonded paclitaxel and albumin then that would be enough.

79 Overall, I agree with the applicant’s submissions that *Forsgren* states, in principle, that covalent bonding does not delineate between an active and a non-active ingredient. I do not think the issue of the presence or absence of a covalent bond between albumin and paclitaxel is determinative here to deciding whether albumin and paclitaxel act as a single active ingredient.

80 In summary, having studied the Patent I consider the nab-paclitaxel particles consists of paclitaxel (which is referred to as a “pharmacologically active agent”) coated with albumin; the coating has free albumin associated with it and portions of paclitaxel are associated with both the albumin coating and free albumin.

81 Taking *Pall et. al.*, *Gardner et.al.* and the Patent together I am content to accept that albumin and paclitaxel are tightly bound together in nab-paclitaxel nanoparticles and that the interaction between albumin and paclitaxel in these particles is stronger than between ‘free’ albumin and paclitaxel and also that the albumin in nab-paclitaxel can be cross-linked.

82 However, at this stage I do not see that these physical-chemical properties of the particles somehow creates a new active ingredient which is materially different from the sum of its parts. I am minded that both the literature and the Patent refer to albumin as a carrier and, in particular, the Patent itself suggests albumin is providing a structural support in the nanoparticle.

Pharmacological properties of nab-paclitaxel

- 83 Dr Goodfellow made a series of submissions that nab-paclitaxel was more effective than paclitaxel therapeutically; that nab-paclitaxel treated new cancers that paclitaxel did not treat and that nab-paclitaxel had a significantly better pharmacological profile than paclitaxel. I will take each of these points in turn.
- 84 Firstly, therapeutic efficacy. Dr Goodfellow pointed to several papers in support of the therapeutic effectiveness of nab-paclitaxel over paclitaxel.
- 85 Dr Goodfellow referred to *Blum et. al.*⁷. which relates to a phase II trial of albumin-bound paclitaxel in women who still had progressive metastatic breast cancer after being treated with paclitaxel. It concludes that 31% of patients treated with weekly albumin-bound paclitaxel had either an objective response or stable disease for at least 16 weeks and it goes on to say the patients “*likely derived benefit from albumin-bound paclitaxel*”. The paper also says albumin-bound paclitaxel had a better safety profile than in patients previously on paclitaxel and that it is “*well tolerated with no hypersensitivity reactions*”. Dr Goodfellow emphasised that the patients in these trials had previously failed to be treated by paclitaxel.
- 86 He also referred to a paper by *Gradishar et.al.*⁸. This concerns a phase III comparative trial of paclitaxel and Abraxane in women with metastatic breast cancer. The data show that the patients treated with Abraxane displayed significantly better responses, in particular that the patient’s tumours took a significantly longer time to progress than those treated with paclitaxel. It also says that Abraxane had a more favourable safety profile than paclitaxel and particularly that it does not need corticosteroid premedication (which reduces hypersensitivity) which is required to mitigate the adverse effects of castor-oil in conventional cremaphor-paclitaxel preparations. Dr Goodfellow referred to *Irizzary et.al.*⁹ which points out that anaphylactic responses to cremaphor-paclitaxel preparations lead to the death of some patients.
- 87 On the theme of the relative safety of nab-paclitaxel, Dr Goodfellow referred to a report¹⁰ which shows that Abraxane activates the complement cascade (the products of which kill cells and potentiate other immune-related cytotoxicity) to a lesser degree than paclitaxel.

⁷ Blum et. al., Phase II Study of Weekly Albumin-Bound Paclitaxel for Patients with Metastatic Breast Cancer Heavily Pretreated with Taxanes. *Clin Breast Cancer* 2007; 7(11): 850-856

⁸ Gradishar et. al., Phase III Trial of Nanoparticle Albumin-Bound Paclitaxel Compared with Polyethylated Castor Oil-based Paclitaxel in Women with Breast Cancer. *J Clin Oncol* 2005; 23(31): 7794-7803

⁹ Irizzary et al., Cremophor EL-containing paclitaxel-induced anaphylaxis: a call to action. *Commun Oncol* 2009; 6(3):132-134

¹⁰ National Cancer Institute, Nanotechnology Characterization Lab, NCL Data Summary. Presented to Abraxis Biosciences, October 2010. *In vitro* study comparing activation of human complement by paclitaxel but not by Abraxane®

- 88 Dr Goodfellow also referred to studies of nab-paclitaxel in the treatment of pancreatic cancer and non-small lung cell cancer. He referred to *Whitehead et.al.*¹¹ and said this shows that conventional paclitaxel has limited efficacy in treating pancreatic cancer. He also said that the SmPC submitted with the present application for nab-paclitaxel is authorised for the treatment of pancreatic cancer. I note that the data in the SmPC concerns a comparison of a combination of nab-paclitaxel and gemcitabine versus gemcitabine alone.
- 89 I also note the paper by *Alvarez et.al.*¹² which refers experiments in a mouse cancer model. It says that (page 928, right hand column, paragraph 5) "*Gemcitabine alone treatment resulted in minor responses, while nab-paclitaxel alone did not show any anti-tumour activity. Consistently, nab-paclitaxel plus gemcitabine significantly increased the proportion of apoptotic cells (dying cells) compared with the control*". The paper concludes that (page 931, third paragraph) that "*nab-paclitaxel plus gemcitabine exerts significant anti-tumour activity in primary advanced pancreatic cancer*". However, it goes on to acknowledge that the number of patients in the study was small and says that the results "*are striking enough to warrant additional studies...*".
- 90 I note that the bundle includes a conference abstract by *Van Hoff et.al.*¹³. This provides data which shows that gemcitabine and nab-paclitaxel combined produce statistically significant positive clinical effects in treating pancreatic cancer compared with gemcitabine alone. I also note that *Rajeshkumar et.al.*¹⁴ (discussed below) references a paper by *Van Hoff et.al.* in relation to its statement which says that "*nab-paclitaxel....in combination with gemcitabine resulted in statistically significant and clinically meaningful overall survival advantage compared to patients receiving gemcitabine alone*".
- 91 Dr Goodfellow pointed to clinical data showing pictures of a woman with non-small lung cell carcinoma with metastases on her chest, treated firstly with paclitaxel and then nab-paclitaxel. It is evident from these pictures that the number of lesions/deposits on her chest were much reduced after nab-paclitaxel treatment. However, the legend to this figure indicates the patient had received extensive pre-treatment with a number of drugs including carboplatin A. I note that the SmPC for nab-paclitaxel says that nab-paclitaxel is to be used in conjunction with carboplatin for the treatment of non-small lung carcinoma.

