BL O/146/12

02 April 2012

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

APPLICANT Astra Zeneca AB

ISSUE First relevant Marketing Authorisation for SPC/GB/09/059 under Article 3(d) and Duration of protection under Article 13

HEARING OFFICER Dr L Cullen

DECISION

Introduction

1. This decision relates to an application for a supplementary protection certificate (SPC) which was filed by AstraZeneca AB ("the applicant") on 11 December 2009 and accorded number SPC/GB09/059 ("the application"). The product for which an SPC is sought is Gefitinib, or a pharmaceutically acceptable salt thereof, and it is the active ingredient in the medicinal product marketed by the applicant under the name IRESSA[1]. IRESSA is a quinazoline derivative used in the treatment for non-small cell lung cancer.

2. The basic patent upon which the SPC application relies is EP(UK) 0823900 entitled "*Quinazoline derivatives*", which was filed on 23 April 1996, with a priority date of 27 April 1995, and was granted on 27 December 2000. The expiry date of this patent is 22 April 2016. The patent describes the synthesis of a group of quinazoline-based compounds which inhibit Class 1 receptor tyrosine kinases which are important in transmission of the biochemical signals that initiate cell replication. Such class I receptor kinases, which include the EGF (Epidermal Growth Factor) family of receptor tyrosine kinases, are often present in the common human cancers, e.g., breast, lung and colon cancer. Compounds which display such an inhibitory activity thus have anti-proliferative effects, which can be used to treat such cancers[2].

3. The European marketing authorisation (MA), EU/1/09/526/001, for the medicinal product IRESSA, supplied in support of the application, was granted on 24 June 2009 by European Commission Decision C(2009)5203. This MA is valid for the UK.

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[1] IRESSA is a Registered Trade Mark in the UK.

[2] See discussion in paragraphs [0002]-[0012] and [0053]-[0065] of basic patent EP(UK) 0823900 B1,

4. The applicants also referred to an earlier MA for IRESSA that was granted on 2 March 2004 in Liechtenstein, hereafter referred to as LI, through that state's regional legal arrangements with Switzerland, hereafter referred to as CH. This MA was granted by *SwissMedic,* the relevant national competent authority for Switzerland.

5. In their initial application form SP1 and accompanying letter, dated 10 December 2009, the applicants identified the European MA as the relevant MA for the purposes of Article 3(d) and Article 13.

The Examiner's view

6. The view of the examiner, first expressed in his examination report dated 24 January 2011, was that the MA granted by *SwissMedic* and thus valid in Liechtenstein, was deemed to be the first MA for medicinal product IRESSA in the European Community. This is because a marketing authorisation which has been granted by Switzerland is recognised or deemed valid in Liechtenstein through the bilateral arrangements in place between the two countries. Liechtenstein, unlike Switzerland, is a member state of the European Economic Area (EEA), and such an MA can serve as the earliest valid MA in the EEA for a medicinal product for the purposes of calculating the duration of a certificate under Article13 of the Regulation[3]. As a consequence, the duration of SPC protection will, using the algorithm in Article 13, run from 23 April 2016 until 1 March 2019 and not until 22 April 2021 based on the European MA, as claimed by the applicant.

7. In support of this view, the examiner cited the judgement of the Court of Justice of the European Union (CJEU) in combined cases C-207/03 and C-252/03, *Novartis and others*[3]. In further correspondence with the applicant, he also made reference to the Advocate-General's (AGs) Opinions in CJEU cases C-195/09, *Synthon v Merz,* and C-427/09, *Generics v Synaptech*.

The Applicant's view

8. The applicants have argued that the earlier authorisation valid in CH / LI should be disregarded for two reasons:

> (1) it was suspended by *SwissMedic* in November 2005; and
> (2) there was a further regulatory delay before a MA was granted by the EMA because the data supporting the CH / LI authorisation was insufficient to gain an authorisation from the European Medicines Agency (EMA)[4].

