INTELLECTUAL PROPERTY OFFICE

BL O/096/09

9 April 2009

REGULATION (EC) 1901/2006 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL ON MEDICINAL PRODUCTS FOR PAEDIATRIC USE

and

COUNCIL REGULATION (EEC) 1768/92 CONCERNING THE CREATION OF A SUPPLEMENTARY PROTECTION CERTIFICATE FOR MEDICINAL PRODUCTS

APPLICANT E I du Pont de Nemours & Co.

ISSUE Whether the application for an extension to SPC number SPC/GB/95/010 is a valid application

HEARING OFFICER Dr L Cullen

DECISION

Introduction

1 This relates to an application dated 18 February 2009 that was filed by E I du Pont de Nemours & Company ("the applicant") for a six month extension to the period of protection provided by a supplementary protection certificate (SPC)[1] granted to the applicant, and accorded the number SPC/GB/95/010.

2 This SPC was granted on 13 October 1995 and, subsequent to payment of the required fees, entered into force on 9 July 2007. The active ingredient for which the SPC was granted is Losartan, as a potassium salt, which is used to treat hypertension in humans through its action as an antagonist of the angiotensin II receptor. The product is marketed by in the UK under the name COZAAR (RTM) by Merck & Co., Inc., a licensee under the SPC.

3 The basic patent upon which the granted SPC relies is EP (UK) 0 253 310 B1, which was filed on 9 July 1987, has a priority date of 11 July 1986 and was

[1] Although the first time each abbreviation is used in the text it is explained, given that there are a large number of them, a list of these abbreviations is also provided in Annex 1 to this decision

granted on 17 November 1999. The expiry date of this patent is 8 July 2007.

4 An authorisation to place this product on the market in the UK was granted on 15 December 1994. However, this was not the first marketing authorisation to place Losartan on the market in the European Community. The first marketing authorisation (MA) granted under Directive 2001/83/EC (which has superceded Directive 65/65/EEC) to place Losartan on the market in the European Community was Danish Marketing Authorisation No. 15844 granted on 26 September 1994. Taking account of the above data and noting Article 13 of EEC Regulation 1768/92, the date of expiry of the SPC for which the necessary fees have been paid is 1 September 2009.

5 In the letter from the applicant dated 18 February 2009 which was enclosed with the application for the extension to the term of the SPC, the applicant indicates that there are two variations to the marketing authorisation for COZAAR. The first variation is for a new indication, which in this context means a new use and the second is for a new formulation. The new indication is for use to treat proteinuria in paediatric patients. Proteinuria, an excess of proteins in the urine, is associated with kidney impairment and often occurs in patients with diabetes. Losartan is used to treat this condition in adults and the applicant wishes to extend its use to treat this condition in children. The new formulation is one developed for oral paediatric use.

6 The applicant then goes on to summarise the documents that they have enclosed with their application. They contend that these are sufficient to confirm that the assessment of compliance with the agreed PIP is now complete. The Mutual Recognition Procedure, hereafter referred to as MRP, has been used by the applicant, with the Netherlands as the reference member state (RMS), to obtain an updated Marketing Authorisation to show the results of the Paediatric Investigation Plan (PIP). The statement of compliance to be included in all national marketing authorisations has been agreed with the RMS and is not subject to change; the product is licensed in all community member states. As a consequence the applicant claims that they are entitled to seek, as the email from the competent authority in the Netherlands acknowledges, the rewards and incentives provided for in Article 36 of Regulation 1901/2006, i.e. a six month extension to the term of the SPC.

7 In his examination report dated 3 March 2009 the Examiner (Dr Jason Bellia) observed that:

> "It is my preliminary opinion that your application as filed does not meet the requirements of 8(1)(d)(i) of Regulation 1768/92 insofar as it does not comply with Article 36(1) by reference to Article 36(2) of Regulation No 1901/2006. It would appear that the means by which compliance with the PIP is confirmed in the case of an EU wide authorisation is by incorporation of a compliance statement into the corresponding EMEA marketing authorisation. I find support in this view provided in Hearing Officer Cullen's comments especially at paragraph 35 of his decision BL O/035/09.
>
> I have taken note of the evidence you have supplied in particular the statement at recital 3 of the Commission Decision C(2009)488. However, I

do not find that this constitutes a compliance statement as required by Hearing Officer Cullen or as set out by the Commission in the Official Journal of the European union 2008/C 243 particularly under the heading "3. SECTION 2: OPERATION OF THE COMPLIANCE CHECK" (copy enclosed). I have also considered the email from the Netherlands agency whereas such an opinion is persuasive I do not find I am bound to follow it. Therefore balancing the evidence you have provided against the clear requirements set out in Regulation 1901/2006, the Commission guidance in the Official Journal and Hearing Officer Cullen's comments I do not find the requirements of Article 8(1)(d)(i) met and as such I do not find this application complete."

8 The examiner then went on to set a date of 6 July 2009 as the deadline by which this matter should be addressed. He identified two possible options for the applicant to follow:

(i) Supply an EMEA authorisation for Losartan with a compliance statement in accordance with that set out by the Commission in 2008/C 243.

(ii) Provide further argument to show the statement at recital 3 of Commission Decision C(2009)488 meets the requirements of Article 8(1)(d)(i) of Regulation 1768/92.

9 The applicant responded very promptly to this examination report on 10 March 2009. In this letter they indicated that they considered that the issues to be decided in this case were the same as those at issue in the recent Merck case, the decision on which was issued on 6 February 2009 (see IPO decision BL O/035/09)[2]. This decision is currently under appeal to the Patents High Court. Given the urgency to resolve the issues on this case before expiry of the SPC on 1 September 2009, the applicant has invited the Office to issue a decision on the papers thus waiving their right to be heard.

10 The examiner Dr Bellia wrote to the applicant on 16 March 2009 indicating that he had explained the urgency of the present case and the applicant's willingness to waive their right to be heard to a Hearing Officer and that the Hearing Officer agreed that he would issue a decision based on the papers on file as soon as possible. This letter also noted that it would not be possible to comment on the possibility of hearing any appeal from this case at the same time as the appeal of BL O/035/09 until the hearing officer had had an opportunity to examine the facts of the case, and reach a decision. However, it was acknowledged that if the decision did reach a similar conclusion, then it would be sensible to have any appeal arising from the present case heard at the same time as the current appeal on BL O/035/09.

11 A further letter was received from the applicant dated 19 March 2008 which was provided as supporting information to this application. It summarized the experiences of the licensee, Merck & Co. Inc, in relation to the length of time taken by the various national competent authorities to act on decisions to grant marketing authorisations for type II variations approved under MRP and to issue

[2] For text of this decision, see the IPO website at http://www.ipo.gov.uk/pro-types/pro-patent/pro-p-os/p-challenge-decision-results-bl.htm?BL_Number=O%2F035%2F09&submit=Go+%BB

this updated marketing authorizations.

12 My decision, given below, is thus based on the papers already on file.

THE RELEVANT LAW

EC Regulation 1901/2006[3]

13 Regulation (EC) No 1901/2006 concerning medicinal products for paediatric use describes the system for promoting & authorizing paediatric testing of medicinal products in the European Community. The objective of this Regulation is to provide suitable incentives and rewards to companies that produce medicinal products so that they will carry out clinical tests to find out the effectiveness of these drugs when used in children but also ensuring that no unnecessary clinical or other trials take place involving children. It is well established that medicinal products can have different effects when used in adults and when used in children and that tests should be carried out in children to determine if and what these different effects are. This is made clear in the recitals to EC Regulation 1901/2006; see for example recitals 4-6.

