INTELLECTUAL PROPERTY OFFICE

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COUNCIL REGULATION (EC) 469/2009 CONCERNING THE CREATION OF A SUPPLEMENTARY PROTECTION CERTIFICATE FOR MEDICINAL PRODUCTS

APPLICANTS Georgetown University, University of Rochester or Loyola University of Chicago

ISSUE Whether SPC applications SPC/GB 07/069, 07/070, 07/071, 07/073, 07/075, 07/078, 07/079 and 07/080 comply with Article 3 and may be granted

HEARING OFFICER Dr L Cullen

DECISION

Introduction

1 This decision relates to six applications for supplementary protection certificates (SPCs) in the name of Georgetown University, one in the name of Loyola University of Chicago and one in the name of University of Rochester all of which relate to single Human Papillomavirus recombinant L1 proteins which are active ingredients in a number of vaccine products to provide protection against infection by Human Papillomavirus (HPV).

2 The details of these 8 various SPC applications including the product definitions are summarised in Table 1.

3 The basic patent upon which the six Georgetown University applications rely on is EP(UK) 0647140 B1 entitled 'Papillomavirus Vaccines', which was filed on 24 June 1993, with an earliest priority date of 25 June 1992, and was granted on 12 December 2007. The basic patent upon which the University of Rochester application relies on is EP(UK) 0688227 B1, which was filed on 8 March 1994, with an earliest priority date of 9 March 1993, and was granted on 25 May 2005. The basic patent upon which the Loyola University of Chicago application relies on is EP(UK) 0809700 B1, which was filed on 9 October 1995, with an earliest priority date of 7 October 1994, and was granted on 10 May 2006.

Table 1: SPC applications for single Human Papillomavirus (HPV) recombinant L1 proteins

Application	**SPC/GB 07/079**	**SPC/GB 07/073**	**SPC/GB 07/080**	**SPC/GB 07/078**	**SPC/GB 07/071**	**SPC/GB 07/070**	**SPC/GB 07/075**	**SPC/GB 07/069**
Applicant	Georgetown University	Georgetown University	Georgetown University	Georgetown University	Georgetown University	Georgetown University	University of Rochester	Loyola University of Chicago
Patent	EP 0647140	EP 0647140	EP 0647140	EP 0647140	EP 0647140	EP 0647140	EP 0688227	EP 0809700
Marketing Authorisation	Gardasil	Gardasil	Gardasil	Gardasil	Cervarix	Cervarix	Cervarix	Cervarix
Definition of Product (from form SP1)	"The recombinant L1 protein of Human Papillomavirus type 6"	"The recombinant L1 protein of Human Papillomavirus type 11"	"The recombinant L1 protein of Human Papillomavirus type 16"	"The recombinant L1 protein of Human Papillomavirus type 18"	"The recombinant L1 protein of Human Papillomavirus type 16 as expressed by an insect cell"	"The recombinant L1 protein of Human Papillomavirus type 18 as expressed by an insect cell"	"The recombinant L1 protein of Human Papillomavirus type 16 as expressed by an insect cell"	"The recombinant L1 protein of Human Papillomavirus type 18 as expressed by an insect cell"
Strain of Human papillomavirus (HPV) covered	HPV6	HPV11	HPV16	HPV18	HPV16	HPV18	HPV16	HPV18

4 Two marketing authorisations (MAs) are supplied in support of these various applications: EU/1/06/357/001-017 for the medicinal product Gardasil (RTM) granted on 20 June 2006 by Commission Decision C(2006)4281 to Sanofi Paster MSD, France; and EU/1/07/419/001-009 for the medicinal product Cervarix (RTM) granted on 20 September 2007 by Commission Decision C(2007)4440 to GlaxoSmithKline Biologicals, Belgium. I note that the applicant has also provided a copy of another MA (EU/1/06/358/001-017) for the medicinal product Silgard (RTM), also granted on 20 June 2006, by Commission Decision C(2006)4283 in addition to those applications based on the MA for Gardasil. I note from the Summary of Product Characteristics (SmPC) annexed to the decision granting the marketing authorisation for Silgard that it appears to be an identical medicinal product to that in Gardasil. The same recombinant techniques were used to produce the vaccines covered by each of these MAs[1]. The only difference is that the authorisation for Gardasil is granted to Sanofi Pasteur MSD (part of Merck, Sharp & Dohme) in France while that for Silgard is granted to Merck, Sharp & Dohme in the UK. Details of the medicinal products covered by these marketing authorisations are provided in Table 2. These authorisations are all valid in the UK. In the following discussions I will refer only to Gardasil and Cervarix as the comments in relation to Gardasil below apply equally to Silgard.

Table 2: Combinations of active ingredients listed in the UK Marketing Authorisations provided in support of SPC applications SPC/GB 069, 07/070, 07/071, 07/073, 07/075, 07/078, 07/079 and 07/080

Medicinal Product	**Gardasil [1]**	Silgard [1]	**Cervarix [2]**
EU Marketing Authorisation EU/	1/06/357/001-017	1/06/358/001-017	1/07/419/001-009
Human Papilloma Virus type 6 L1 protein [1]	✓	✓	
Human Papilloma Virus type 11 L1 protein	✓	✓	
Human Papilloma Virus type 16 L1 protein	✓	✓	✓
Human Papilloma Virus type 18 L1 protein	✓	✓	✓
Total # of active components	4	4	2

5 GlaxoSmithKline Biologicals SA, Belgium, (GSK) is a licensee under the three basic patents referred to above and under the related SPC applications. As indicated above, they are also the holder of the marketing authorisation for Cervarix.

[1] The L1 proteins in Gardasil and Silgard are produced using the same recombinant DNA procedures to obtain the recombinant L1 proteins in the form of virus like particles (VLPs): for Silgard and Gardasil, the VLPs are produced in yeast cells - *Saccaromyces cervisiae CANADE 3C-5 (strain 1895)*; see respective Marketing Authorisation for further details.