9. Following an interview held on 1 March 2011, the applicants maintained that the MA granted in CH should be disregarded, and that a teleological approach should be

[3] MAs granted in Switzerland can also have effect in Liechtenstein which is one of the EEA member states and thus may serve as the first MA valid in the Community, see joined cases C-207/03 and C-252/03, *Novartis and others,* see also footnote 6.

[4] The European Medicines Agency, EMA (sometimes also referred to as the EMEA), is the European agency that carries out the assessment of all applications for marketing approval for medicinal products valid for the whole of the territory of the European Community. The European Commission grants the marketing authorisation based on the recommendation of the EMA. For further details see http://www.ema.europa.eu/ema/index.jsp?curl=pages/home/Home_Page.jsp&mid=&jsenabled=true.

used to interpret the relevant European Community (EC) law – in this case regulation 469/2009[5] – to allow grant of the applied for SPC for the maximum period. This would result in an SPC that took effect on 23 April 2016 and ran until 22 April 2021, i.e., the maximum five year period allowed under Article 13. The applicants also provided evidence to support their assertion that the dossier that was approved in Switzerland did not meet the standards required by the EMA.

10. After a number of rounds of correspondence and, following the above mentioned interview with the applicants, the examiner still maintained his view that the earlier Swiss MA, which is valid in Liechtenstein, is the first relevant MA within the community for the purposes of calculating the duration of the SPC.

11. The applicant, in their letter dated 13 October 2011, provided further arguments, waived their previously expressed request for an oral hearing and requested that a decision be made based upon the papers on file.

12. I apologise for the delay in issuing this decision.

The Issue to be decided

13. The issue to be decided is thus: (a) what was the first relevant marketing authorisation granted within the EEA under Article 3(d); and, consequently, (b) what is the appropriate duration of protection under Article 13 of the SPC Regulation for a certificate granted in respect of this application.

The Relevant Law and its interpretation

14. Recitals 1-6, 9 and 10 of Council Regulation (EC) 469/2009 concerning the creation of a supplementary protection certificate for medicinal products ("the Regulation") state:

> '(1) Council Regulation (EEC) No 1768/92 of 18 June 1992 concerning the creation of a supplementary protection certificate for medicinal products [OJ 1992 L 182, p. 1] has been substantially amended several times. In the interests of clarity and rationality the said Regulation should be codified.
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> (2) Pharmaceutical research plays a decisive role in the continuing improvement in public health.
>
> (3) Medicinal products, especially those that are the result of long, costly research will not continue to be developed in the Community and in Europe unless they are covered by favourable rules that provide for sufficient protection to encourage such research.
>
> (4) At the moment, the period that elapses between the filing of an application for a patent for a new medicinal product and authorisation to place the medicinal product on the market

[5] Regulation (EC) No 469/2009 of the European Parliament and of the Council of 6 May 2009 concerning the Supplementary Protection Certificate for Medicinal Products, see OJ L 152, 16.6.2009, p 1. This regulation codified and superceded Regulation (EEC) No. 1768/92 concerning the creation of a Supplementary Protection Certificate for Medicinal Products (as also explained in para 14 of the decision).

["MA"] makes the period of effective protection under the patent insufficient to cover the investment put into the research.

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

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

…

(9) The duration of the protection granted by the certificate should be such as to provide adequate effective protection. For this purpose, the holder of both a patent and a certificate should be able to enjoy an overall maximum of 15 years of exclusivity from the time the medicinal product in question first obtains [MA] in the Community.

(10) 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.'

15. Article 2 of the Regulation defines the scope of the regulation (emphasis added) and reads:

> ***Any product protected by a patent in the territory of a Member State and subject, prior to being placed on the market as a medicinal product, to an administrative authorisation procedure as laid down in 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*** *or Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products may, under the terms and conditions provided for in this Regulation, be the subject of a certificate.*

16. Article 3 of the Regulation defines the conditions for obtaining a certificate (emphasis added) reads:

> *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 if 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"***

wherein "medicinal product" and "product" are defined in Article 1 of the Regulation as follows:

> *For the purposes of this Regulation:*
>
> *(a) 'medicinal product' means any substance or combination of substances presented for treating or preventing disease in human beings or animals and any substance or combination of substances which may be administered to human*