14 In order to fulfill its objective to reward companies that produce medicinal products for carrying out paediatric testing of these products in addition to their testing for adult use, EC Regulation 1901/2006 has amended EEC Regulation 1768/92 to specify how an additional 6 month extension to the term of protection provided by the SPC can be obtained.

15 For the purposes of this case, Articles 7, 8, 23, 24, 29 and 36 are especially relevant. Article 36 of EC Regulation 1901/2006, which refers to the six month extension to the term of the SPC as a reward for carrying out an approved and validated set of paediatric study, reads:

> **Article 36**
>
> (1) Where an application under Article 7 or 8 includes the results of all studies conducted in compliance with an agreed paediatric investigation plan, the holder of the patent or supplementary protection certificate shall be entitled to a six-month extension of the period referred to in Articles 13(1) and 13(2) of Regulation (EEC) No 1768/92.

[3] Full title of the Regulation is Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004. The community legislation which is amended by this regulation is (i) Regulation (EEC) No 1768/92 of the European Parliament and of the Council of 18 June 1992 concerning the creation of a supplementary protection certificate for Medicinal products; (ii) Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the member states relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use; (iii) Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the community code relating to medicinal products for human use, as amended; and (iv) Regulation (EEC) 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.

The first subparagraph shall also apply where completion of the agreed paediatric investigation plan fails to lead to the authorisation of a paediatric indication, but the results of the studies conducted are reflected in the summary of product characteristics and, if appropriate, in the package leaflet of the medicinal product concerned.

(2) The inclusion in a marketing authorisation of the statement referred to in Article 28(3) shall be used for the purposes of applying paragraph 1 of this Article.

(3) Where the procedures laid down in Directive 2001/83/EC have been used, the six-month extension of the period referred to in paragraph 1 shall be granted only if the product is authorised in all Member States.

(4) Paragraphs 1, 2 and 3 shall apply to products that are protected by a supplementary protection certificate under Regulation (EEC) No 1768/92, or under a patent which qualifies for the granting of the supplementary protection certificate. They shall not apply to medicinal products designated as orphan medicinal products pursuant to Regulation (EC) No 141/2000.

(5) In the case of an application under Article 8 which leads to the authorisation of a new paediatric indication, paragraphs 1, 2 and 3 shall not apply if the applicant applies for, and obtains, a one-year extension of the period of marketing protection for the medicinal product concerned, on the grounds that this new paediatric indication brings a significant clinical benefit in comparison with existing therapies, in accordance with Article 14(11) of Regulation (EC) No 726/2004 or the fourth subparagraph of Article 10(1) of Directive 2001/83/EC.

16 A paediatric investigation plan (hereafter 'PIP') is defined in Article 2(2) as meaning:

> "a research and development programme aimed at ensuring that the necessary data are generated determining the conditions in which a medicinal product may be authorised to treat the paediatric population"

17 For medicinal products which are already the subject of a supplementary protection certificate, Article 8 describes the procedure for obtaining an update to the marketing authorisation for such products following completion of the paediatric testing.

Article 8

In the case of authorised medicinal products which are protected either by a supplementary protection certificate under Regulation (EEC) No 1768/92, or by a patent which qualifies for the granting of the supplementary protection certificate, Article 7 of this Regulation shall apply to applications for authorisation of new indications, including paediatric indications, new pharmaceutical forms and new routes of administration.

For the purposes of the first subparagraph, the documents referred to in Article 7(1) shall cover both the existing and the new indications, pharmaceutical forms and routes of administration.

18 Article 8 refers back to Article 7 for details of the further evidence that must be provided and in the present case sub-paragraph (a) of this article applies which reads:

Article 7

(1). An application for marketing authorisation under Article 6 of Directive 2001/83/EC in respect of a medicinal product for human use which is not authorised in the Community at the time of entry into force of this Regulation shall be regarded as valid only if it includes, in addition to the particulars and documents referred to in Article 8(3) of Directive 2001/83/EC, one of the following:

(a) the results of all studies performed and details of all information collected in compliance with an agreed paediatric investigation plan;

(b) ……

For the purposes of point (a), the decision of the Agency agreeing the paediatric investigation plan concerned shall also be included in the application.

(2). …….

19 Articles 23 and 24 concern the issue of compliance with the PIP and make clear that this compliance must be verified by the appropriate competent authority in each Member State:

Article 23

(1). The competent authority responsible for granting marketing authorisation shall verify whether an application for marketing authorisation or variation complies with the requirements laid down in Articles 7 and 8 and whether an application submitted pursuant to Article 30 complies with the agreed paediatric investigation plan.

Where the application is submitted in accordance with the procedure set out in Articles 27 to 39 of Directive 2001/83/EC, the verification of compliance, including, as appropriate, requesting an opinion of the Paediatric Committee in accordance with paragraph 2(b) and (c) of this Article, shall be conducted by the reference Member State.

(2). The Paediatric Committee may, in the following cases, be requested to give its opinion as to whether studies conducted by the applicant are in compliance with the agreed paediatric investigation plan:

(a) by the applicant, prior to submitting an application for marketing authorisation or variation as referred to in Articles 7, 8 and 30, respectively;

(b) by the Agency, or the national competent authority, when validating an application, as referred to in point (a), which does not include an opinion concerning compliance adopted following a request under point (a);

(c) by the Committee for Medicinal Products for Human Use, or the national competent authority, when assessing an application, as referred to in point (a), where there is doubt concerning compliance and an opinion has not been already given following a request under points (a) or (b).

In the case of point (a), the applicant shall not submit its application until the Paediatric Committee has adopted its opinion, and a copy thereof shall be annexed to the application.

(3). If the Paediatric Committee is requested to give an opinion under paragraph 2, it shall do so within 60 days of receiving the request.

Member States shall take account of such an opinion.

Article 24

If, when conducting the scientific assessment of a valid application for Marketing Authorisation, the competent authority concludes that the studies are not in conformity with the agreed paediatric investigation plan, the product shall not be eligible for the rewards and incentives provided for in Articles 36, 37 and 38.

20 The procedures to follow for updating the marketing authorisation for an application made under Article 8 are given in Article 28 and Article 29 of EC Regulation 1901/2006. For the purposes of this case, which concerns a medicinal product which has been authorized in at least one Member State already using one of the procedures described in Directive 2001/83/EC, Article 29 outlines the procedure to follow for authorisation of a new indication or new pharmaceutical form. This directive describes marketing authorisation procedures based on national procedures which work in cooperation with each other through the process of mutual recognition. Article 29 reads:

Article 29

In the case of medicinal products authorised under Directive 2001/83/EC, an application as referred to in Article 8 of this Regulation may be submitted, in accordance with the procedure laid down in Articles 32, 33 and 34 of Directive 2001/83/EC, for authorisation of a new indication, including the extension of an authorisation for use in the paediatric population, a new pharmaceutical form or a new route of administration.

That application shall comply with the requirement laid down in point (a) of Article 7(1).