[2] For Cervarix, the recombinant L1 proteins VLPs are produced in a *Baculovirus* expression system which uses Hi-5 Rix4446 cells derived from *Trichoplusia ni*; see respective Marketing Authorisation for further details.

6 The view of the Examiner, expressed most recently in his examination report of 16 July 2009, is that these eight SPC Applications do not meet the requirements of Article 3(b) of EC Regulation 469/2009 (hereafter the SPC Regulation). He considered that the marketing authorisation supplied in support of each SPC application is not a valid authorisation to place the product, for which an SPC application has been made, on the market as a medicinal product. As such, these applications do not meet the condition for the grant of a certificate required under Article 3(b) of the Regulation. As indicated in Table 2, each of the authorisations supplied is for a medicinal product which is identified as having a combination of active HPV vaccine ingredients, whereas the product for which protection is being sought in each application is a single HPV active ingredient. Therefore, in his opinion, the authorisations do not relate to the products, the active ingredients of which are the subject of SPC applications SPC/GB 07/069, 07/070, 07/071, 07/073, 07/075, 07/078, 07/079 and 07/080.

7 In their response, dated 15 September 2009, the applicant explained in detail the reasons why they disagreed with the examiners view. This response summarised the arguments made by the applicant in the previous rounds of correspondence with the examiner and also provided some additional material including a witness statement from Mr John Stephen Miles, Registered Patent Attorney and European Patent Attorney, who has been handling these SPC applications on behalf of the licensee in the UK and related Exhibits 1-21. The applicant provided these materials to indicate that SPCs have been granted in various other EU[3] (Austria, France, Italy and Sweden) EFTA[4] jurisdictions (Switzerland) for products specified as single active ingredients but where the medicinal product authorised for human use comprising the product has more than one active ingredient. The applicant also provided copies of relevant authorities cited in their letter of response. Finally, the applicant provided a copy of a letter from the Office in relation to SPC applications SPC/GB 99/009-011 wherein the Office was prepared to make an exception in relation to SPC applications for vaccines and grant an SPC on this basis.

8 In their response dated 15 September 2009 the applicant also indicated that they were happy to have a decision based on the papers already on file. In addition, they requested that no further action be taken in relation to a number of other SPC applications where GSK is also the licensee[5]. Five of these cases SPC/GB 07/018,

[3] European Union
[4] European Free Trade Association
[5] These are:
(i) SPC/GB 07/13 for the combination of recombinant L1 proteins of HPV virus types 6,11,16 & 18 in the name of Medimmune Inc and relying on EP(UK)1015561 and the marketing authorisation for Gardasil referred to above;
(ii) SPC/GB 07/072 for the combination of HPV virus types 6,11,16 & 18 in the name of Georgetown University and relying on EP(UK) 0647140 B1 and the marketing authorizations for Cervarix referred to above;
(iii) SPC/GB 07/074 for the combination of HPV virus types 16 & 18 in the name of Georgetown University and relying on EP(UK) 0647140 B1 and the marketing authorisation for Gardasil referred to above;
(iv) SPC/GB 07/018 for the combination of HPV virus types 6,11,16 & 18 in the name of University of Rochester relying on EP(UK) 0688227 B1 and the marketing authorisation for Gardasil referred to above; and
(v) SPC/GB 07/076 for the combination of HPV virus types 16 & 18 in the name of University of Rochester relying on EP(UK) 0688227 B1 and the marketing authorisation for Cervarix referred to above; and
(vi) SPC/GB 07/077 for the combination of HPV virus types 16 & 18 in the name of Loyola University of

07/072, 07/074, 07/076 and 07/077 all relate to combinations of HPV vaccine active ingredients and are based on the same three basic patents and two marketing authorizations as the applications under consideration in the present case. In addition, GSK is also the licensee under basic patent EP(UK)1015561 and SPC application SPC/GB 07/13 in the name of Medimmune Inc for the combination of recombinant L1 proteins of HPV6,11,16 & 18 based on the marketing authorisation for Garadsil and deferral of the grant of this SPC was also requested. These six cases would all appear to be ready for grant but GSK would like to defer this until the question at issue in the eight present SPC applications is resolved, i.e., the correct interpretation of Article 3(b). In these eight SPC applications and the further six applications which GSK has also licensed, it is clear that SPCs have been applied for that cover all the possible single HPV vaccine active ingredients as well as all possible combinations of 2 and 4 HPV vaccine active ingredients covered by the marketing authorisations for Gardasil and Cervarix.

9 I would like to thank the applicant and the examiner for quality of the written materials they have provided in this case. The examiner's reports and the applicant's responses have been clear and well written and relevant supporting materials have been provided. This has been very helpful to this Hearing officer in the preparation of this decision.

10 The only issue at question in this case in relation to SPC applications SPC/GB 07/069, 07/070, 07/071, 07/073, 07/075, 07/078, 07/079 and 07/080 is the interpretation of Article 3(b), and the definition in Article 1(b), of Council Regulation (EC) 469/2009.

The Relevant Law and its Interpretation

11 Article 3 of Council Regulation (EC) 469/2009 concerning the creation of a supplementary protection certificate for medicinal products ("the Regulation") defines the conditions for obtaining a certificate (emphasis added):

> **"Article 3**
>
> 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"

12 Article 1 of the Regulation provides definitions for these terms as follows:

> "**Article 1**
>
> 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

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Chicago relying on EP(UK) 0809700 B1 and the marketing authorisation for Cervarix referred to above

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) 'certificate' means the supplementary protection certificate."

13 Thus for the purposes of the Regulation, the term "product" means the active ingredient or combination of active ingredients of a medicinal product whilst the term "medicinal product" refers to any substance or combination of substances presented for treating or preventing disease in human beings of animals. This makes clear that certificates are not granted for the medicinal product but rather for the active ingredients present in a medicinal product. Article 1(c) makes clear that the basic patent must protect the product.