¹¹ Whitehead et. al., Phase II Trial of Paclitaxel and Granulocyte Colony-Stimulating Factor in Patients with Pancreatic Carcinoma: a Southwest Oncology Group Study. *J Clin Oncol* 1997; 15: 2414-2419

¹² Alvarez et. al., Stromal disrupting effects of nab-paclitaxel in pancreatic cancer. *Br J Cancer*, 2013, 109, 926-933.

¹³ Von Hoff et al., Randomized phase III study of weekly nab-paclitaxel plus gemcitabine versus gemcitabine alone in patients with metastatic adenocarcinoma of the pancreas (MPACT), *J Clin Oncol*, 2012; 30 (suppl 34); LBA148

¹⁴ Rajeshkumar et. al., Highlights of the Innovative Preclinical Studies which Guided the Rapid Bench to Bedside Development of Nab-paclitaxel plus Gemcitabine Combination for the Treatment of Pancreatic Cancer (American Association for Cancer Research 2014, poster accompanying abstract LB-94), San Diego, CA.

- 92 I also note another paper in the bundle by *Desai et.al.*¹⁵ which indicates Abraxane had significantly higher anti-tumour activity compared with cremaphor-paclitaxel when tested on a variety of human tumour cell lines a mouse-human tumour xenograft model.
- 93 In relation to his points on the pharmacological properties of nab-paclitaxel Dr Goodfellow's drew my attention to Jacob LJ's remarks in *Daiichi* (paragraph 68) where his Lordship said "*It (levofloxacin) has its own distinct activity, bioavailability and toxicity*". Dr Goodfellow submitted that nab-paclitaxel has its own activity, bio-availability and low toxicity profiles and that it treats new diseases.
- 94 Dr Goodfellow also pointed to paragraph 27 in *Forsgren* as being relevant. It reads:
- "The answer to the question whether a substance which is part of the medicinal product is an active ingredient with the meaning of Article 1(b) of Regulation No 469/2009 depends, therefore, on whether that substance has a pharmacological, immunological or metabolic action of its own, independently of any covalent binding with other active ingredients"*
- 95 Dr Goodfellow said, in effect, that while the immunological or metabolic criteria referred to in *Forsgren* were not particularly relevant to the issue here, the pharmacological action of nab-paclitaxel is completely beyond question.
- 96 Having considered the body of pharmacological evidence cited by the applicant I am content to accept that nab-paclitaxel has a distinct pharmacological activity compared with paclitaxel, in particular that it: (i) is more effective than paclitaxel in the treatment of metastatic breast cancer; (ii) shows effectiveness in treating two other tumours (pancreatic cancer and non-small cell lung carcinoma) in combination with other anti-neoplastic agents and (iii) that nab-paclitaxel has a better safety profile than paclitaxel in that it is less likely to cause allergic side effects.
- 97 As the findings of the papers I have referred to above and the SmPC indicate that nab-paclitaxel is clinically effective, it follows that nab-paclitaxel is getting to the site of action, a tumour site, in at least a relatively effective manner. This is supported by *Desai et.al.* which reports on the basis of *in vitro* studies that nab-paclitaxel showed much higher binding to and transport across endothelial cell membranes (the cells that line blood vessels) than paclitaxel. It also says that (page 1322, third paragraph) "*intratumour concentrations of paclitaxel were 33% higher following administration of ABI-007 (nab-paclitaxel) compared with equal doses of cremaphor-based paclitaxel in the MX-1 (breast cancer) xenograft model*".
- 98 I now turn to what happens within the tumour interstitium, the micro-environment around tumour cells, and also within tumour cells themselves.

¹⁵ Desai et. al., "Increased Antitumor Activity, intratumor Paclitaxel Concentrations, and Endothelial Cell Transport of Cremophor-Free, Albumin-Bound Paclitaxel, ABI-007, Compared with Cremophor-Based Paclitaxel", *Clinical Cancer Research* 2006, 12(4): 1317-1324

The tumour micro-environment

- 99 In the applicant's skeleton argument they make the point that the action of therapeutics on the tumour microenvironment is an important consideration in modern cancer therapy, in addition to the direct effect of drugs on tumour cells. A key element of the applicant's submission was that nab-paclitaxel is effective in destroying the three-dimensional structures around a tumour. In their letter of 14 December 2015 (page 6) the applicant's say the "...*data demonstrate a completely different mechanism of action of nab-paclitaxel compared with CrEL-based paclitaxel*".
- 100 Dr Goodfellow pointed me to *Alvarez et.al* and *Rajeshkumar et.al.* to support his submission that nab-paclitaxel depletes some of the major components surrounding a tumour - the fibrotic stroma, in which collagen and cancer-associated fibroblasts are major components.
- 101 *Alvarez et.al.* says patients treated with gemcitabine and nab-paclitaxel had less abundant collagen matrix around tumour glands and lower numbers of cancer-associated fibroblasts compared with controls. In particular *Alvarez et.al.* shows that the density of the stroma surrounding the tumours was less in patients treated with nab-paclitaxel compared to the controls. However, it says in the discussion that the sample size in these studies was small and that the content of the stroma and the numbers of cancer-associated fibroblasts may change with different cancer states. It goes on to say (page 931, paragraph 2) there was "*no randomised control arm of patients treated with gemcitabine alone (in these studies) that would make the comparison more conclusive*". Moreover, it also says in the discussion (page 931, paragraph 1) that "*the effects of nab-paclitaxel in PDA (pancreatic cancer) stroma are not fully understood and to some extent controversial*".
- 102 *Rajeshkumar et.al.* describes studies in a mouse model of pancreatic tumour xenografts. (This document appears to be a conference poster, which is unlikely to have been peer-reviewed. I note it is authored by the John Hopkins School of Medicine, a respected American medical research institution, the applicant company and others). It show images of histological tumour specimens and says that "*Abraxane robustly depletes the stroma of orthotopically implanted pancreatic cancer models*". In their letter of 14 Dec 2015 (page 5), the applicant highlights the histological staining experiments reported in *Rajeshkumar et.al.* These show the staining of tumours in mice which were treated with Abraxane, Abraxane plus gemcitabine and gemcitabine plus paclitaxel. It is clear that the tumour specimens taken from mice treated with Abraxane show greater stromal disorganisation than in mice treated with taxol alone, a combination of gemcitabine plus Taxol, or in the controls.
- 103 Dr Goodfellow also drew my attention to Hawkins *et.al*¹⁶ which shows that tumour uptake of Abraxane is 26% higher in a mouse breast tumour model compared with solvent-based paclitaxel while nab-paclitaxel shows relatively lower uptake than paclitaxel in a variety of normal tissues.