The procedure shall be limited to the assessment of the specific sections of the summary of product characteristics to be varied.

Directive 2001/83/EC

21 The European system for the authorisation of medicinal products for human and animal use was introduced in January 1995 with the objective of ensuring that safe, effective and high quality medicines could quickly be made available to citizens across the European Union. Directive 2001/83/EC sets out the community code relating to medicinal products for human use, as amended, and describes all the provisions currently governing the production, placing on the market, distribution and utilisation of medicinal products for human use.

22 No medicinal product may be placed on the market of a Member State unless an authorisation has been issued by the competent authorities of that Member State or by the European Medicines Agency (hereafter the EMEA) which provides a central authorisation procedure that covers the whole of the EC. Only applicants established in the Community may be granted such a marketing authorisation.

23 The European system offers three routes for the authorisation of medicinal products, the so-called **centralized procedure** (set up in May 2004 by Regulation (EC) No 726/2004) using the EMEA and two procedures based on mutual recognition of national authorisation procedures; the **decentralized procedure** (DCP), also introduced in 2004, for medicinal products which have not been authorized before in any member state and allows for the marketing

authorisation application to be submitted simultaneously in several Member States, one of which acts as the reference member state and coordinates the process and at the end of this procedure national marketing authorisations are granted in all the Member States involved. If the medicinal product has already been granted a marketing authorisation in one of the EC members states, then the **mutual recognition procedure** (MRP), is used which is based on the principle of recognition by one or more Member States of an already existing national marketing authorisation.

Mutual Recognition Procedure

24 Basic arrangements for implementing the mutual recognition procedure (MRP), laid down in Directive 2001/83/EC have been made in all EU Member States. Since 1 January 1998, this procedure is compulsory for all medicinal products to be marketed in a Member State other than in the one they were first authorised. Any national marketing authorisation granted by an EU Member State's national authority can be used to support an application for its mutual recognition by other Member States. Articles 27-35, but especially Articles 32-34, of Directive 2001/83/EC describe the MRP process. Article 29 of Regulation EC 1901/2006 refers explicitly to the use of MRP for the approval of variations to the marketing authorisation to include a new indication, i.e. paediatric use, which also includes a new pharmaceutical form.

25 An application for mutual recognition may be addressed to one or more Member States. The applications submitted must be identical and all Member States must be notified of them. As soon as one Member State decides to evaluate the medicinal product [at which point it becomes the "Reference Member State" (RMS)], it notifies this decision to other Member States [which then become the "Concerned Member States" (CMS)], to whom applications have also been submitted. Concerned Member States will then suspend their own evaluations, and await the Reference Member State's decision on the product

26 This evaluation procedure undertaken by the RMS may take up to 210 days and ends with the granting of a marketing authorisation in that Member State[4]. It can also occur that a marketing authorisation had already been granted by the Reference Member State. In such a case, it shall update the existing assessment report in 90 days. As soon as the assessment is completed, copies of this report are sent to all Member States, together with the approved summary of product characteristics (SmPC), labelling and package leaflet. The Concerned Member States then have 90 days to recognise the decision of the Reference

[4] While the basic timelines for the different market authorisation procedures, including MRP, are laid down in Articles 27-39 of Directive 2001/83/EC, an explanation and summary chart of these steps that is easier to understand and assimilate is provided in Chapter 5 'Variations'; of Volume 2A 'Procedures for Marketing Authorisations' of 'The Rules governing Medicinal Products in the European Community'. The Rules governing Medicinal Products in the European Community' compiles the body of European Legislation in the pharmaceutical sector for medicinal products for human use. It is presented in 10 Volumes in the EudraLex database and is available from http://ec.europa.eu/enterprise/pharmaceuticals/eudralex. Volume 1 covers the Relevant Directives, Regulations and Miscellaneous Legislative Provisions; Volume 2 covers Regulatory Guidelines related to procedural and regulatory requirements.

Member State and the SmPC, labelling and package leaflet as approved by it. National marketing authorisations shall be granted within 30 days after acknowledgement of the agreement.

EEC Regulation 1768/92

27 EEC Regulation 1768/92 concerning the creation of a supplementary protection certificate (SPC) for medicinal products describes the circumstances and means by which an applicant can obtain up to five years additional protection for a medicinal product being marketed for use in humans to compensate for the time taken to obtain regulatory approval to put this product on the market. The additional term of protection provided by the SPC relates to the active ingredient in the medicinal product that is being sold in the market and its scope is defined by the basic patent on which the application is based.

28 In order to fulfill its objective to reward companies that produce medicinal products for carrying out paediatric testing of these products in addition to their testing for adult use, EC Regulation 1901/2006 has amended EEC Regulation 1768/92 to specify how an additional 6 month extension to the term of protection provided by the SPC can be obtained.

29 Article 8 of EEC Regulation 1768/92, as amended by Regulation 1901/2006, lays down the requirements for an application for a six month extension to the SPC and now reads:

Article 8

1. The application for a certificate shall contain:

(a) a request for the grant of a certificate, stating in particular:

(i) the name and address of the applicant;

(ii) if he has appointed a representative, the name and address of the representative;

(iii) the number of the basic patent and the title of the invention;

(iv) the number and date of the first authorization to place the product on the market, as referred to in Article 3 (b) and, if this authorization is not the first authorization for placing the product on the market in the Community, the number and date of that authorization;

(b) a copy of the authorization to place the product on the market, as referred to in Article 3(b), in which the product is identified, containing in particular the number and date of the authorization and the summary of the product characteristics listed in Article 4a of Directive 65/65/EEC or Article 5a of Directive 81/851/EEC;

(c) if the authorization referred to in (b) is not the first authorization for placing the product on the market as a medicinal product in the Community, information regarding the identity of the product thus authorized and the legal provision under which the authorization procedure took place, together with a copy of the notice publishing the authorization in the appropriate official publication.

(d) where the application for a certificate includes a request for an extension of the duration:

(i) a copy of the statement indicating compliance with an agreed completed paediatric investigation plan as referred to in Article 36(1) of Regulation (EC) No 1901/2006;

(ii) where necessary, in addition to the copy of the authorisations to place the product on the market as referred to in point (b), proof that it has authorisations to place the product on the market of all other Member States, as referred to in Article 36(3) of Regulation (EC) No 1901/2006.";

(1a) Where an application for a certificate is pending, an application for an extended duration in accordance with Article 7(3) shall include the particulars referred to in paragraph 1(d) and a reference to the application for a certificate already filed.

(1b). The application for an extension of the duration of a certificate already granted shall contain the particulars referred to in paragraph 1(d) and a copy of the certificate already granted.";

2. Member States may provide that a fee is to be payable upon application for a certificate and upon application for the extension of the duration of a certificate."