14 The interpretation of Articles 1(a) and (b) was set out in *Draco A.B.'s SPC Application* [1996] RPC 417. The importance of the definitions provided by Articles 1(a) and 1(b) and the role of the marketing authorisation was considered by Jacob J, as he then was, and he noted that the distinction made in these definitions must also be applied in reading recitals 8 and 9 of the Regulation. Thus he makes clear that the protection granted by a certificate is strictly confined to the active ingredient which is presented for treatment. At page 438, lines 30 to 35 of his judgement, Jacob J stated:

> "*It will be noted that the two recitals use both the phrase medicinal product and product. Without more there could be ambiguity. This is because authorisations typically are not for active ingredients as such. They are much more tightly drawn, generally to dosage and formulation or presentation. That has to be so because the actual performance of an active ingredient depends on these matters in addition to the active ingredient itself.*"

He went on to note that the authors of the Regulation had thought about the difference between the active ingredient and the actual formulation, and in so doing had defined "medicinal product" and "product" in Article 1. He then stated at page 439, lines 1 to 5:

> *"I have no doubt, nor do I think anyone else would have any doubt, that recitals 8 and 9 must be read as using these definitions. So strictly confined to the product which obtained authorisation means: strictly confined to the active ingredient of that which is presented for treatment."*

15 As a result, the protection afforded by a certificate extends only to the product, i.e., the active ingredient or combination of active ingredients, covered by the authorisation to sell the corresponding medicinal product. Thus, it is clear that a marketing authorisation for a medicinal product which comprises a single active ingredient does not meet the condition for grant laid down by Article 3(b) in the situation where an SPC is sought for a combination of active ingredients. The converse is also true as a marketing authorisation for a medicinal product which comprises a combination of active ingredients does not meet the condition for grant laid down by Article 3(b) in the situation where an SPC is sought for a single active ingredient.

16 In the same way that the authors of the Regulation used the terms 'product' and 'medicinal product' to bring out the distinction referred to by Jacob J in *Draco*, I consider that the same has to be said in relation to use of the terms 'any active substance or combination of active substances' in Article 1(a) and 'the active ingredient or combination of active ingredients' in Article 1(b). I consider that these terms were chosen so as to indicate that more than one active ingredient in a product indicates that it is a combination of active ingredients not that one can choose either option. If this was the case, why did the authors of the Regulation not just say any active ingredient or substance and leave it at that? In my view they intended that the medicinal product and product should be defined as accurately as possible.

17 The balance to be struck by the Regulation is referred to in recital (10) of the Regulation as:

> *"All the interests at stake, including those of public health, in a sector as complex and sensitive as the pharmaceutical sector should nevertheless be taken into account. For this purpose, the certificate cannot be granted for a period exceeding five years. The protection granted should furthermore be strictly confined to the product which obtained authorisation to be placed on the market as a medicinal product."*

To achieve this purpose two elements are seen as important – a maximum period of 5 years additional protection and a strict definition of the product to which this additional protection applies.

18 Lord Justice Jacob has considered the interpretation of the Regulation and Article 1 especially in the Court of Appeal decision in *Generics UK v Daiichi*, 2009 EWCA CIV 646. At paragraph 58 he states:

> *"58. In the Regulation "product" means "the active ingredient or combination of active ingredients" (Art.2(b)). Clearly that must be read with the words "as the case may be" at the end. If you have two active ingredients the "product" is the pair of them. And ofloxacin is a combination of significantly active ingredients. So it is that combination which was the subject of the 1990 and 1985 authorisations. The authorisation for levofloxacin was the first authorisation for that active ingredient alone."*

19 It is clear that Jacob LJ considers that when a medicinal product is a combination of actives then, for the purposes of the Regulation, it is that combination which is the product as defined by Article 1(b) and for which a certificate could be granted. The corollary is thus also true, where the medicinal product is a single active ingredient then for the purposes of the Regulation it is that active ingredient which is the product as defined by Article 1(b) and for which a certificate could be granted

20 Further Article 4 of the Regulation defines the subject matter of protection of a certificate in the following terms:

> *"Within the limits of the protection conferred by the basic patent, the protection conferred by a certificate shall extend only to the product covered by the authorisation to place the corresponding medicinal product on the market and for*

any use of the product as a medicinal product that has been authorised before the expiry of the certificate."

Thus whilst the protection is within the limits of the patent, it "*extends only to the product covered by the authorisation...*" and so it is apparent that it is not possible to break up a combination into its component parts.

21 In *Gilead Sciences SPC Application* [2008] EWHC 1902 (Pat) (hereafter referred to as Gilead), Kitchin J recognized, at para 28, that the Regulation may produce a "harsh result" in some circumstances so that not every application for a certificate was successful. He considered in para 29 the possibility of breaking up a combination of active ingredients into its individual actives so that each might be protected. However, he recognised that such an approach was "hard to reconcile" with Article 4 and the definitions set out in Article 1 of the Regulation:

"A possible answer, canvassed briefly before me in argument, is to regard such a medicine as containing, effectively, three products, that is to say the two active ingredients separately and in combination. In such a case an SPC could then be granted for the ingredient claimed by the basic patent. This solution has its attractions and would permit the holder of the basic patent claiming only one of two active ingredients to secure an SPC for that particular ingredient, assuming, of course, it is not already the subject of a certificate (Article 3(c)) and the authorisation is the first authorisation to place that ingredient on the market in a medicinal product (Article 3(d)). However, it must depend upon the proper interpretation of, at least, Articles 1(b) and 4 and it is my initial impression that it is hard to reconcile with the words of Article 4 which specify that protection shall extend only to the product covered by the marketing authorisation".

Discussion

22 In the following paragraphs I will discuss the issues as they apply to all eight SPC applications making specific reference to each application as required. I also discuss the general points in relation to the interpretation of both marketing authorizations using Gardasil as the main example and, unless specifically stated otherwise, the comments in relation to the MA for Gardasil apply equally in relation to that for Cervarix.