¹⁶ Hawkins et al., Rationale, Preclinical Support, and Clinical Proof-of-Concept for Formulating Water-insoluble Therapeutics as Albumin-stabilized Nanoparticles: Experience with Paclitaxel. 2000 AACR 1189 Poster

- 104 Dr Desai said that “*there are other types of cells (compared with cancer cells) in the stroma that we know, clearly, are killed with Abraxane but not with conventional paclitaxel*”.
- 105 As Dr Goodfellow submitted, the Patent provides a logical basis for apparent advantages gained by the particular size of the nanoparticles - the size sweet spot- which would enable them to be delivered effectively to a tumour site. However, I note the SmPC says “*Upon intravenous administration, the nanoparticles dissociate rapidly into soluble, albumin bound paclitaxel complexes of approximately 10 nm in size*”. Nonetheless, I am prepared to give the applicant the benefit of the doubt on the contribution that the size of the nab-paclitaxel particle makes to its delivery.
- 106 On the basis of the evidence before me I am content to accept that nab-paclitaxel is more effective than paclitaxel in getting across blood cell membranes and into the tumour interstitium. Furthermore, despite some of the questions raised in *Alvarez et.al* concerning the effects of nab-paclitaxel alone on the stroma, I am happy to accept that nab-paclitaxel has stromal-depleting properties in pancreatic tumours and that it kills cells other than cancer cells. However, this data does not tell us how nab-paclitaxel is killing the non-cancer cells.

Actions of nab-paclitaxel at the cellular level

- 107 The examiner had considered that *MIT* applies particularly in this case as it concerns the determination of the characteristics of an active ingredient in a combination of substances. However, Dr Goodfellow and Mr Georgiou were keen to point out that *MIT* and *GSK* concerned a combination of products while their primary position was that nab-paclitaxel is a single active ingredient. The key question that arises in my mind is whether, in substance, this distinction actually exists.
- 108 At this stage I was not able to determine whether nab-paclitaxel is a single active ingredient or a combination of ingredients. As I have indicated above in relation to the nature of the particle itself I do not see evidence that nab-paclitaxel is active as a single ingredient. While the data relating to the effects of nab-paclitaxel on cancer cells and on the tumour microenvironment are convincing, this of itself does not answer the question of whether we are dealing with a single active ingredient or combination of ingredients. If I decide that nab-paclitaxel represents a combination of ingredients then *MIT* and *GSK* are particularly relevant.
- 109 The kernel of the issue to me is then what evidence is there that the albumin component of nab-paclitaxel contributes to the activity of paclitaxel - is it paclitaxel alone that kills tumour cells, or is its cytotoxicity critically dependant on the albumin component of nab-paclitaxel.
- 110 I will proceed to look at the question of whether nab-paclitaxel is single active ingredient or a combination of ingredients in light of the applicant's submissions on the activity of nab-paclitaxel at the cellular level and then consider my findings in light of the case law.

- 111 Dr Goodfellow drew my attention to substances for which SPCs had been granted where it was accepted that only a part of the substance in question had the 'final' biological effect. In particular, he referred to SPCs which had been granted for vaccine cases where the active ingredient was a protein molecule - an antigen. He rightly pointed out that it is only a fragment of an antigen, the epitope that actually elicits an immune response. That may be the case but it is not on all fours with what we have here with nab-paclitaxel. A peptide that forms the epitope was always an integral component of a protein from which it originated, being present in the continuous chain of linked amino acids within the larger protein itself. Also the amino acids that do not make up an epitope can still influence the three dimensional nature of it.
- 112 Dr Goodfellow also drew my attention to SPCs which had been granted for both prodrugs and their corresponding active components separately (Fosaprepitant/Aprepitant; Paliperidone palmitate/Paliperidone) and for a PEGylated protein (Pegfilgrastim) which has an earlier marketing authorization for the protein component (Filgrastim).
- 113 I appreciate Dr Goodfellow's point here that in certain circumstances it may be possible, in principle, to regard molecules and their more complex forms as different for the purposes of Article I(b). More generally, while it was not unreasonable for Dr Goodfellow to make these submissions I would say that the present case needs to be determined on its particular facts in light of the case law. Moreover, to my mind, the grant of an SPC in any part of the EU does not create a *ratio decidendi*.
- 114 Dr Goodfellow made several submissions that focussed on the activity of nab-paclitaxel at the cellular level. He referred to *Zhang et al.*¹⁷ which shows that significantly less (between 8-155 fold less) nab-paclitaxel compared with paclitaxel was required to kill cells in 'IC50' tests involving five neuroblastoma cell lines. This is good evidence that nab-paclitaxel is much more effective in killing cells *in vitro* than paclitaxel.
- 115 This raises two important questions. Does nab-paclitaxel get into the cell intact? If it does, do the two components fall apart or do they act in consort?
- 116 I referred to the 'YouTube' video¹⁸, which had been included in the applicant's submissions. This video provides an elegant illustration of how paclitaxel is transported by albumin and transferred into cells by an endocytotic process mediated by the protein caveolin. However, at the hearing Dr Desai said that this was now only regarded as a putative mechanism and Dr Goodfellow asked me to treat it with some caution. He said "*We don't know whether the nanoparticles are getting into cells. It looks from the in vitro work as if it probably is*".

¹⁷ Libo Zhang et al., Nab-Paclitaxel is an Active Drug in Preclinical Model of Pediatric Solid Tumours, Clin Cancer Res 2013, 19; 5972-5983

¹⁸ <https://www.youtube.com/watch?v=BsLLZxXLSfA>

- 117 Here, I consider the paper by *Chen et.al*¹⁹, cited by the applicant, is important in terms of determining whether paclitaxel behaves differently when bound to albumin, compared to on its own.
- 118 *Chen et.al.* has a range of experiments that look at nab-paclitaxel and albumin in cell transport. It shows that the paclitaxel and albumin are located within vesicles. This suggests that albumin and paclitaxel are bound to each other.
- 119 However, on close inspection *Chen et.al.* does not say categorically that nab-paclitaxel is transported across the membrane as a single entity, although the abstract suggests that both components are “co-transported”. On page 703 paragraph 1 line 10 *Chen et.al.* says “*The combined results (of studies with fluorescently labelled albumin and nab-paclitaxel) demonstrate that paclitaxel can be found in punctae of endothelial cells, and that their pattern and proximity to albumin-containing vesicles suggests that paclitaxel utilizes the same endocytosis and transcytosis mechanism to albumin*”.
- 120 This could mean that nab-paclitaxel remains intact inside the cell or that albumin and paclitaxel use the same intracellular processes and mechanisms but separately. I referred the applicant to *Chen et.al.* after the hearing. In reply they said:

“Figure 2C therefore shows that paclitaxel when administered in a complex with albumin is found in the cell at the same place and at the same time as albumin... This indicates that paclitaxel, when administered in a complex with albumin (such as present in nab-paclitaxel), is taken up by the endocytic pathway as an intact substance in complex with albumin, rather than as paclitaxel alone. This type of co-location experiment is the standard and widely accepted approach to show physical interaction between biological molecules and is supportive of the view that nab-paclitaxel is transported intact across the cell membrane”.