ANALYSIS & ARGUMENT

Preliminary Opinion of the Examiner

30 Before looking in detail at whether or not the present application for an SPC extension meets all the requirements of Article 8(1)(d)(i) of EEC Regulation 1768/92 , it is necessary to look first at the grounds on which the preliminary opinion was issued by the examiner (see para 7 above). In this case the examiner considered that the application did not meet the requirements of Article 8(1)(d)(i) of EC Regulation 1768/92 because "*the means by which compliance with the PIP is confirmed in the case of an EU wide authorisation is by incorporation of a compliance statement into the corresponding EMEA marketing authorisation*". This is not correct in relation to this case as the product is not authorised for use in the EU by a central EMEA marketing authorisation. As the product in this case, Losartan/COZAAR, was already authorised in at least one EU member state, the Mutual Recognition Procedure laid down in Chapter 4 of Title III of Directive 2001/83/EC and especially Articles 32-34 is the authorisation procedure used to obtain a variation or change to the marketing authorisation (MA) for this product. However, the same objection is valid in relation to the means by which compliance with an agreed, completed PIP is confirmed – inclusion of a statement of compliance by a competent authority into the granted varied MA obtained via the MRP that fulfils all the requirements of Article 28(3) of EC Regulation 1901/2006 as a means to qualify for the reward of a 6 month SPC term extension under Article 36 of this Regulation.

31 In the following paragraphs I will look at the details of the authorisation procedure in more detail and consider whether the materials provided by the applicant in support of their application do in fact meet the requirements of Article 8(1)(d) of EEC Regulation 1768/92.

Evidence to meet the requirements under Article 8(1)(d)

32 In this case, as an SPC has already been granted for the medicinal product, Losartan, the situation in Article 8(1)(b) of EEC Regulation 1768/92 applies. Thus, the application for the extension is valid if all the requirements of

Article 8(1)(d) have been fulfilled. If this is the case, then according to Article 10, an extension to the duration of the certificate shall be granted. Thus, the essential question to consider is does the application meet the requirements of Article 8(1)(d)?

33 This is essentially the same question that was at issue in recent Office decision BL O/035/09, hereafter referred to as the Merck decision[1], in relation to a request from Merck & Co Inc for an extension to an SPC as a reward for carrying out paediatric testing on the use of medicinal product CANCIDAS (RTM) comprising active substance caspofungin to treat fungal infections in children. However, a number of differences exist between that case and the present one particularly in relation to the procedure being used to vary (i.e. update) the marketing authorisation to include the new paediatric indication, i.e. the new use in children, and the new pharmaceutical form. As a consequence there are differences in terms of the steps that the applicant needs to fulfil in order to gain an updated marketing authorisation containing the necessary statement of compliance and proof of authorisation in all member states required under article 8(1)(d) of EEC Regulation 1768/92. In order to determine if the present applicant has met these requirements, it is first necessary to consider the status of the present application before turning to consider the relevance of the earlier Merck decision to this case.

34 I am aware from their letter of 10 March 2009 that the applicant considers the issue in question in this case to be the same as in the Merck decision and that they consider it unlikely that the outcome of the present case will be different. However, that is not a conclusion that, I, as Hearing Officer, can draw until I have considered the facts of the present case.

35 As mentioned already, to obtain an extension to a granted SPC, it is necessary to meet the requirements of Article 8(1)(d) of EEC Regulation 1768/92. This Article has two components, (i) the first relates to the provision of evidence that an agreed scheme of paediatric tests have been carried out, that an assessment has been made to show that these tests and results comply with the agreed PIP and that an updated varied MA has been granted which clearly indicates compliance with the agreed, completed PIP; (ii) The second component relates to the provision of evidence that the applicant has authorisation to market the product in all countries in the EC. I will consider the evidence filed by the applicant in support of their application for an SPC extension in light of these two components.

36 The applicant has filed the following documents, listed in order of date, in support of their application for an extension to SPC/GB/95/010:

a. Commission Decision P(2009)488 dated 22 January 2009 issued under Article 29 of Regulation (EC) 1901/2006 concerning medicinal product COZAAR containing the active substance Losartan as its potassium salt (also referred to as Losartan potassium)

b. A Preliminary Variation Assessment Report (hereafter PVAR), dated 28 January 2009, for a type II variation under MRP for Losartan/COZAAR prepared by the competent authority for marketing authorizations in the

Netherlands,(NL) *the College ter Beoordeling van Geneesmiddelen*, hereafter the CBG. The NL is acting as the RMS for this application via MRP and the CBG has appointed a rapporteur to coordinate this application through the procedure

c. Opinion of the Paediatric Committee (PDCO) of the EMEA issued on 6 February 2009 under Article 23(2) of Regulation (EC) 1901/2006 concerning the compliance check with the PIP for Losartan/COZAAR in hypertension, proteinuria and heart failure.

d. A statement dated 6 February 2009 from a Mr Axel Breistadt, Executive Director, Regulatory Affairs of Merck & Co. Inc, which indicates that Losartan/COZAAR is licensed in all EU member states and that Merck & Co. Inc are the holders of the marketing authorisation for Losartan/COZAAR in the UK.

e. Email dated 13 February 2009 from a Ms Desiree Bergamin-Egenberger, Regulatory Project Leader and rapporteur at the CBG, the NL competent authority of the RMS dealing with this application. It is addressed to all her counterparts in other member states dealing with this MRP procedure. The email describes the progress that has been made with this application under MRP and I note from the subject header of the email that the application is at day 59.

First component – updated Marketing Authorisation to show compliance with PIP

37 Article 8(1)(d)(i) of EEC Regulation 1768/1992 refers to "*a statement indicating compliance with an agreed <u>completed</u> paediatric investigation plan as referred to in Article 36(1) of EC Regulation 1901/2006*"(my emphasis). Article 36(1) of EC Regulation 1901/2006 refers to a "*statement indicating compliance with an agreed paediatric investigation plan*". But Article 36(2) of EC Regulation 1901/2006 indicates that a statement such as that referred to in Article 28(3) of EC Regulation 1901/2006 shall be used to apply Article 36(1) of this Regulation. Article 28(3) of EC Regulation 1901/2006 uses the same words as Article 8(1)(d)(i) of EC Regulation 1768/1992 i.e. it refers to an 'agreed <u>completed</u> paediatric investigation'. As set out in the earlier Merck decision (BL O/035/09)[1], the hearing officer (Dr L Cullen) considered that the inclusion of the additional word "*completed*" in these Articles is relevant and indicates that, not only must the PIP be agreed, the testing it describes must have been completed and there must be something to corroborate that the PIP has been complied with.

38 Commission Decision C (2009) 488 dated 22 January 2009 is issued under the procedure referred in Article 29 of EC Regulation 1901/2006 (see cover page of this decision). Looking at this article of the Regulation, three points are clear; firstly, the MRP can be used to obtain authorisation of a new indication, a new pharmaceutical form, and/or a new route of administration. In this case it is being used for two of these three possibilities, authorisation of a new indication, i.e., use in the paediatric population and of a new pharmaceutical form, i.e. an oral suspension. Secondly, the MRP will focus only on the assessment of the specific parts of the SmPC that the applicant seeks to vary (see third para of Article 29); and thirdly, such an application has to include the results of all studies performed and details of all information collected in compliance with an agreed PIP to meet the requirements to comply with Article 7(1)(a).

39 Looking at the decision itself, the following facts are clear:

(i) a PIP was agreed with the EMEA (see recital (2) of the decision);

(ii) the application submitted by Merck, Sharp & Dohme BV includes all the results and details of all information collected in compliance with the agreed PIP (my emphasis) (see recital (3) of the decision);

(iii) as a result, the application complies with Article 7(1)(a) of EC Regulation 1901/2006 (see recital (4) of the decision);

(iv) the application for the new pharmaceutical form at a new strength following the PIP investigations has been assessed by the Committee for Medicinal Products for Human Use (CMPH) and it has concluded that the marketing authorisations for Losartan/COZAAR should be amended to allow this new pharmaceutical form associated with a new strength (see recitals (5) and (6) of the decision.