23 The applicant in their response of 15 September 2009 accepts that Gardasil contains HPV6, HPV11, HPV16 and HPV18 virus-like particles (VLPs) and that Cervarix contains HPV16 and HPV18 VLPs and that these VLPs are composed of multiple copies of the L1 protein from the particular HPV obtained using recombinant DNA technology.

SPC Applications SPC/GB 07/073, 07/078, 07/079 and 07/080

24 These four applications are based on basic patent EP0647140 and the marketing authorisation for Gardasil. As indicated in Table 1 above, they each claim one of the four HPV recombinant L1 proteins listed in the MA for Gardasil.

25 I will use SPC/GB 07/080 as an example in the following discussion. The arguments and conclusions in relation to this application apply in the same way to the others,

except where I make a specific comment to the contrary.

26 There have been many rounds of correspondence between the applicant and the examiner on each of these cases. Having reviewed these, I consider that the position of the examiner can be summarised in the following fashion:

(1) The product as defined in Article 1(b) of the Regulation, for which an SPC is sought is the recombinant L1 protein of HPV16.

(2) The medicinal product Gardasil which is authorised for human use comprises a combination of four active substances, the recombinant L1 proteins of HPV 6, HPV11, HPV16 and HPV18.

(3) This marketing authorisation is not a valid one to place the product on the market because the product, as defined in Article 1(b), that it covers is a combination of active ingredients, the recombinant L1 proteins of HPV6, HPV11, HPV16 and HPV18 virus-like particles and not the single recombinant L1 protein of HPV16.

(4) Hence Article 3(b) of the Regulation is not satisfied

(5) The examiner finds support for his view in *Draco AB's SPC Application* [1996] RPC 417; *Generics v Daiichi* [2009] EWCA (Civ) 646 and *Gilead Sciences SPC Application* [2008] EWHC 1902 (Pat).

27 The argument presented by the applicant / agent can be summarised in the following fashion

(1) The authorised product Gardasil contains a combination of active ingredients - the recombinant L1 proteins of HPV6, HPV11, HPV16 and HPV18 virus-like particles. None of these individual active ingredients have been the subject of a marketing authorisation before. Each component of Gardasil can be considered to be effective against a different disease. The recombinant L1 protein of HPV16 only provides protection against HPV16 mediated cervical cancer.

(2) A teleological interpretation of Article 1(b) allows the product to be defined as each of the individual active ingredients as well as the combination of active ingredients. It is for the applicant to choose how it defines the product. This is the only way to provide the applicant with adequate effective protection it deserves and for which the Regulation exists given the contribution that the invention claimed in the patent has made to the field of cancer prevention and the investment that has been required to bring authorised products to the market.

(3) The single active ingredient - the recombinant L1 protein of HPV16 – is presented for treating or preventing disease in human beings as part of the authorised product Garadsil.

(4) The applicant disagrees with the interpretation of Article 1(b) set down in *Generics v Daiichi* [2009] EWCA (Civ) 646

(5) The applicant finds support for their view in the practice in other European jurisdictions; in previous practice at the Office, in ECJ Case C-392/97 (*Farmitalia Carlo Erba Srl's SPC Application*), the explanatory memorandum to the Regulation,

and as a consequence of the variation between the different, but equally authentic, official language versions of the Regulation.

SPC Applications SPC/GB 07/070, 07/071, 07/069 and 07/075

28 SPC applications SPC/GB 07/070, 07/071, in the name of Georgetown University, are based on basic patent EP0647140 and the marketing authorisation for Cervarix. SPC applications SPC/GB 07/069 and 07/075 which relate to the same product as SPC/GB 07/071, the L1 recombinant protein of HPV16, are also based on the marketing authorisation for Cervarix but are made by different applicants, Loyola University of Chicago and the University of Rochester respectively, and are based on different basic patents as indicated in Table 1.

29 The same position has been adopted in these cases by the examiner and the applicant, the only difference being that in these applications the authorisation to place a product on the market as a medicinal product comprises a two active ingredients (rather than four) - the recombinant L1 proteins of HPV16 and HPV18.

30 The issue to be decided in relation to each of these cases is whether or not the product for which an SPC has been applied for is covered by a valid authorisation to place it on the market as a medicinal product.

Specific Issues with Vaccines as Medicinal Products

31 I will consider first the specific nature of vaccines as medicinal products and then go on to consider how the SPC regulation applies to such medicinal products.

32 Vaccination is a term used to describe to those procedures for immunisation of individuals to provide protection against disease, in particular those diseases that are caused by viruses (e.g., measles, mumps, polio, tetanus)[6]. A vaccine is given to an individual who has not yet had the disease in order to induce an antigenic response which results in the production of antibodies that can attack the causative agents of the disease, the virus, and so prevent infection and illness in that individual. Immunisation from infection is achieved through passive or active immunity. Passive immunity is provided by administering antibodies directly, such as varicella zoster immunnoglobulin, (VZIG) for preventing chickenpox in pregnant women. Active immunity is achieved through stimulating the individual's immune system by an inactive vaccine (e.g. a toxoid such as tetanus, an inactivated organism such as hepatitis A vaccine, or subunit vaccines such as acellular pertussis vaccine) or a modified, attenuated live organism (such as oral polio vaccine or the measles mumps & rubella vaccine). As the above makes clear, vaccination is thus a method of protection – preventing the illness from occurring in the individual as distinct from a method of therapy – providing a means such as a drug (e.g. aspirin) or combination of drugs (e.g., HIV anti-retroviral drugs) to cure or alleviate the illness once the individual has been infected.