- 121 In its summary *Chen et.al.* says (final paragraph, page 710) “...compared with the solvent-based paclitaxel, nab-paclitaxel demonstrates more efficient transport across endothelial cells, greater penetration, cell uptake and mitotic arrest induction in tumour xenografts, and enhanced extravascular distribution in patients that are attributable to carrier-mediated transport”.
- 122 On the basis of the evidence the applicant has supplied, I am content to accept that albumin and paclitaxel are transported across the cell membrane as a single unit with the concomitant benefits as summarised by *Chen et.al.*
- 123 However, the fact that the albumin component of nab-paclitaxel facilitates its passage into the cells is not at all surprising in view of the well-established membrane transport function of this protein. Proteins that carry molecules across membranes would be regarded as having a carrier function. I note in particular, the reference to “carrier-mediated transport” in the conclusions of *Chen et.al.*, with the assumption being that albumin is acting as the carrier for paclitaxel.

¹⁹ Nianhang Chen et. al., Albumin-bound nanoparticles (nab) paclitaxel exhibits enhanced paclitaxel tissue distribution and tumor penetration, *Cancer Chemother Pharmacol* 2015, 76: 699-712

- 124 The question then is what happens once inside the cell. Here it is necessary to consider the microtubules, which paclitaxel is known to act on (as the SmPC says under the “mechanism of action” of paclitaxel, page 18, section 5.1). Microtubules are made up of tubulin polymers; tubulin has alpha and beta subunits. Microtubules provide a variety of functions within the cell, for example, a structural framework, platforms for transport and in chromosome separation. Chromosome separation is part of the mitotic cell cycle. Dr Desai summarised the common understanding that paclitaxel achieves its cytotoxic effects by binding microtubules which arrests the cell cycle.
- 125 Dr Desai and Dr Goodfellow both indicated that it is not clear what is actually happening in terms of the interaction of albumin and paclitaxel with microtubules. Dr Desai said it was a hypothesis that paclitaxel can still bind to microtubules when in the form of nab-paclitaxel. He went on to say *“it is possible that it enhances-it is a hypothesis again-the level of binding to microtubules... So imagine how albumin bound to paclitaxel, and it somehow helps its binding to microtubules in a different way, that we don't know-this is all hypothesis-so you could well assume that it changes the way it (I assume Dr Desai means “paclitaxel”) acts directly on the cell kill”*.
- 126 This helpfully focusses the issue - is the albumin materially enhancing the effects of paclitaxel on the microtubule? We only have Dr Desai's hypothesis for this which could turn out either way.
- 127 In this event, I think we have to look at what is known about albumin. Dr Goodfellow was keen to say that because human serum albumin is conventionally considered as a carrier *“it's been around for years...and we've all used it in our experiments for years”*, that this should not prejudice my view of albumin. While I agree I should keep an open mind about the scope of the possible functions of human serum albumin, I believe it is appropriate to give weight to conventional view - that human serum albumin, the most abundant protein in human serum, functions as a transporter protein (and also regulates osmotic pressure).

Is nab-paclitaxel a single active ingredient or a combination of active ingredients?

- 128 I should pause at this juncture to answer the question- is nab-paclitaxel a single active ingredient or a combination of active ingredients? On the basis of all the evidence I have considered to this point, I do not see that albumin and paclitaxel form a single active ingredient. Rather, I consider that albumin and paclitaxel are a combination of ingredients. However, I will revisit the question of whether nab-paclitaxel is single active or combination of actives definitively after my consideration of the case law relating to combinations of active ingredients.
- 129 Next, I will consider nab-paclitaxel in light of *MIT* and *GSK* and also in view of CJEU cases in the plant protection field - *Bayer and Söll GmbH v Tetra GmbH C-420/10* (“*Söll*”) to determine whether nab-paclitaxel is a combination of active ingredients as required by Article 1(b). Firstly, I will summarise the background in *MIT*.

130 *MIT* had a patent that covered two elements (i) polifeprosan, a polymeric, biodegradable excipient and (ii) carmustine, an accepted active ingredient which the CJEU acknowledged had already been used with inert excipients and drug additives for the treatment of brain tumours. The medicinal product at issue was Gliadel, an implantable device in which polifeprosan acts as a biodegradable matrix and releases carmustine slowly and gradually. An MA for Gliadel was granted in Germany in 1999. The German Patent Office rejected the application for an SPC as carmustine was the active ingredient and had been authorised well before Gliadel.

131 The examiner had pointed to the phrase in the ruling in *MIT* which says that Article 1(b):

“.....must be interpreted so as not to include in the concept of “combination of active ingredients of a medicinal product” a combination of two substances, only one of which has therapeutic effects of its own for a specific indication, the other rendering possible a pharmaceutical form of the medicinal product which is necessary for the therapeutic efficacy of the first substance for that indication”

132 Moreover, in a subsequent judgment, *GSK*, the CJEU explicitly re-affirmed the principles they had established in *MIT* regarding an active ingredient. This is explicitly stated in each of paragraphs 27-34 in *GSK*.

133 *GSK* concerned an adjuvant and an active ingredient. Mr Georgiou submitted that *GSK* was not relevant as it concerns an adjuvant which was described as such in the SmPC supporting *GSK*'s SPC application. I appreciate the distinction between the categorisation in an MA of an adjuvant and the categorisation of albumin in the Abraxane MA. Nonetheless, I consider I should pay heed to the fact that the CJEU in *GSK* strongly reaffirmed the teaching of *MIT* concerning the principles by which two substances would qualify as an active ingredient for the purposes of Article 1b.

134 Dr Goodfellow sought to distinguish *MIT* from the issue here by saying that the *MIT* patent was really about polifeprosan, “*a piece of plastic*” in his words. He said if you put Gliadel on cells *in vitro* they would not be more active than carmustine alone, whereas the applicant had provided data which shows that nab-paclitaxel is a lot more effective in killing cells *in vitro* than paclitaxel. Dr Goodfellow rightly pointed out that the patent in *MIT* did not mention carmustine specifically and submitted that the innovation lay in the polifeprosan. However, there was no argument that the patent did not cover the combination of carmustine and polifeprosan. Dr Desai emphasised that, in contrast to albumin, polifeprosan is a scaffold which breaks down and would not have any enhancing effects on drug activity *in vitro*, whereas he said nab-paclitaxel stays intact, at least until it enters the cell.