(v) Articles (1) and (2) of the decision make it clear that the member states shall amend the national marketing authorisations to include the new pharmaceutical form and its use in the paediatric population and that these amended national marketing authorisations will be based on the summary of product characteristics (SmPC), labelling & package leaflet information, and follow-up conditions laid out in the Annexes to the decision.

(vi) Article (3) makes it clear that this decision is addressed to the member states.

40 A consideration of Annex 2 attached to the decision includes the changes or variations that the applicant proposes to use to update the SmPC. These are the changes that must be assessed as part of the MRP (as referred to in the third paragraph of Article 29). These changes describe if, how and when Losartan/COZAAR can be used in the paediatric population, according to the applicant, based on the results of the study they have performed as part of the agreed PIP. In this case, changes or variations to the SmPC are shown under such headings as:

(i) '4.2 Posology and method of administration' (use of Losartan to treat paediatric hypertension in children and adolescents (6-16 years) - see page 16-17 of decision);

(ii) '4.4 Special warnings & precautions for use' (Losartan is not recommended for children with hepatic impairment and renal impairment under certain conditions - see page 18 and 19 of decision);

(iii) '4.8 Undesirable Effects' (similar to those in adults, see page 24 of decision);

Annex 2 then goes on to describe the changes that the applicant proposes to make to the section of the SmPC dealing with the pharmacological properties of Losartan under:

(iv) '5.1 pharmacodynamic properties' (paediatric hypertension, see page 27 of decision) and

(v) '5.2 Pharmacokinetic Properties (in paediatric patients – see page 28 of decision);

Finally, Annex 2 describes the steps necessary to prepare the new pharmaceutical form associated with the new strength under;

(vi) '6.6 Special precautions in disposal and other handling' where it describes how to reconstitute the oral suspension of COZAAR to give 2.5 mg/ml of Losartan as its potassium salt.

41 Following this decision, the next step is for the bodies responsible for granting national marketing authorizations to amend the marketing authorisations for Losartan/COZAAR in each member state to allow the new indication and the new pharmaceutical form. In its role as RMS, the competent authority in the NL, the CBG, has prepared the PVAR to provide a detailed assessment of the proposed variation to the SmPC. The assessment of the variation to the SmPC involves an analysis of the methodology of the studies carried out by the applicant as part of the agreed PIP and the results obtained from these studies (see page 2 of the PVAR for details of who carried out this assessment).

42 I do not need to comment on this assessment in detail other than to note that that assessment has identified problems with the study carried out and that as a result the recommendation is that the new indication, i.e., treatment of proteinuria in the paediatric population is not approved (see for example, para I on page 4; see Assessor's Comments on page 6-7 and the request for Supplementary Information as proposed by the Rapporteur on page 17). The PVAR also includes suggested changes that the applicant should make to the proposed SmPC to take account of the problems identified with the study (see Annex 1 of the PVAR, pages 19-22). It is clear from the Assessors Comment's in relation to the SmPC that they consider that the current proposed wording provided by the applicant will have to change (see for example Assessor's Comments on pages 21 and 22).

43 As mentioned in para 26 above, under the MRP, there is a fixed time within which the national competent authorities of the RMS and CMS are required to complete and agree the variation procedure. In this case there is a period of 90 days from the issue of the Commission decision referred to above for the RMS and the CMS to complete and agree their assessment and to update the marketing authorizations for each country[3]. From a consideration of the e-mail dated 13 February 2009, it is clear that the PVAR has already been circulated to each CMS[5] and that some have replied with or without additional comments.

[5] This is done through the Eudralink electronic network which allows the secure exchange of all such information relevant to Marketing Authorisations between the relevant competent authorities in the member states and the central EU authorities such as the EMEA and the European Commission. For further information see the website of the EMEA at http://www.emea.europa.eu/, the MHRA (the UK national competent authority) at http://www.mhra.gov.uk/index.htm or the relevant part of the European Commission, the Enterprise Directorate General at http://ec.europa.eu/enterprise/pharmaceuticals/index_en.htm.

This email also indicates that the 'clock has stopped' on the variation assessment procedure to provide the holder of the marketing authorisation in NL, Merck, Sharpe & Dohme BV, the opportunity to address the comments and issues raised by the assessment that are listed in the PVAR.

44 This email also indicates that the marketing authorisation holder has received a positive opinion from the Paediatric Committee of the EMEA indicating that all the measures in the agreed paediatric investigation plan have been complied with. A copy of this positive opinion has been provided by the applicant with this application (see para 36(c) above). This opinion provides verification from the Paediatric Committee of the EMEA that the agreed paediatric investigation has been completed. It also confirms that these studies have been carried out according to the necessary timeline as required under article 45(3) of EC Regulation 1901/2006 i.e. , that these studies have been completed after entry into force of the Regulation. The status of such an opinion in providing support for an SPC extension was discussed in detail in the Merck decision[1] (see especially paras 41 & 42). Although the process used to obtain a varied MA is different in this case – MRP in the present case, the centralised procedure in the Merck decision, the opinion of the Paediatric Committee is used in both situations to confirm compliance with an agreed completed PIP. An opinion of this committee is not a decision on compliance by a relevant competent authority but, as mentioned in the Merck case, it is an essential step in reaching such a decision. Confirming compliance is not the end of the story, as in order to secure the reward under Article 36 of EC Regulation 1901/2006, all the elements referred to in Article 28(3) of this Regulation must be in place.

45 The final paragraph of the email of 13 February 2009 provides the second important confirmation needed as part of the compliance check. It states:

> "In reference to Article 24 of the Regulation, the Reference Member state has <u>not</u> concluded during the scientific assessment of this application for variation that the studies are not in conformity with the agreed paediatric investigation plan. Hence, the product shall be eligible for the rewards and incentives provided for in Articles 36, 37 and 38"

Thus it confirms that the scientific assessment of the completed PIP studies and their results has not identified any major problems or flaws that would prevent the applicant from obtaining any of the rewards provided for in EC Regulation 1901/2006. It is important to note in this regard that this does not mean that the scientific assessment of the completed PIP studies by the RMS has concluded that the paediatric use should be approved or recommended. That is still under consideration and will depend upon the response from the holder of the MA in NL as referred to above (in para 43). However, it does mean that the completed studies were conducted in the way proposed by the applicant in the PIP and agreed by the Paediatric Committee of the EMEA. It means, for example, that the methodology followed for the studies was the agreed and expected one and that this has been verified. It does not mean that the studies were successful in showing that the active substance was useful for treating children. This is an important distinction, the reward available under Articles 36, 37 or 38 of the Regulation 1901/2006 are not dependent on the studies showing that the active substance tested is effective in the paediatric population. As Article 36(1) makes

clear the rewards are available even if the agreed studies described in the PIP have been completed but do not result in a paediatric indication as long as this has been validated and verified by a suitable competent authority and the SmPC of the granted varied MA has been updated to include the details of these studies (see discussion in paras 34 and 35 of earlier Merck decision[1]).