33 In order to ensure an adequate level of protection, it is important that a vaccine is given to a sufficient portion of the relevant population to provide protection. Thus, it is

[6] see Department of Health website at www.dh.gov.uk; for details about vaccination and its role in public health in the UK and details of the UK Immunisation programme, see http://www.dh.gov.uk/en/Publichealth/Healthprotection/Immunisation/index.htm.

important to make taking such vaccines as easy and as convenient as possible because this will encourage uptake and so make protection more effective. One way of achieving protection in the population is to provide as many of the vaccines needed as possible in as few doses as possible (i.e. one single delivery) to those who may be exposed to such infections. This clearly is a difference in the way that a vaccine acts to achieve its effect in contrast to the effect, i.e. treatment or curative impact, provided by a pharmaceutical substance that has been chemically or biochemically synthesised. In the latter case this pharmaceutical substance only has to be given to those individuals who have the illness that this agent can treat. The applicant considers that this difference is a strong reason for taking a different approach when considering the grant of an SPC in the vaccine art in relation to the grant of SPCs in relation to non-vaccine products.

34 However, as indicated by this hearing officer in recent Office decision BL O/357/09 (*Medeva's SPC applications*)[7], issued in November 2009 and currently under appeal, there is no provision made in the SPC Regulation for treating active ingredients or combinations of active ingredients in a product that are vaccines, which have been placed on the market as a medicinal product, in any way different to other products which do not comprise vaccines as the active ingredient or combination of active ingredients. Indeed, medicinal products comprising vaccines are subject to the same authorisation procedures under Directive 2001/83/EC as medicinal products comprising chemically or biochemically synthesised pharmaceutical substances. It is also clear that the definition of medicinal product in Article 1(a) of the Regulation includes medicinal products for preventing disease in human beings (i.e. vaccines) as well as those for treating disease in humans and so sees no difference between the two.

35 As indicated in the three basic patents (EP0647140, EP0688227 and EP0809700) for these applications, there are a large number of HPV viral strains which cause various types of lesions, both benign and malignant, in epithelial (i.e., skin) tissue in humans. These vary from relatively benign warts of the skin and mucous membranes to more serious growths such as genital warts and tumours of the female uterine cervix. The two medicinal products provided under the marketing authorisations in this case are Cervarix and Gardasil. As indicated in Table 2, Cervarix is a vaccine comprising the recombinant L1 proteins of HPV16 and HPV18 which, from the SmPC annexed to the MA decision, is effective in providing protection against female uterine cancers. The combination of recombinant L1 proteins of HPV6, HPV11, HPV16 and HPV18 in the vaccine product Gardasil provides protection against female uterine cancer via the presence of HPV16 and HPV18, genital warts infections via the presence of HPV6 and HPV11 and abnormal cervical growths (dysplasias) via the presence of all 4 components (see the SmPC annexed to the MA decision). Such abnormal growths can develop into tumours. Thus these two medicinal products comprise a combination of active ingredients that provide protection in humans against infections by HPV.

36 The applicant argues that account needs to be taken of the specific issues around the way vaccines provide this protection. The reason for this is that vaccines which have a number of active ingredients should be treated as in effect being a collection of individual active ingredients that can be considered to be separate or independent from the other active ingredients in the medicinal product because (a) each active ingredient

[7] For text of decision see http://www.ipo.gov.uk/pro-types/pro-patent/pro-p-os/p-challenge-decision-results-bl.htm?BL_Number=O35709.

is targeted at a specific disease and none of the other active ingredients provide any protection against that disease. Thus, the recombinant L1 protein VLP of HPV16 only provides protection against infections that are caused by HPV16. The applicant provides a copy of a scientific article[8] from 2002 which confirms that a vaccine comprising such a HPV16 L1 recombinant protein (in a virus-like particle) is effective at preventing infection by HPV16 and growths and cancers caused by HPV16. This confirms, in some greater detail, the evidence provided in the SmPC of the respective MA that one of the active ingredients in the medicinal product Gardasil or Cervarix can provide protection against HPV16 viral infections including cervical cancer. The applicant then argues that as this active ingredient has no impact against any growths caused by other HPV virus strains, the medicinal product can, in effect, be considered to be a number of single active ingredients placed together on a single delivery means. Thus the fact that Cervarix or Gardasil comprise 2 or 4 active ingredients is determined by the need to deliver effective protection against HPV infections in as few doses as possible. The applicant argues that putting more than one active ingredient on a delivery dose is determined by the need to make immunization with the vaccine easier to achieve, i.e. it is driven by factors downstream of the authorisation process which in turn limits what medicinal products will be approved for human use.

37 As I understand the argument from the applicant, a vaccine to HPV16 infections on its own while effective against all HPV16 infections would not prevent enough HPV infections in the population that result in cervical cancer, so the relevant authorisation authority (the EMA in this case) would only approve HPV16 when included with HPV18 as this provides protection against cervical cancer to a greater number of individuals in the population even though these are caused by different and distinct viral strains. The applicant considers that disease caused by HPV16 infection has to be considered as completely separate and independent to those caused by HPV18 infection.

38 However, I consider that the significance of this fact is, not that this approval has been granted merely to provide an acceptable delivery means for a collection of active ingredients that can be considered to be acting as single ingredients, but rather that this approval indicates that a medicinal product which includes a specified combination of active ingredients has been found to pass all the requirements of Directive 2001/83/EC (as referred to in Article 3(b) of the Regulation) and so is approved for human use. In my view the marketing authorisation provides for the use of all these active ingredients together and does not cover the use of the single active ingredients on their own.

Marketing Authorisations for vaccines

39 Marketing authorisations for vaccines are not controlled or limited to those products that can be used in an immunisation programme, such as that in the UK by the Department of Health (DH)[6]. Decisions about what vaccines will be used in such immunisation programmes are a matter of policy for DH. Given the nature of governments and the need to set and update policies, I consider that such decisions from the DH on such matters will be made on a shorter timescale, e.g. yearly or five yearly (the typical term of a government between elections). This timescale is also a much shorter one than the life of a patent and often the time taken to obtain a marketing authorisation for a product can be longer than this also. Thus, in considering whether or not to grant an

[8] The New England Journal of Medicine (N Engl J Med), vol 347, no. 21, pp 1645-1651 (November 21, 2002), Koutsky, LA et al (see www.nejm.org)

SPC, I am not certain that I should be taking account of the any such policy considerations in relation to the use of vaccines made by the DH at present. If anything I should consider what the situation was when the patent was applied for or granted, i.e. the time when the applicant made the innovation for which ultimately they are seeking additional time to make use off because of the delay in getting regulatory approval for human use.