> *beings or animals with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in humans or in animals;*
>
> *(b) 'product' means the active ingredient or combination of active ingredients of a medicinal product;*
>
> *……*

17. Article 13 of the Regulation indicates how the duration of an SPC will be calculated as follows:

> 1. The certificate **shall take effect at the end of the lawful term of the basic patent for a period equal to the period which elapsed between the date on which the application for a basic patent was lodged and the date of the first authorisation to place the product on the market in the Community, reduced by a period of five years**.
>
> 2. Notwithstanding paragraph 1, the duration of the certificate may not exceed five years from the date on which it takes effect.
>
> …

18. Directive 2001/83/EC[6] as amended ("the Directive"), relating to medicinal products for human use, states at Article 6 (emphasis added):

> ***No medicinal product may be placed on the market of a Member State unless a marketing authorization has been issued by the competent authorities of that Member State in accordance with this Directive*** *or an authorization has been granted in accordance with Regulation (EEC) No 2309/93.*

19. The Court of Justice of the European Union (CJEU) in joined cases C-207/03 and C-252/03, *Novartis and others*[7], (hereafter *Novartis*) has considered the so-called '*Liechtenstein question'*. In this judgement, the court ruled

> *"In so far as an authorisation to place a medicinal product on the market issued by the Swiss authorities and automatically recognised by the Principality of Liechtenstein under that State's legislation is the first authorisation to place that product on the market in one of the States of the European Economic Area, it constitutes the first authorisation to place the product on the market within the meaning of Article 13 of Council Regulation (EEC) No 1768/92 of 18 June 1992 concerning the creation of a supplementary protection certificate for medicinal products, as it is to be read for the purposes of the application of the Agreement on the European Economic Area***."**

In doing so, the court acknowledged that MA's obtained in Liechtenstein may be obtained in one of two ways, either through an MA obtained in Switzerland, under

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[6] 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. This directive updates and replaces original Council Directive 65/65/EEC of 26 January 1965 which was the first directive to deal with such medicinal products.

[7] See paras 29-33 of joined cases C-207/03 and C-252/03, *Novartis and others*, also referred to in footnote 3.

Swiss technical regulations and standards, or through an MA obtained in Liechtenstein in accordance with the Directive. An MA awarded in Switzerland, and thus recognised in Liechtenstein, must be regarded as the first MA for the purposes of Article 13 of the Regulation. The court considered that this would be within the spirit of the Regulation with respect to the limitations on the period of exclusivity; if the MA issued by the Swiss did not constitute the first MA within the EEA then there would be the risk of exceeding the 15 years of exclusivity in the EEA (as referred to in recital 9 of the Regulation) due to the relationship of Switzerland with Liechtenstein.

20. The CJEU has also considered, in two recent decisions, what is the first relevant marketing authorisation for the purpose of granting an SPC. Both of these cases, C-195/07, *Synthon v Merz*, (hereafter *Synthon*), and C-427/09, *Generics v Synaptech*, (hereafter *Generics*), concerned products which were placed on the market in the Community on the basis of marketing authorisations issued by the respective national competent authorities. These national authorisation procedures were not in accordance with Directive 65/65 as they did not involve safety and efficacy testing as is required under this Directive[5] (see, in particular, paras 23-26 of *Synthon* and paras 19-26 & 28 of *Generics*). In both cases, the court found that a product, which was placed on the market in the Community as a medicinal product for human use before obtaining a marketing authorisation in accordance with Directive 65/65, and, in particular, without undergoing safety and efficacy testing, is not within the scope of Article 2 of Regulation No 1768/92 (now superceded by Regulation No. 469/2009) see footnote 4) and may not, therefore, be the subject of an SPC. Thus, in considering any request for an SPC for a product which has been authorised for human use in the Community based on a marketing authorisation issued by a national competent authority, it is necessary to confirm that this authorisation process involves similar safety and efficacy testing to that required under Directive 65/65 or it successors[5].