46 The applicant argues in their letter of 18 February 2009 that the contents of the email of 13 February 2009 when taken with the supporting documents provided by the applicant are sufficient to show that "the assessment of compliance with the agreed PIP is now complete". As a result, the applicant argues that the statement of compliance specified in this email "is not subject to change and is the actual statement of compliance which will be included in all the national varied Marketing Authorisations". However, the applicant also acknowledges in this letter that the marketing authorisation variation procedure for Losartan/COZAAR will continue.

47 I do not agree with this assessment by the applicant. I accept that there is evidence to show the following:

(a) that the applicant has carried out the agreed PIP;

(b) that this agreed PIP has been completed;

(c) the agreed completed PIP is being subjected to a compliance check as required under Articles 23 and 24 of EC Regulation 1901/2006 using the MRP (according to Articles 32-34 of Directive 2001/83/EC); and

(d) that, as part of (c), information on the studies conducted as part of the agreed, completed PIP have been included in a proposed summary of product characteristics to be included in a draft varied marketing authorisation which has not yet been agreed.

I do not consider that a varied marketing authorisation has been agreed with the relevant competent authority acting for the RMS or that it has been agreed or approved by the CMS. Until the RMS is in a position to confirm what the final version of the SmPC and the corresponding changes to the labelling and package information are and to recommend these to the CMS, there is still uncertainty as to what information regarding the results from the studies in the paediatric population will be included in the updated varied MA. Providing such information is one of the key objectives of EC Regulation 1901/2006 and one of the justifications for the rewards available under Articles 36-38 of this Regulation (see also recital (28) and the discussion in para 43 of the Merck decision[1]). In addition, there is currently no statement of compliance from a competent authority in the updated varied MA as required under Article 28(3). I do not consider that there is anything in the e-mail of 13 February 2009 or the proposed variations to the SmPC submitted by the Applicant as Annex 2 to decision C(2009)488 or the proposed changes or comments made in the scientific assessment of the proposed variations to the SmPC made in the PVAR (including Annex 1 to the PVAR) that corresponds to a statement of compliance that meets the requirements of Article 28(3) and thus Article 36(2) of EC Regulation 1901/2006.

48 As discussed in the earlier Merck decision (see paras 38 & 40)[1], there is nothing in EC Regulation 1901/2006 to indicate what format the statement of compliance should have and where in the MA it should be found. However, guidelines on this matter have been issued by the European Commission[6], as referred to by the examiner in his preliminary opinion of 3 March 2009 and these appear to represent the most up-to-date and relevant information on this topic that I am aware of. These guidelines are clearly relevant because they are drawn up in response to Article 10 of EC Regulation 1901/2006 and as such are relevant to operation of the compliance check under Article 28(3). Thus, I find I am unable to satisfy myself that all the requirements of Article 28(3) of EC Regulation 1901/2006 have been met, particularly, in regard to a statement of compliance with the agreed completed PIP from a competent authority. At present, as the RMS has not agreed an updated varied MA for the Netherlands I cannot even confirm that such a statement of compliance has been included by the CBG, the Netherlands competent authority, in the draft varied MA to be recommended to the CMS for grant under the MRP.

49 The e-mail of 13 February 2009 does not, in my view, contain any wording that could be construed as a statement of compliance from a competent authority to be included into an updated varied MA. Nor does it in my view, contrary to that of the applicant, indicate that the assessment of compliance is complete. It verifies in my view that the relevant competent authority acting as RMS has been able to confirm that the application has passed the compliance test of Article 24 and so is eligible for the rewards available under Articles 36-38. From Directive 2001/83/EC (see Article 35) and the related guidelines on variations[3], there is still a possibility that agreement between the holder of the MA, the RMS and/or the CMS as to the final form of the MA cannot be reached and arbitration will be required before a final updated varied MA for all EU member states is agreed under MRP.

50 The timetable for completion of the MRP depends whether it is being used to obtain a new MA or to vary an existing MA and, in this case where a type II variation to the MA is being sought, there is a period of up to 90 days within which this variation procedure is to be completed by the RMS[3]. This is the total number of days that the relevant competent authority can take to do things, once a stage has been completed, for example the PVAR, and returned to the applicant for comment, the clock stops and only begins again when the applicant replies and the ball is back in the court of the relevant competent authority. As noted above, from the e-mail of 13 February 2009, the variation procedure has reached day 59 and the clock has stopped and a reply from the applicant is awaited (regarding the scientific assessment and the PVAR). Until this procedure is completed, approval or refusal of the variation is in doubt.

[6] Communicaton from the Commission 2008/C 243/01 published in the Official Journal of the European Union, 24.9.2008. This communication has been drawn up to meet the requirement under Article 10 of EC Regulation 1901/2006 to "draw up the detailed arrangements concerning the format and content which applications for agreement or modification of a PIP ….. must follow in order to be considered valid and concerning the operation of the compliance check referred to in article 23 and 28(3)".

Second Component – Product is authorised to be placed on the market in all EU member states

51 Article 8(1)(d)(ii) of EEC Regulation 1768/92 requires that in addition to the authorisations required under Article 3(b) of that Regulation, i.e. a copy of the first MA to place the product on the market in the community and a copy of the MA to place the product on the market in the member state where the application is being made, the application for an extension must also contain, "*proof that it has authorisations to place the product on the market of all other Member States, as referred to in Article 36(3) of EC Regulation 1901/2006"*. The application must include reference to the already granted SPC [see Article 8(1)(b)].

52 Article 36(3) of EC Regulation 1901/2006 requires that for an SPC extension to be granted for a product that has been authorised using the procedures described in Directive 2001/83/EC, as in this case then that "*product must be authorised in all Member States*". As this Directive refers to the decentralised and mutual recognition procedures which are based on marketing authorisation by national competent authorities, this provision makes explicit that the authorised product must be approved for use on the market in all EU member states if the reward is to be gained. It does not appear necessary to make a similar provision for those products approved using the centralised procedure as the MA granted by the EMEA will automatically be valid in all EU member states. As noted above and in the Merck decision[1] referred to earlier (see para 37), although Article 36(3) does not refer to an agreed completed PIP (my emphasis) explicitly, because of its relationship to Articles 36(2) and 28(3), this is in my view, also the requirement under Article 36(3).

53 The applicant has provided a signed statement dated 6 February 2009 from Mr Axel Breistadt, Executive Director, Regulatory Affairs, Merck & Co., Inc., stating that Losartan/COZAAR is authorised to be marketed in all EU member states and to support this he refers to the list of such authorisations provided as Annex I to Commission Decision C(2009)488 (see para 4 of Mr Breistadt's statement). It also states that an application for authorisation of the paediatric indication and a new pharmaceutical form have been made in all EU member states (see para 3 of this statement).

54 The applicant argues that this is as much as they can do to show that the application meets the requirements under Article 8(1)(d)(ii) of EEC Regulation 1768/92. The remaining steps are those that are now completely in the hands of the relevant national competent authorities under the MRP and, as mentioned above (see paras 49 and 50 above), this includes agreeing and approving the recommendation of the updated varied MA prepared by the RMS including, if necessary, arbitration, followed by the actual issue of updated varied MAs for Losartan/COZAAR in each EU member state. Thus it appears that the time when the present application was made, the authorisation of the varied MA was in progress but was not complete.