40 Also my impression is that the decisions made by the DH in relation to the use of vaccines has no impact whatsoever on whether or not a vaccine product will be authorised for human use. Decisions about the authorisation of a vaccine are made by the MHRA[9] for the UK or by the EMA[10] for the whole of the European Community and are based on the evidence filed by the applicant following completion of clinical trials and an assessment of safety and effectiveness.

41 I can accept that when an applicant is deciding what medicinal product to put on the market, the product they are likely to seek to get authorised will be influenced by factors such as what are the likely markets or customers for such a product and I acknowledge that DH is likely to be a significant purchaser of vaccine products in the UK for its Immunisation programme. However, for the purposes of the present case, I am not satisfied that this is a consideration for the Office when deciding whether or not to grant an SPC. When an application for an SPC is made, the MA has already been granted. The choice of whether or not to apply for an SPC and whether or not to do so for a single component or for a combination of components is one that is entirely in the hands of the applicant. It is up to the applicant to choose what MA and what basic patent to use as the basis for their SPC application. In the present case, the applicant has made that choice, and so the relevant question to ask now, in my view, is whether or not, the applicant has a basis for obtaining a single product SPC when the MA used in support of it relates to a product that comprises a combination of active ingredients?

Relevance of Article 1

42 The applicant considers that it is significant that Article 1(a) which defines 'medicinal product' does not refer to a marketing authorisation and also refers to 'any substance or combination of substances presented for treating or preventing disease in human beings'. Thus it is possible in their view to consider medicinal product as being any possible substance or combination of substances covered by the MA. I disagree with this view. As I have indicated above, in both Article 1(a) and 1(b) the text of the Regulation refers to the single active substance or ingredient or combination of active substances or ingredients. Thus a combination of elements is clearly envisaged as something that is different to a single element. The determining factor as to whether something is a single active or a combination of actives, is, following the reasoning in ECJ case C-431/04 (*MIT*)[11], determined by whether or not all the elements have a therapeutic activity (as referred to in the MA) and do not just improve or enhance the therapeutic activity of another element. In this case, I consider that the product on the market as a medicinal product comprises a combination of active ingredients for protection against HPV infections. In the case of Cervarix, this is protection against HPV infections that can lead to cervical cancer and, in the case of Gardasil, this is

[9] Medicines & Healthcare products Regulatory Authorithy, see www.mhra.gov.uk
[10] European Medicines Agency, until recently referred to as the EMEA or EMeA, see www.ema.eu
[11] [2006] RPC 34

protection against HPV infections that can lead to cervical cancer, genital warts and other growths. In all cases the therapeutic activity that is being exhibited by the respective combination of active ingredients is the ability to prevent infection of the skin and mucosa by HPV that can lead to cancer.

43 Having given some consideration to the purpose and nature of the authorised medicinal product, I find the words of Kitchen J in para 39 of *Gilead* helpful in reminding me of the general approach to be taken in questions relating to the Regulation. In relation to what depth or degree of consideration should be given to whether or not a product is protected by a basic patent (a question in relation to the interpretation of Article 3(a) of the Regulation), Kitchen J stated that such consideration should not involve an analysis of whether or not the claim is inventive or the result of any significant research effort. He went one to decide that the approach to be taken is the simplest one possible based on the requirements of the Regulation:

> "*…. It can be no part of a determination as whether a product is protected by a basic patent to embark upon an analysis of whether the patent or the claim in issue is obvious or invalid for any other reason. Nor can it be right to investigate the extent of research that lies behind it. The scheme of the Regulation is to provide a simple and straightforward system for the grant of SPCs based only upon a consideration of the requirements laid down in the Regulation. Such is also apparent from the Commission Proposal COM (90) 101 of 11 April 1990 which says in terms at paragraph [16] that the proposal provides a simple transparent system which can easily be applied by the parties concerned and does not lead to excessive bureaucracy. I would add that any person may apply to have an SPC declared invalid if the basic patent is revoked or limited to the extent that the product for which the SPC was granted would no longer be protected by the patent claims (Article 15(1)(c)).*" *(emphasis added as underline)*

44 I consider that this is also the correct approach for me to adopt in the present case in relation to the requirements of Article 3(b) of the Regulation. I consider that the simplest way to decide if a valid authorisation to place the product on the market as a medicinal product has been granted in accordance with Directive 2001/83/EC is, firstly, to consider what is the product that has been granted an authorisation to be placed on the market as a medicinal product; and then to compare this to the product for which an SPC is being sought; if these agree, the SPC can be granted, if not the SPC may not be granted.

45 In the medicinal product Cervarix, the product that has been authorised is a combination of the recombinant L1 proteins of HPV16 and of HPV18 which provides protection against HPV infections. In the medicinal product Gardasil, the product that has been authorised is a combination of the recombinant L1 proteins of HPV6, HPV11, HPV16 and of HPV18 which provide protection against HPV infections. I do not consider that, for the purpose of granting an SPC, I need to take any greater account of what HPV infections these are in the way I am being asked to do by the applicant. It is sufficient that all the ingredients in the product show the ability to provide protection against HPV infections and that to be authorised for use in humans, they were authorised as a combination of active ingredients. These combinations are what have been granted MAs in accordance with Directive 2001/83/EC based on an assessment of all the clinical data to determine what medicinal products should be approved as safe and effective for human use. Thus, as none of the SPC applications define the product

in terms of a combination but only as single recombinant L1 proteins of the various HPV strains, then none of the applications under consideration meet the requirement of Article 3(b).