135 Carriers, excipients etc. can be expected to promote the therapeutic efficiency of active ingredients in formulations. A common reason for improving the formulation of a drug is to improve its effectiveness. Indeed, the CJEU recognised this in paragraph 28 of *MIT* where it said:

“it is apparently not unusual for substances which render possible a certain pharmaceutical form of the medicinal product to influence the therapeutic efficacy of the active ingredient contained in it.”

- 136 To my mind, the CJEU, having recognised the influence that carriers can have in the therapeutic efficacy of medicines, considered it was not enough for such substances to be considered as forming an active ingredient if they did not have a therapeutic effect on their own.
- 137 Dr Goodfellow submitted that the examiner was looking at nab-paclitaxel through “too fine a microscope”, for example by focussing on the known interaction of paclitaxel and beta tubulin from which cell death occurs. I consider it is absolutely appropriate to consider the action of nab-paclitaxel at the highest level of detail possible - the molecular level - to determine whether its therapeutic effects are due to paclitaxel alone or a combined action of albumin and paclitaxel. I believe the contemporary scientist in this field, a cell biologist, would naturally consider the issue at the molecular level. Cells are often described as huge factories - with a plethora of different processes, thousands of different molecules interacting and moving around. Large research teams are often devoted to a small number of the myriad of intracellular molecules.
- 138 In summary, Dr Goodfellow provided a strong case for the pharmacological and cytotoxic effectiveness of nab-paclitaxel over paclitaxel and evidence that nab-paclitaxel is transported as a single unit across the cell membrane and is present as a single unit in intracellular vesicles. However, despite this I cannot see that the albumin and nab-paclitaxel components are acting as a single active ingredient therapeutically or that the albumin component of nab-paclitaxel is active in the cytotoxic effect of paclitaxel.
- 139 I think the applicant’s central submission that nab-paclitaxel is a new single entity represents an attempt to distinguish the rulings in *MIT* and *GSK* from the present case. I do not think this distinction is valid.
- 140 The applicant says in their skeleton that if I find that nab-paclitaxel is a combination of ingredients, then they ask me to consider their submissions that it represents a new combination. In this vein, they point to two CJEU cases which concern plant protection products - *Bayer*, which came after *MIT* and *GSK*, and *Söll*.
- 141 While Dr Goodfellow did not refer to these cases at the hearing, I asked him if he would like to make submissions on the combination argument to which replied that the applicant did not have anything to add further to what they had raised in the skeleton. In the circumstances, I think it appropriate to consider these authorities and the applicant’s alternative case for the sake of completeness.
- 142 The thrust of the applicant’s argument in their skeleton in relation to *Bayer* and *Söll* is that these cases support their contention that the action of an active does not need to be direct but maybe indirect. The skeleton says (paragraph 5.5) “...*the applicant maintains that the albumin portion of nab-paclitaxel does have at least an indirect effect of its own in the treatment of the authorised conditions*”.
- 143 *Bayer* concerned a plant “safener” which essentially is a product that is added to compositions of plant protection products to protect certain plants against the toxic effects of a plant protection product, such as a herbicide. The applicant’s skeleton highlights a passage (underlined) in paragraph 33 of *Bayer* which reads:

It follows from the above that the term 'active substances', for the purposes of the application of Regulation No 1610/96, relates to substances which have a toxic, phytotoxic or plant protection action of their own. In this regard, since Regulation No 1610/96 makes no distinction according to whether that action is direct or indirect, there is no need to restrict the term 'active substances' to those whose action may be characterised as direct ..."

144 However, that is not the whole context of *Bayer* as paragraph 35 goes on to say:

"The answer to the question whether a safener is an active substance, within the meaning of Article 1.3 of Regulation No 1610/96, therefore depends on whether that substance has a toxic, phytotoxic or plant protection action of its own".

145 *Bayer* also refers to *MIT* and *GSK*. My view is that the facts in *Bayer* are significantly different to what we have in the case of nab-paclitaxel. There was no question in *Bayer* that safeners were not active in the sense that they protected plants from the toxic effects of other plant protection products and thus improved the effectiveness of those products. The question was then whether this contribution to the overall effectiveness of a plant protection products was indirect. This is different to the situation with albumin and paclitaxel. My view is that while *Bayer* acknowledges that an active substance may have an indirect effect, it remains that a candidate substance (safener) must have the necessary plant protection effect on its own. This, in effect, reaffirms the message from *MIT* and *GSK*.

146 The applicant highlighted a passage (underlined) in the ruling in *Söll* where the CJEU said:

"the concept of 'biocidal products' set out in Article 2(1)(a) of Directive 98/8/EC...must be interpreted as including even products which act only by indirect means on the target harmful organisms, so long as they contain one or more active substances provoking a chemical or biological action which forms an integral part of a causal chain, the objective of which is to produce an inhibiting effect in relation to those organisms"

147 I consider that *Söll* is too distant on its facts from the present case. Briefly, in *Söll* the circumstances were that a soluble chemical (aluminium hydroxide) which when poured into pond water becomes insoluble - it precipitates - and causes flocculation of algae in the pond water which thereby aides the removal of the algae from the pond. The CJEU held that a compound which functioned as the aluminium hydroxide did, albeit indirectly, could be considered as an active ingredient for the reasons which are underlined in the passage above.

148 However, I consider that the facts in *Söll* are materially different to those under consideration in this case. In *Söll*, when the aluminium hydroxide was added to the water a visible net formed, gathering (flocculating) the algae within it. It was recognised that the transition from a soluble to insoluble form of aluminium hydroxide in *Söll* is a classical chemical reaction which the CJEU recognised as such. I do not consider that the skilled addressee in the art of particulate drug formulation and delivery would equate a chemical reaction with a carrier function of a protein such as albumin; the processes of a chemical reaction and protein transport are significantly different.

- 149 Even if I were to take the general teaching from *Söll* that I should look for a chemical or biological action which forms an integral part of a causal chain, I cannot see evidence of that in the relationship between albumin and paclitaxel. Albumin is bound to paclitaxel and it is reasonable to assume that at some point the paclitaxel component exerts its known effects on microtubules. To me, albumin in that scenario is not provoking an action in a causal chain.
- 150 In conclusion, I consider that neither *Bayer* nor *Söll* assist the applicant's alternative submission that the albumin portion of nab-paclitaxel has at least an indirect effect in treating cancers.