21. In Office decision *BL O/066/10*[8], this Hearing Officer considered the situation where the national competent authority in Switzerland, *SwissMedic*, and the EMA each granted a different MA based upon the same facts – the Swiss authorities granted a MA for a combination product whereas the EMA approved an MA for a single product even though the same data was provided by the applicant to both authorities. The MA approved by the EMA was determined to be the MA valid in the UK and therefore it was the one that would be taken into account for the purposes of Articles 3 and 13 of the Regulation. This conclusion was confirmed by the UK Court on appeal and was not part of the subsequent reference to the CJEU[9]. Thus, in considering the merits of MAs granted by the EMA and *SwissMedic*, it is possible that different conclusions may be reached by both authorities in relation to the same data.

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[8] Imclone Systems Inc & Aventis Holdings, IPO decision BL O/066/10, see http://www.ipo.gov.uk/pro-types/pro-patent/pro-p-os/p-challenge-decision-results-bl.htm?BL_Number=o%2F066%2F10&submit=Go+%BB.

[9] Yeda Research and Development Company Ltd v Comptroller General of Patents [2010] EWHC 1733 (Pat), see http://www.bailii.org/cgi-bin/markup.cgi?doc=/ew/cases/EWHC/Patents/2010/1733.html&query=title+(+yeda+)&method=boolean.

22. Finally, I note that the applicants request that a teleological approach be taken when construing the Regulation. I agree that the Regulation should be interpreted and applied in accordance with its underlying principles, but at the same time I cannot ignore the facts of the case and the precedent case law in this area.

Analysis and Argument

23. In the applicants' view, the purpose of the SPC Regulation is based on two assumptions:
    (i) that the EU regulatory process leading to the grant of the first MA is lengthy and burdensome, and
    (ii) that the grant of the first MA enables the patent holder to start and continue to see a return on his investment.

24. The applicants argue that the fact that the Swiss MA was granted on the basis of a dossier that was not considered to be sufficient by the EMA demonstrates how the route within the EU was more burdensome that the route in Switzerland. In addition they received no financial return in the EU from the approval of IRESSA by *SwissMedic* in 2004 up to the EMA approval in 2009. Moreover, significant further investment was required before IRESSA could enjoy access to the EU market. In their arguments they referred to the aims of the Regulation, and, in particular, recitals 4 and 9 of the Regulation (see above). They argue that the purpose of the Regulation is to allow the patent holder to obtain a return on their investment despite the "lengthy and burdensome" EU regulatory process leading to the grant of the first MA. In their view, what is essential is that the applicant has to be able to start and continue to see a return on their investment. If for some reason the applicant is not able to continue to enjoy a return on their investment – for example, because the MA is suspended (as in this case) – this is not fulfilling the overriding purpose of the regulation. In effect, they appear to be arguing that it is only the first MA which is granted and remains in force that is relevant for the purposes of determining the first relevant MA in the community and so calculating the duration of the MA. Thus, if the marketing authorisation valid in CH / LI is considered to be the first valid authorisation in the EEA, it leads to a situation with IRESSA that, in their opinion, frustrates the overall purpose of the SPC regulation.

25. I do not disagree that the purpose of an SPC is to allow a return on a patent holders' investment, and that in order to do so the patent holder must be able to market his product within the European Community (EC), and therefore a valid MA must be in effect. I acknowledge that the applicants could not begin to see a return on their investment into IRESSA in the EC until after the MA was approved by the EMA in 2009. However, the issue in this case is not whether the applicant is able to gain a return on their investment in IRESSA, clearly they are, as the medicinal product is approved for human use in the EC, it is rather, how long a period of exclusive protection can the applicant have to do so based on the duration of the SPC. If the MA granted by *SwissMedic* on 2 March 2004 was the first authorisation to place the IRESSA on the market in the EC for the purposes of Article 13 of the Regulation this period of exclusivity will be shorter than if the MA approved by the EMA on 26 June 2009 is considered to be the first authorisation to place the IRESSA on the market in

the EC for the purposes of Article 13. I therefore need to look closely at whether IRESSA was lawfully placed on the market in the EC, as a result of a valid MA granted in Switzerland.