46 The applicant considers that there is sufficient doubt over the correct interpretation of Article 1(b), and thus of Article 3(b), to make their interpretation equally valid as the one I have outlined above. In support of this view they provide:

(a) copies of SPC grant certificates, and translations thereof, showing that that SPCs have been granted to-date for individual L1 recombinant HPV virus strains in Switzerland (EFTA state, national legislation on SPCs is very similar to the that in the Regulation) and a number of European Community member states (Sweden, Austria, France) based on the marketing authorizations for Cervarix and Gardasil;

(b) copies of SPC grant certificates, and translations thereof, from Belgium, Italy and France for a plant protection product, flufenacet, where the SPC was granted for one active ingredient but the marketing authorisation is for a product comprising a combination of flufenacet and metosulam. This SPC application was granted by the French Office as a combination but this was appealed and the court found the Office did not have the right to change the product definition and that the SPC should be granted with the definition as originally specified by the applicant (Bayer CropScience).

(c) a summary of the inconsistency between the various official language versions of the Regulation in relation to Article 1(b). Some versions include the definite article 'the' in the definition of product (i.e., as in the English version, 'product' means **'the** active ingredient or combination of active ingredients); some include the indefinite article 'an' and some have no article at all. For this reason they argue that it is an equal valid interpretation to consider that a product may be an active ingredient or a combination of active ingredients and that either can be chosen as the basis for defining an SPC. They also refer to a portion of the explanatory memorandum[12] to the Regulation which they consider supports there view and should be taken note of when considering how the Regulation is to be interpreted.

(d) copies of correspondence with French attorneys that indicates that the practice in France is that the choice of product definition for the SPC can be exercised only if an SPC has not already been obtained for any of the single actives or for a combination of the actives. A medicinal product which comprises a product with active ingredients A and B, can serve as the basis for the grant of an SPC for A on its own, B on its own, or A and B as long as this choice is supported by the basic patent. The choice of product definition is up to the applicant.

47 Despite the view of the applicant, I am not sure that these materials are all relevant to the interpretation of Article 3(b) and the definition of product in Article 1(b). Much of the discussion in these materials relates in my view to the protection that is provided by the basic patent and thus in my view is more correctly related to the requirements for the grant of an SPC under Article 3(a).

48 The extract from para 39 of the explanatory memorandum to the Regulation[12] which the applicant brings to my attention refers to the protection provided by the SPC for its duration as defined by the basic patent under Article 4. This part of the explanatory memorandum is often used by applicants in response to reports from the Office which indicate that if the patent covers a single product only and the MA is for a combination product, the patent cannot be used as the basis for granting a SPC for the single product. It does not relate to the requirements for the grant of an SPC under Article 3 in my view. This point was considered as part of the appeal of the *Astellas* decision referred to above and does not appear to be have been persausive in that instance by the appeal judge, Kitchen J. I do not consider that it is persuasive in this instance either.

49 Having considered these materials and the eloquent written argument that has accompanied them explaining why the applicant considers that their view is an equally valid one, I am not persuaded that I can make the exception I am being asked to do in regards to vaccine related products as distinct from other types of pharmaceutically active products which also require a market authorisation and may be entitled to protection by an SPC. The Office as the lowest tribunal dealing with such matters in the UK must take account of the decisions of the higher tribunals, i.e., the UK courts, in these matters. The decisions of other jurisdictions outside the UK, while of interest, cannot be given greater precedence than those from the UK. However, I acknowledge that such materials have in the past been considered by the UK courts when reaching their decisions, especially in relation to EU legislation such as the Regulation. On some occasions they have been helpful in deciding matters, on others they have not.

50 The applicant considers that ECJ decision C-392/97 (*Farmitalia Carlo Erba Srl's SPC application* hereafter referred to as *Farmitalia*)[13] in answering the first question referred to it provides support for the general principle that the Regulation aims to confer an extended protection on the product covered by the patent (i.e. the innovation) not the product that has been authorised in the marketing authorisation to be placed on the market as a medicinal product. This general principle would in their view be frustrated if the SPC application for a product defined in terms of the single active ingredient, e.g. the recombinant L1 protein of Human Papillomavirus type 16, is not granted. This is because without this any third party would be able to sell other useful combinations comprising the recombinant L1 protein of HPV16 after expiry of the basic patent even though the basic patent discloses and claims such products for the first time. An SPC for either the two or four component combination which includes HPV16 will not provide any protection against this. Paras 18 and 22 of the decision in particular are cited in support of this view.

51 However, I do not consider that such a wide interpretation can be placed on the *Farmitalia* decision. This principle I think applies to what would be considered to be identical forms of the same product not different products. The conclusion from *Farmitalia* is that an active ingredient in one salt form (e.g., sodium salt) can be considered to be identical to another salt from (e.g., potassium, hydrochloride salt) or the free base of the same active ingredient and that, similarly, one ester of an active ingredient can be considered to be the same as another ester or the free base in that all

[12] Explanatory Memorandum on the proposal for a Council Regulation concerning the creation of Supplementary Protection Certificates for Medicinal Products COM(90) 101 final – SYN 255.
[13] [2000] RPC 580-586

of these forms were all equivalent means of getting the same active ingredient into a human i.e. of providing the therapeutically active ingredient.

52 If a patent relates to active ingredient A on its own or in combination with active ingredient B and the MA relates only to a combination of A and B, then, in my view *Farmitalia* allows the grant of an SPC for the combination of A and B in different salt forms to that disclosed in the MA but which has been disclosed in the basic patent. It does not allow the grant of an SPC for active ingredient A on its own in either the same salt form or a different salt form if the MA is only for a combination. In the present case, the applicant considers that the patent covers the recombinant L1 proteins of each HPV strain as single active ingredients and in combination with any number of other recombinant L1 proteins of any of the HPV strains disclosed in the patent and that this is the innovation i.e. making both the single active ingredients and any combination thereof available for use in humans and that this should also be what they are entitled to protect with the SPC. This is not different forms of the same product in the way that salts, esters and free bases are, these are different products – they are different types of recombinant L1 protein. A combination of active ingredients that all display therapeutic activity is a combination and this is different to a single active ingredient. Such a combination of active ingredients cannot, in my view (as expressd here and in Office Decision BL O/347/09), be considered to be a collection of single active ingredients in the manner suggested by the applicant.