Question 1 - summary

- 151 I will summarise my deliberations on the examiner's first question. Notwithstanding Dr Goodfellow's elegantly put submissions that nab-paclitaxel is a single active, I consider that I am, in reality, dealing with two substances here - albumin and paclitaxel. An argument along the lines that 'because two components "X" and "Y" are tightly bound they necessarily act as one' could easily be made in relation to several medicinal products comprising common carriers and active substances. It would be perverse if the principle established in *MIT* could be circumvented by such an argument. That would be a matter of form over substance. In addition, the applicant's alternative submission, based on *Bayer* and *Söll*, that the albumin portion of nab-paclitaxel has an indirect effect, does not hold water.
- 152 I recognise that I need to give careful consideration to the findings of the Court of Appeal in *Daiichi* and I also need to pay strong attention to the judgments of the CJEU. I do not consider that these authorities drive me in different directions but rather deal with different issues. *Daiichi* gives me a steer on how to approach the purpose of the Regulation in the circumstances and the consequences of the MA and the Patent in the present case. *Daiichi* encourages me, in general terms, to allow the SPC application for nab-paclitaxel. However, as a Hearing Officer I must be particularly cautious not to overreach from what I see as the CJEU's central position on the law on the qualifying characteristics of substances which make up an active ingredient, which it has been deliberate in stating in *MIT* and clearly reaffirmed in *GSK*: that a substance which is part of an active ingredient must have a therapeutic effect on its own.
- 153 I think particularly germane to this case is the context of the term "active ingredient". Here, I note the statement by the CJEU in *Massachusetts Institute of Technology (C-431/04) ("MIT")*, which it reaffirmed in *GSK* (paragraph 27). In *MIT* the CJEU said at paragraph 17:
- "In the absence of any definition of the concept of "active ingredient" in Regulation No 1768/92, the meaning and scope of those terms must be determined by considering the general context in which they are used and their usual meaning in everyday language"*
- 154 Taking the applicant's submissions and the documentary evidence presented to me in light of what is known about albumin and paclitaxel, I am unable to reach a

conclusion that albumin is acting with paclitaxel in killing tumour cells as a single active ingredient or that it has cytotoxic activity on tumour cells on its own. I am therefore of the view that the albumin component of nab-paclitaxel does not have a therapeutic function on its own but rather it acts as a carrier - it enables paclitaxel to be effective in exerting its own cytotoxic effects on tumours. I accept that albumin in nab-paclitaxel offers advantages over conventional cremaphor-based formulations of paclitaxel in terms of patient tolerability but that is the sort of advantage that new formulations can have.

- 155 The CJEU is the highest court in this instance and I am bound by it. I conclude, in light of CJEU's judgment in *MIT*, that nab-paclitaxel does not qualify as an active ingredient because albumin does not have a therapeutic effect on its own.
- 156 In relation to the examiner's first question therefore, I hold that the product "paclitaxel formulated as albumin nanoparticles" does not constitute a new active ingredient as defined in Article 1(b) of the Regulation.

Does the application nonetheless qualify because of the precedent in *Neurim*?

- 157 The examiner stated in his final letter of 25 February 2016 (paragraph 10) that "*I remain of the view...that the Neurim judgment requires that the basic patent protects a new therapeutic use that is covered by the MA supporting the application*".
- 158 The CJEU case of *Neurim* concerned the protection afforded by an SPC to a new application of a pharmaceutical. It is the interpretation of "new application" that is at issue here.
- 159 Firstly, the legal process in *Neurim*. The UK high court upheld the IPO's decision that *Neurim* was not entitled to an SPC for its product Circadin as it did not comply with Article 3(d) because an earlier authorisation existed for the same product. *Neurim* appealed to the Court of Appeal which then referred a number of questions to the CJEU. The Advocate General (Trstenjak) gave her Opinion for the CJEU in May 2012. The CJEU gave its judgment in July 2012.
- 160 The CJEU and the Advocate General considered the questions, *inter alia*, about the scope of Article 3(d). Essentially, the first question which is relevant to the present case was about whether a second authorisation for a second medicinal product which had the same active ingredient as an earlier first medicinal product which had a corresponding first authorisation for the same active agent, but where the patent supporting the SPC application for the second medicinal product did not protect the active ingredient in the first medicinal product, could form the basis of an SPC.
- 161 Secondly, I will give a brief account of the relevant facts in *Neurim*. The company Neurim Pharmaceuticals Ltd applied for a patent in 1992 relating to the formulation of melatonin which could be used to treat insomnia. This patent was granted in 1999 and contained formulation claims and second-medical use claims for the use of the formulation in treating insomnia. Melatonin *per se*, a natural hormone, had not been patented and had been known for a long time. The formulations protected by Neurim's patent were made and trade marked as Circadin. In 2007, fifteen years

after Neurim's "insomnia" patent was applied for, Neurim obtained an MA for Circadin. Neurim then applied for an SPC for Circadin. However, another marketing authorization for the use of melatonin in veterinary medicine (sheep) trade marked as "Regulin" had been granted in 2001. The Court of first instance in the UK had held that the MA for Regulin represented the first MA for melatonin (the question of the distinction between medicinal and veterinary products, regarding Article 3(d) is not an issue in the present case).

162 Dr Goodfellow's main submission was that *Neurim* was not limited to therapeutic applications and that the examiner (and the IPO previously) had interpreted *Neurim* too narrowly, in particular the interpretation of "application" in *Neurim*.

163 The applicant's skeleton argument referred to a part of the Advocate General's Opinion in *Neurim* which summarises her position on the question at issue where she said at paragraph 57 (the applicant's emphasis is underlined):

a supplementary protection certificate for a product which is protected by a basic patent in force may be granted under Article 3(d) of Regulation No 1768/92 only on the basis of the first authorisation which permits that product to be placed on the market as a medicinal product within the scope of protection conferred by the basic patent in the Member State for which the application is made. The fact that the same product has previously been authorised as a medicinal product for human use or a veterinary medicinal product in the Member State for which the application is made does not preclude the grant of a supplementary protection certificate based on a later authorisation to place that product on the market as a new medicinal product, provided the first-authorised medicinal product is not within the scope of protection conferred by the patent designated by the applicant as the basic patent.

164 Dr Goodfellow made several lines of argument in relation to *Neurim* which I have identified as: i) That UK Court of Appeal had emphasised that the innovation behind the Patent in *Neurim* was a formulation; ii) that the Advocate General in her Opinion (paragraph 41) underlines the point that "genuine innovation" is an important consideration in awarding an SPC; iii) the basic patent supporting the SPC application in the present case protects the application of the active ingredient (nab-paclitaxel); iv) that the *Neurim* judgment does not limit the scope of a different application of a medicinal product to the therapeutic application and, in particular that; v) the application of a medicinal product is not limited to "second medical use" inventions.