55 In the supporting documents provided with their letter of 19 March 2009, the applicant has summarised their experience in relation to the actual time taken by various EU national competent authorities to produce granted varied marketing authorisations which include details of type II variations such as a new paediatric

use or a new pharmaceutical form. In their experience this can vary quite significantly from approximately one month to up to 2 years depending on which national competent authority is concerned. However, it is clear both from the guidelines[3] and the relevant articles in Directive 2001/83/EC, in particular, Article 34, that such varied MAs should be issued within 30 days. Thus there would appear to be a significant discrepancy in some cases between what is laid down in the relevant EU legislation and related rules & guidelines on variations and what is actually happening.

56 Herein lies the source of the concern for the applicant, especially in relation to applications for extensions to SPCs made under Article 7(5) of EEC Regulation 1768/92. Such applications for the first five years after entry into force of EC Regulation 1901/2006 must be made at least six months before expiry of the SPC. It is clear that the applicant is concerned that once the MRP has reached the point where the varied marketing authorisation in its final format has been agreed and the draft decision to this effect has been issued by the RMS to all the CMS, it will still take a significant extra period of time for some of the CMS to actually produce an updated varied marketing authorisation. If an application for an SPC extension cannot be made until these updated varied MAs have all been granted by each national competent authority in the EU because this is the only way to meet the requirement under Article 8(1)(d)(ii) of EEC Regulation 1768/92, then this may well lead to the applicant being placed in the position where the SPC will have expired before all these MAs are available. The applicant considers that they should not be placed at such a disadvantage that they will not be able to qualify for the six month extension to the SPC period because of the time taken by the competent authorities of the member states to carry out an administrative duty i.e., to issue updated varied marketing authorizations once the decision has been made on the final form of this MA using the MRP. The applicant has made it clear that this issue is of real concern to them in the present case as the SPC for Losartan/COZAAR expires on 1 September 2009.

57 The applicant appears to be suggesting that (a) provided the product is authorised in all the member states already; (b) a stage has been reached in the MRP whereby no further action is required by the applicant in relation to the proposed variations to the MA and (c) the RMS has concluded that the application meets the eligibility under Article 24 of EC Regulation 1901/2006 to qualify for a reward under Article 36, then all the actual steps in the process necessary for approval of the varied marketing authorisation have been completed. The applicant considers that the remaining steps will not have any impact on this even though the final form of the marketing authorisation hasn't been agreed or the statement required under Article 28(3) has not been included in the marketing authorisation that has been approved and granted and is valid in all the member states.

58 I can sympathise with the concern expressed by the applicant that delays by the relevant competent authority in one or more EU member states beyond the 30 days provided for in the MRP should not be allowed to prevent them from obtaining a reward they are entitled to when they have completed the principal objective of the Regulation, i.e., they have completed, and paid for, all the necessary paediatric testing and made available the results of these studies for

assessment and verification. However, the purpose of EC Regulation 1901/2006 is also to provide information about the effect of pharmaceutical compounds on children, to develop safe and effective means for carrying out such tests and for making the results of such tests available throughout all the EU (see, for example, recitals (17) and (28) of EC Regulation 1901/2006 and discussion in para 43 of BL O/035/09). In the present case we do not yet know what will be the final version of the updated varied MA proposed by the RMS for adoption by the CMS under the MRP and what information will be included in the SmPC and labelling information. The applicant may suggest that one has a good idea of what this will be at this stage on the basis of the papers they have filed in support of their application. However, this does not take account of the fact that the varied MA must be updated and must include a statement of compliance issued by a national competent authority before the reward under Article 36 can be claimed. Also, it is clear that when using the the marketing authorisation procedures described in Directive 2001/83/EC which are all based on mutual recognition of national MAs, it is an explicit requirement under Article 36(3) of EC Regulation 1901/2006 that the product is approved in all EU member states.

59 While it may be considered that Article 36(3) requires only that the product is authorised in all EU member states and so does not require that the authorisation covers the new paediatric indication or new pharmaceutical form, I do not think that this is a valid interpretation. Article 36(2) makes clear that a statement of compliance such as that referred to in Article 28(3) is required to qualify for the reward laid down in Article 36(1). This in effect means that the MA must be updated and varied and include a statement of compliance issued by a competent authority. By implication and taking note of Article 36(3), I consider that this leads to the unavoidable conclusion that the authorisation must be varied in all EU member states and it is proof of this varied authorisation that is required for compliance with Article 8(1)(d)(ii) of EEC Regulation 1768/92

60 In the current case there is still some uncertainty as to what the final varied MA and associated SmPC will look like for Losartan/COZAAR and thus this application for an SPC extension is not in my view at the stage suggested by the applicant where all the remaining steps are those that must be completed by the national competent authorities and the applicant no longer has a role. Indeed in the present application a reply from the Applicant to the PVAR is awaited. Also, in this case, the RMS is the Netherlands and at the time of the application the new use and oral form are not yet approved in the NL, yet alone for any of the other EU member states (such as the UK).

Present case and its relationship to the Merck decision, BL O/035/090

61 I have mentioned at various points in the above discussion where I think consideration of the earlier Merck case is relevant in the present case. Turning now to consider the similarities between this case and the earlier Merck case, I find that:

(a) in both cases the steps necessary to produce an updated varied marketing authorisation have not been fully completed. In the earlier Merck case, use of the centralised procedure through the EMEA meant fewer steps were involved in this process than in the current case where the mutual recognition procedure is being

used because the product had already been approved in at least one of the member states of the EU.

(b) In both cases, the evidence provided by the applicant has showed that an agreed PIP has been successfully completed but that information in relation to the studies completed and the outcome from these studies that needed to be included in the updated SmPC to produce the updated MA had not yet occurred. In the current case, I have extra evidence to take account of because of the further steps that the application has to undertake to gain approval. But in both cases the Hearing Officer was unable to confirm what the final granted varied marketing authorisation will look like or what and where the statement required under Article 28(3) to indicate compliance with the agreed completed implementation plan issued by a competent authority will be included in the varied MA. There is no prescribed form for this statement although the guidance provided by the European Commission[6] (and referred to by the examiner in his preliminary opinion of 3 March 2009) does give an indication of the kind of statement that needs to be included. Thus, in the absence of such a statement in a updated, varied MA that concerns a product authorised for the new indication and form and is authorised for use in all EU member states, it is not possible in the present case, as in the earlier Merck case, to conclude that the reward under article 36 can be granted.

(c) While it is my view that the documents provided by the applicant with the present application indicate that the marketing authorisation procedures have not been completed, they do appear to be at an more advanced stage in comparison to the situation in the earlier Merck decision. Despite this, the same conclusion has been drawn from a consideration of the current case, i.e., in this case, as in the earlier Merck case, there is not an updated varied marketing authorisation available in all the member states which contains updated information in the SmPC and a statement from a competent authority to confirm that paediatric studies have been carried out in compliance with the agreed paediatric investigation. As a result, it would appear valid to suggest, as the applicant does in their letter of 10 March 2009, that an appeal raised in relation to the earlier Merck decisionmight also raise issues relevant to the present case.