53 The effect of accepting the view put forward by the applicant is that the distinction which I consider is clear from the Regulation and the case law between a combination of actives and a single active on its own would no longer exist. In the present case where a basic patent covers both single active ingredients on their own as well as combinations of this active ingredient with other active ingredients, the possibility for both different products to exist and so qualify for possible SPC protection would no longer exist. As mentioned above, the simplest and most precise definition of the product authorised for use in humans is what is required when deciding what can be protected by an SPC.

54 The applicant also asks why if the Office has granted SPCs in the past on the same basis as they are seeking in the present cases, it cannot now continue to do so. However, in the intervening period – just under 10 years - since this correspondence, there has been a significant amount of additional case law – as referred to above – which the Office has to take account of in setting its practice in this area. I do not agree with the applicant that this case law in relation to Article 3(b) and Article 1(b) has, in fact, been consistently misinterpreted or misapplied. Even if I did consider that this might be the case, it would not be for me, as a hearing officer in a lower tribunal, to decide matters in a manner contrary to this case law. This is a matter for the higher courts and I leave it to the applicant to decide whether to pursue matters on appeal as is their right.

55 The applicant has continually emphasised that the single recombinant L1 proteins of the various HPV strains covered by these various SPC applications were not already the subject of a granted SPC either on their own or as part of a combination in the UK. The applicant sought to use this as a means to indicate that the applicant had not yet received any compensation for the time it had taken to get approval for making these products available for human use and that it should be allowed to choose which product

definition it wanted when doing so.

56 I do not consider that the fact that the applicant has not yet obtained an SPC, i.e. compensation for the loss of time in exploiting the innovation covered by the patent while securing regulatory approval, to be relevant because, as I have indicated above, the applicant has a number of applications before the Office for SPCs that can be granted and so they will be able to secure compensation for the time taken to obtain regulatory approval when they could not exploit the innovation covered by the basic patents. Thus, I do not consider that the applicant is in some way being prevented from gaining compensation for the loss of time to get regulatory approval

57 However the compensation available, i.e., the SPC, may not be one that the applicant wants. This is the crux of this case and is a different issue. As indicated above, recital 10 sums up the compromise that the Regulation has to meet in balancing all the various interests which sets the maximum period of additional protection provided by the SPC as being 5 years but strictly confines this additional protection to "the product which obtained authorisation to be placed on the market as a medicinal product". The Regulation and the UK and ECJ case law referred to above do not require that the combination of active ingredients in the product, which has been authorised as a medicinal product, act upon the same or similar disease conditions only that they all have therapeutic or preventative activity. Also they do not require that a combination of active ingredients must have a synergistic effect. They require only that the active ingredient or combination of active ingredients are in the product. Indeed, the ECJ has found consistently that the intended use of the medicinal product is not a factor in deciding whether or not an SPC can be granted [see for example para 19 of C-202/05 (*Yissum Research and Development Company of the Hebrew University of Jerusalem v Comptroller-General of Patents*)[14] and discussion therein]. This is consistent with the fact that the Regulation, at Article 4, recognises that further uses for the medicinal product may be found and that these will also be protected by the SPC although they were not known at the time that the SPC was obtained (within the limits of the protection provided by the basic patent).

58 Thus I am satisfied that if the product authorised to be placed on the market as a medicinal product comprises more than one active ingredient that, as in the case of a vaccine, provides protection in the population than this is a combination of active ingredients. In this case all the components provide protection against HPV infections. I do not think that the correct approach is to consider that this may be one or more single active ingredients or one or more combinations of these active ingredients.

59 As indicated by this hearing officer in Office decision BL O/357/09, which is the only other Office decision concerning SPCs in the vaccine field, there may be specific requirements from a wider public policy perspective in relation to the development, authorisation and use of vaccines that also have a bearing on this case. I have taken account of the points made by the applicant in the papers on file in this regard but the evidence to support this view is limited and not sufficient in this case to justify my coming to a different conclusion to the one that I have reached. I would also like to point out that I consider that this issue is a separate one to that concerning the interpretation of Articles 1(b) and 3(b) discussed above. As I have indicated I am not convinced by the applicants arguments that their interpretation of these articles is

[14] [2004] EWHC 2880 (Pat)

correct.

Conclusion

60 For the above reasons, I conclude that the product as defined in applications SPC/GB 07/069, 07/070, 07/071, 07/073, 07/075, 07/078, 07/079 and 07/078 does not comply with Article 3(b) of the Regulation (see Table 3 for product definitions). Since in accordance with Article 10(3) an opportunity to correct the irregularity in each application has been given, as required by Article 10(4), I reject these applications.

61 In relation to the additional SPC applications SPC/GB 07/013, 07/018, 07/072, 07/074. 07/076 and 07/077 the grant of which were delayed while the issue in relation to Article 3(b) was considered for these eight applications, I consider that there is no longer a need to delay their grant and arrangements should be made to do so as soon as possible once the period set for any appeal has expired.

62 I consider that some of the applications in question could be granted if the product specifications were amended to refer to the product as the combinations of active ingredients referred to in the relevant marketing authorisation. However, these combinations, as indicated above, are already the subject of additional SPC applications. Given the requirement under Article 3(2) of EC Regulation 1610/96 which applies *mutatis* mutandis to EC Regulation 469/2009, that each applicant is only entitled to have one SPC for the same product, the grant of these further applications may also need to await the outcome of the appeal to ensure that only one SPC for the same product is granted to each applicant.

Appeal

63 Under the Practice Direction to Part 52 of the Civil Procedure Rules, any appeal must be lodged within 28 days.

Dr L Cullen
Deputy Director acting for the Comptroller