165 Taking Dr Goodfellow's first two points (i-ii) first- that both the UK Court of Appeal and the Advocate General had recognised that the innovation in *Neurim* was a formulation. The Advocate General refers to genuine innovation in the context of weighing up the balance of different stakeholder interests and that state health systems have a desire to prevent slightly modified forms of active ingredients obtaining SPCs. She does not opine on what the characteristics of a "genuine innovation" are but says in paragraph 42 of her Opinion, to which I have already referred to previously (paragraph 46 above), in effect that great caution is required in making teleological interpretation of the individual provisions of the Regulation.

166 In this vein, Dr Goodfellow highlighted paragraph 48 of the Advocate General's Opinion which reads:

According to the referring court, this kind of pharmaceutical research, where new formulations and uses of known active ingredients are investigated, is an important part of research in the pharmaceutical sector. Neurim Pharmaceuticals also states in this context that increasingly pharmaceutical research involves new formulations of old active substances.

167 I think the context of these comments become clear in the paragraph which follows this, paragraph 49, which reads:

“This statement, to the effect that inventions deserving of protection can also be produced in pharmaceutical research into known active ingredients, is supported by Article 54(5) of the European Patent Convention (EPC), which was inserted into the EPC by the revision in 2000. Article 54(5) EPC expressly recognises the Patentability of 'second and further medical uses' of substances whose use in other medical processes already forms part of the state of the art. Such second medical uses are essentially the new and inventive specific use of known medical active ingredients. Legal literature emphasises that such patent protection for second and further uses takes account of legitimate interests because research into therapeutic effects of known substances has considerable health and economic importance.”

168 In my view the Advocate General was considering the new uses of active ingredients, which may be formulated in a new way. It is often the case that medicines require adjustments in their formulations when they are used to treat new medical conditions so that they can target those new conditions effectively. A new use may not require a new formulation, however. A medicine can be taken for one condition only to be found to treat another and the same form of that medicine, e.g. a tablet, can be prescribed specifically for that new condition.

169 Dr Goodfellow submitted that it was incorrect to confine *Neurim* to second medical use claims, as it does not refer to these specifically. I agree to the extent that the question of coverage of second medical use claims was not an issue in the referring questions, although I note that the Advocate General gives weight to the role of second medical use claims in protecting new therapeutic applications. Overall, I do not think it is necessary for me to consider, in particular, whether *Neurim* confines a new application of a therapeutic product to second medical use claims in relation to the point at issue in the present case. I interpret these passages in the Advocate General's Opinion as recognising the significance of the new uses that medicinal products can have in relation to Article 3(d). This addresses Dr Goodfellow's fifth point, at least.

170 On the third point I have identified in Dr Goodfellow's arguments, I accept that the protection afforded by the basic patent in the present case is limited to the medicinal product in the supporting MA, nab-paclitaxel, but the critical question is whether the Patent protects a new application of that product.

171 In relation to Dr Goodfellow's fourth point as I have identified it above, the applicant's skeleton makes several points why they consider *Neurim* is not limited to therapeutic

application of a product. Dr Goodfellow made a series of related submissions on this point at the hearing. This is arguably the crux of the issue in relation to *Neurim*.

- 172 In their skeleton (paragraph 6.22) the applicant highlights the phrase “a *patent protecting a new application of a new or known product*” in paragraph 24 in the *Neurim* judgment which also refers to paragraph 29 of the explanatory memorandum which reads (applicant’s emphasis underlined):

“The proposal does not provide for any exclusions. In other words, all pharmaceutical research, provided that it leads to a new invention that can be patented, whether it concerns a new product, a new process for obtaining a new or known product, a new application of a new or known product or a new combination of substances containing a new or known product, must be encouraged, without any discrimination, and must be able to be given a supplementary certificate of protection provided that all of the conditions governing the application of the proposal for a Regulation are fulfilled”

- 173 The skeleton (paragraph 6.26) then makes the point that “No mention is made here of a requirement for the basic patent relied upon to be one to a specific application of a product, let alone explicitly to that application being a new therapeutic use of the product”. While that is true I think the selection of particular phrases here, particularly in the explanatory memorandum, runs the risk of undermining the overall context.

- 174 Dr Goodfellow referred to paragraphs 25 and 27 of the *Neurim* judgment. I consider these are particularly relevant to the issue here. They read as follows:

“25. Therefore, if a patent protects a therapeutic application of a known active ingredient which has already been marketed as a medicinal product, for veterinary or human use, for other therapeutic indications, whether or not protected by an earlier patent, the placement on the market of a new medicinal product commercially exploiting the new therapeutic application of the same active ingredient, as protected by the new patent, may enable its proprietor to obtain an SPC, the scope of which, in any event, could cover, not the active ingredient, but only the new use of that product.”

“27. In the light of all the above considerations, the answer to the first and third questions is that Articles 3 and 4 of the SPC Regulation are to be interpreted as meaning that in a case such as that in the main proceedings, the mere existence of an earlier MA obtained for a veterinary medicinal product does not preclude the grant of an SPC for a different application of the same product for which an MA has been granted, provided that the application is within the limits of the protection conferred by the basic patent relied upon for the purposes of the application for the SPC”.

- 175 Dr Goodfellow emphasised that the penultimate line in paragraph 27 uses the word “application” alone and not “therapeutic application”.

- 176 To my mind, paragraph 27 of *Neurim* concerns the question about whether an MA for a veterinary medicine precludes the grant of an SPC to a human medicinal product where the new application is limited to the protection conferred by the basic patent for the human medicine. In the overall context of *Neurim*, I do not read this paragraph as saying that the *application per se* of a new formulation of a medicinal

product provides a basis for an SPC. In particular, I consider that paragraph 27 must be read in the context of paragraph 25 which, to my mind, is confined to the question of whether the new application of a medicinal product is a new therapeutic application. In *Neurim*, the motivation to make a new formulation of melatonin appears to have been to enable its new therapeutic use.

177 At the hearing Dr Goodfellow referred to a passage in paragraph 17 of *Neurim* which reads:

“....the basic patent for which the application for the SPC was made protects an application of that active ingredient...”