Conclusion

62 Taking all the above together, I have concluded that the papers filed by the applicant in support of their claim for a six month extension to the period of the SPC for Losartan/COZAAR do not meet the requirements of Article 8(1)(d)(i) of the EEC Regulation 1768/92. A varied marketing authorisation has not (yet) been agreed by the RMS (reference member state) for recommendation to the concerned member states (CMS), therefore the varied marketing authorisation has not been granted and approved in all the member states. The application does not include a marketing authorisation that contains a statement of compliance with an agreed completed paediatric investigation plan as referred to in Article 36(1) of EC Regulation 1901/2006.

63 I have also concluded that this application does not meet the requirements of Article 8(1)(d)(ii) of the EEC Regulation 1768/92. The application does not provide the necessary proof that the product has been approved for use on the

market in all EU member states. I have taken note of what the applicant has said in relation to the time required by some national competent authorities in the EU to make updated, varied MAs available and the impact that this has in turn on the requirement to provide proof that the product is authorised in all EU member states before an applicant can gain the reward under Article 36(1). I consider that if such a situation was to arise, it is not the intended consequence that an applicant would be prevented from gaining a reward they are entitled to having carried out the required paediatric testing because of such administrative delays. In that situation, it would be necessary to consider the issue of what type of proof the applicant could use to demonstrate that the product was authorised for use in all EU member states in the absence of an updated, varied MA for each state.

64 Furthermore the reward under Article 36 requires that the varied marketing authorisation must include the results of all the studies conducted on the paediatric population and a statement indicating compliance with the agreed completed paediatric investigation plan. In the documents supplied by the applicant I cannot find a statement of this type in the proposed summary of product market characteristics or the other parts of the varied marketing authorisation.

65 Thus, I find that the application for the SPC term extension filed by the applicant E I du Pont de Nemours has a number of irregularites. The examiner in his preliminary report allowed the applicant a period within which to rectify the irregularites with their application for an extension to SPC/GB/95/010 and set a deadline of 6 July 2009 for them to do so. For the reasons I have indicated above the problem identified by the examiner in relation to Article 8(1)(d)(i) remains with this application as does the additional problem in relation to Article 8(1)(d)(ii). The applicant still has a significant period of time left to rectify this irregularity before the deadline of 6 July 2009 set by the examiner expires. If they fail to do so, then as the examiner also indicated in his preliminary report, the application will be refused in accordance with Article 10(3) and 10(4).

Relevance of documents filed on 6 April 2009

66 On 6 April 2006, as final preparations were made for the issue of this decision, the applicant filed a further set of documents in relation to this application. While the applicant considers that the supporting documents already filed (see para 36 above) are sufficient for the grant of the extension applied for, as Hearing Officer, I considered that it is relevant to the issues in question for me to take account of these documents before issuing the decision.

67 This additional documents comprised;

a. A further e-mail dated 6 April 2009 from Ms Desiree Bergamin-Egenberger, Regulatory Project Leader and rapporteur at the CBG, the NL competent authority of the RMS dealing with this application. It is addressed to all her counterparts in other member states dealing with this MRP procedure. The email indicates that the end of the variation procedure has been reached (day 90) on 4 April 2009.

b. A copy of the agreed Summary of Product Characteristics (SmPC) and package leaflet information which indicates that losartan/COZAAR can be used to treat paediatric patients with hypertension but use in such patients with kidney impairment is not recommended (see section entitled '4.2 Posology and method of administration' of SmPC – page 3);

68 The email dated 6 April 2009 provides a number of further facts in relation to the application to obtain a varied MA in addition to those provided in the email from the same source dated 13 February 2009 (see para 43-45 above). These are;

(i) that comments have been received from other CMS in addition to those received already;

(ii) that the holder of the MA in NL, Merck, Sharpe & Dohme BV, has responded to the comments in the PVAR (see discussion in para 49 and 50 above); and that the CBG, the competent authority in of the RMS, considers that the proposed changes to the SmPC and the associated package leaflet are considered satisfactory and the variation procedure can be positively concluded;

(iii) as a consequence of (ii), the RMS requests that the CMS implement the changes to the SmPC, labelling and package leaflet information within 30 days after receipt of the translation form the applicant;

(iv) the applicant will send a translation of the final agreed SmPC, labelling and package leaflet information to each CMS in the relevant national language as soon as possible;

(v) the CMS are asked to complete the implementation within 30 days of receiving these translations because the "*company intends to submit a request for a reward in the form of a 6-month extension of the supplementary protection certificate*"; and

(vi) finally, the following statement should be included in the MA of losartan/COZAAR:

> "The development of this product has complied with all measures in the agreed paediatric investigation plan P/9/2008. For the purpose of the application of Article 45(3) of Regulation (EC) No 1901/2006, all studies in the agreed paediatric investigation plan P/9/2008 were completed after the entry into force of that Regulation. The Summary of Product Characteristics reflects the results of studies conducted in compliance with this agreed paediatric investigation plan".

69 These additional documents indicate that the RMS and the holder of the MA have agreed the final form of the updated, varied MA. The steps of the MRP necessary to produce an updated, varied MA to take account of the results and assessment of the studies conducted as part of the agreed completed PIP have now reached a stage where the RMS can confirm and recommend a varied MA for approval by all the CMS. The competent authority from the RMS has provided a suitable statement of compliance to be incorporated into each

updated, varied MA to be issued by the CMS. However, as the e-mail makes clear, this final step is still not complete. There is still also a possibility that a CMS may not agree with this recommendation from the RMS and that arbitration will be required. This cannot be discounted until each of the CMS have indicated their confirmation of the recommendation from the RMS or until the 30 day period for implementation has expired as any objection would need to be made before expiry of this period[4]. Before, the updated, varied MA is approved by the CMS, they each have to receive a translation of the changes to be included in the varied, updated MA in each of their national languages.

70 Thus, I consider that the conclusion I have reached above in relation to this application is still valid. The necessary statement of compliance, while it has been proposed by a relevant competent authority, has still not yet been incorporated into an updated, varied MA that is valid in the UK as required under Article 8(1)(d)(i) of the EEC Regulation 1768/92.

71 In addition, while approval in all EU member states has moved closer, it is still not completed. This is an explicit requirement of Article 8(1)(d)(ii) of the EEC Regulation 1768/92, and as discussed above (see para 52 above) where the MRP is being used to obtain an updated varied MA, the reward under Article 36 is available only if the product is authorized in all EU member states. The applicant has to file translations of the necessary changes with the competent authority is all EU member states and I am not aware that they have yet done so. Even, if I was aware that these translations had been filed, I consider that the requirement of Article 36(3) leaves me with little choice but to conclude that authorisation in all the EU member states must be confirmed before the six-month extension to the SPC can be granted (see para 58 above).

Appeal

72 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

ANNEX 1 to Decision concerning SPC/GB/95/010

List of Abbreviations used

	"the College ter Beoordeling van Geneesmiddele"
CBG	The competent authority for marketing authorizations in the Netherlands
CMS	Concerned Member State
CMPH	Committee on Medicinal Products for Human Use
EMEA	European Medicines Agency
EU	European Union
MA	Marketing Authorisation
MRP	Mutual Recognition Procedure
NL	The Netherlands
PVAR	Preliminary Variation Assessment report
PIP	Paediatric Implementation Plan
PDCO	Paediatric Committee
RMS	Reference member State
RTM	Registered Trade mark
SPC	Supplementary Protection Certificate
SmPC	Summary of Product Characteristics