178 Dr Goodfellow then said *“they are talking about the application of melatonin within a pharmaceutical formulation designed as such to allow controlled release for the treatment of a new therapeutic application, admittedly”*. He then went on to submit in reference to *“therapeutic application”* in paragraph 25 of *Neurim* *“....but that is an application in therapy. Melatonin is applied to a formulation being used in a therapy. I don’t read it as being limited to therapeutic application.”*

179 I think Dr Goodfellow is stretching the interpretation of *Neurim* here beyond its intentions. I do not read *Neurim* as suggesting that the use of an active agent in generating a new formulation renders the resulting medicinal product a “new application”, even if that formulation is specifically protected by a basic patent.

180 Taking the Advocate General’s Opinion and the CJEU’s judgment in *Neurim* in the round, I do not consider that they mean that a new formulation of an active ingredient *per se*, even where that active ingredient falls within the limits of protection conferred by the basic patent, represent sufficient grounds *per se* to warrant an SPC. Rather, I consider that *Neurim* instructs me, in the context of this decision, to interpret the meaning of a ‘new application’ of a medicinal product as a new therapeutic application.

181 Therefore, in regard to the examiner’s second question my answer has to be “No”.

182 I hold that the judgment in *Neurim* does not provide sufficient reasons to grant an SPC in the present case on the basis of the MA and the basic patent filed in support of this application.

Conclusions

183 I will now summarise my findings having regard to the examiner’s first question. The applicant submitted that nab-paclitaxel is a single active ingredient in its own right. I am content to accept that the single nanoparticle of nab-paclitaxel offers advantages for treating tumours on account of its particular size. I am also content to accept that: (i) nab-paclitaxel displays more effectiveness than paclitaxel in treating some tumours either alone or in combination with other anti-cancer agents; (ii) that nab-paclitaxel offers advantages over conventional cremaphor-based formulations of paclitaxel in terms of patient tolerability; (iii) that nab-paclitaxel depletes the tumour microenvironment and kills cells other than cancer cells within it; (iv) that nab-

paclitaxel is better than paclitaxel in killing tumour cells *in vitro*; (v) that nab-paclitaxel is transported particularly effectively to tumour locations and that (vi) nab-paclitaxel remains intact inside the cell.

- 184 Some of this data is quite impressive, particularly the therapeutic effectiveness of nab-paclitaxel over conventional cremaphor-based paclitaxel. But that is not the issue here. The issue is whether the albumin component of nab-paclitaxel combined with paclitaxel creates a new product in its own right or whether albumin has a therapeutic effect on its own. I believe in today's scientific environment it is appropriate to look for the effect of the single nanoparticle at the level of intracellular structures and molecular interactions. At this level I cannot see evidence that the two components of nab-paclitaxel, albumin and paclitaxel, are acting as a single active ingredient.
- 185 I therefore have to consider these components as a combination and I believe the CJEU judgment in *Massachusetts Institute of Technology (C-431/04)* is relevant authority in this case.
- 186 It is widely accepted that albumin's conventional function is as a carrier molecule. Paclitaxel is a well-known neoplastic agent. Nab-paclitaxel has been authorised for treating cancer. The reasonable assumption then is that paclitaxel is the active agent in nab-paclitaxel. *MIT* tells me I need to consider whether the albumin component of nab-paclitaxel has a therapeutic effect; this has been reaffirmed as a matter of principle by the CJEU in *GSK*.
- 187 The question of what constitutes a "therapeutic effect" must be taken in the context of the relevant field. In the case of cancer, this means I need to determine whether albumin has a cytotoxic effect on its own. Having considered all the evidence put to me, I cannot reasonably conclude that it has. I would like to point out that I have been minded to give the applicant the benefit of the doubt on some of the issues of fact, the scientific evidence, but this does not apply to questions of law.
- 188 I therefore believe, on the basis of the evidence before me, that it is reasonable to consider that the albumin component of nab-paclitaxel is behaving as a carrier molecule and does not have a therapeutic effect on its own.
- 189 I should pause here as I have said earlier in this decision I felt that the SPC application for nab-paclitaxel at issue here is broadly consistent with the purpose of the Regulation. Moreover, I recognise that if an SPC were to be granted on the basis of the basic patent and the MA in this case it would have strong circumstantial parallels with the SPC case of levofloxacin in *Daiichi* where Jacob LJ indicated the types of reasons that would warrant the grant of an SPC. I have given this very careful consideration. While I recognise the circumstantial similarities between the present case and *Daiichi* I think the facts which lie at the heart of the present application differ significantly from those that underpin *Daiichi*, which the Court of Appeal must have had in mind in forming its judgment in that case.
- 190 In all, I consider that *Daiichi* does not provide sufficiently strong grounds for me, as a hearing officer, to divert from my conclusions based on the facts of the present case in light of the teaching of the CJEU in *MIT* which has been reaffirmed in *GSK* by the CJEU, the highest court in these matters.

- 191 It is for these reasons that I consider the answer to the examiner's first question (paragraph 12 above) is in the negative. Consequently, I hold that the product claimed in the SPC application, "paclitaxel formulated as albumin nanoparticles" does not constitute a new active ingredient as defined in Article 1(b) of the Regulation. It therefore follows that paclitaxel is the active ingredient in nab-paclitaxel. Consequently the application at issue here, SPC/GB09/046, does not comply with Article 3(d) as the marketing authorisation submitted in support of the application is not the first authorisation in the EU for paclitaxel.
- 192 Secondly, I summarise my findings on the examiner's second question. The applicant submitted that the judgment in *Neurim* should not be interpreted as being limited to new therapeutic applications. The applicant referred to several passages from the judgment in *Neurim* which referred to an application of an active ingredient and of a medicinal product containing an active ingredient which were silent about whether the application was a therapeutic application. I have also considered the applicant's submissions made in relation to the Advocate General's Opinion in *Neurim* regarding the situations in which an SPC is not precluded from being awarded, having regard, *inter alia*, to the protection offered by the basic patent, new formulations and new uses of known active ingredients. Having considered the Advocate General's Opinion and the judgment in *Neurim*, I consider that the application of paclitaxel in nab-paclitaxel in relation to this SPC application, is required to be a new therapeutic application.
- 193 I therefore also hold that SPC/GB09/046 should not be granted on the basis of the present application having regard to the judgment in *Neurim Pharmaceuticals (1991) v Comptroller General of Patents C-130/11* as the application of nab-paclitaxel in the present case is not a new therapeutic application.

Decision

- 194 For the reasons given above I refuse the application as it does not comply with Article 3(d) of the Regulation. This is because the marketing authorisation submitted with the application, EU/1/107/428/001, is not the first marketing authorisation in the EU for the product "paclitaxel formulated as albumin bound nanoparticles", having regard to the definition of a product, pursuant to Article 1(b) of the Regulation.

Appeal

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

Dr Jim Houlihan

Deputy Director acting for the Comptroller-General of Patents