26. The applicants have not disputed that IRESSA was placed on the market in Switzerland following the granting of the MA in March 2004. They have also acknowledged that, following this approval in Switzerland, IRESSA could have been marketed in Liechtenstein, although to their knowledge, sales within Liechtenstein were non-existent. However, they consider that whilst the Swiss MA allowed IRESSA to be lawfully marketed in Liechtenstein for a short period of time, the fact that it was subsequently suspended was of clear relevance.

27. In his report of 24 January 2011, the examiner noted that the fact that an authorisation may be suspended or withdrawn is recognised in the Regulation and this does not negate its role in satisfying the conditions for obtaining a certificate or determining its term. He then goes on to state that as Article 3(b) refers to a valid authorisation that "has been granted", this means that it need not be in force at the time of application, and this has the consequent effect that Article 4 must be construed as allowing for the circumstances where an authorisation is suspended or withdrawn and the corresponding SPC will also be suspended. Indeed Article 14 sets out provisions for just such circumstances. Similarly a provisional authorisation for a plant protection product, which itself may be subject to suspension or expiry, is deemed to satisfy the corresponding requirements under Article 3(1)(b) and, as a result, Article 3(1)(d), of the Plant Protection Product SPC regulation[10] as set out by the CJEU in case C-229/09, *Hogans Lovell*[11]. Accordingly, the examiner considered that periods of suspension of an authorisation are not material in determining the relevant authorisation indicated in Article 8(1)(a)(iv) and 13.

28. I agree with this view in so far as it goes. Clearly, in order to obtain an SPC valid in the UK, the applicant must specify a MA valid in the UK, as required by Article 3(b) and 8(1)(a)(iv). If this MA is subsequently suspended the SPC will lapse, as indicated by Article 14. The applicant also has to identify the first MA for the medicinal product granted in the Community if it is not the same as the MA identified for the purposes of Article 3(b), as required by Article 8(1)(c). This may be a MA granted by a national competent body or one granted by the EMA. It is the date that this latter MA came into force which is required for calculating the duration of the SPC under Article 13. The key fact here is the date on which the first MA in the Community was granted. I do not consider that it is necessary that this first MA must still be in force, it may well have expired or it may no longer be in effect. The purpose of this condition of the Regulation is to ensure that the protection provided to the applicant does not exceed the maximum of 15 years from the date of the grant of the first marketing authorisation in the Community as referred to in recital 9 of the Regulation. This was a significant factor for the CJEU in its decision in *Novartis*[12]. Ensuring that this condition was not breeched was also an important part of the

[10] Regulation (EC) 1610/96 of the European Parliament and of the Council of 23 July 1996 concerning the creation of a supplementary protection certificate for plant protection productss

[11] Case C-229/09, *Hogan Lovells International LLP v Bayer CropScience AG*

[12] see para 31 (and footnotes 3 and 6).

consideration by the CJEU in case C-482/07, *AHP*[13]. In the present case, the applicant argues that this latter point is not relevant because, irrespective of which MA is used to calculate the duration of the SPC, the maximum duration of protection will still be less than 15 years after grant of the MA (see letter from the applicant dated 22 March 2011). The applicant proposes that the teleological approach requires that the duration of the SPC is calculated on the basis of the EMA authorisation so that they have the maximum period possible to gain the return on their investment. The applicant considers that this approach is consistent with the regulation because the dossier used to grant the MA in Switzerland, which was subsequently suspended, was not the same dossier as that used to gain approval from the EMA. It did not contain the same quantity & quality of results and was not for the same specific use, also referred to by the applicant as indication or label.

29. As mentioned above, the authoritative case law in this area is *Novartis*, and the applicants have attempted to distinguish the facts of the present case from those in *Novartis* and maintain that the MA granted in Switzerland was not valid as the first MA in the EEA. Their arguments are based upon two observations:

    (1) In order for it to be a valid authorisation it will need to have been issued in accordance with Directive 2001/83/EC, and

    (2) a teleological approach should be used to interpret and apply EC law, and therefore the purpose of an SPC was to allow the patent holder to see a return on their investment.

    In this case, the MA approved by the EMA should be used because this is the only MA, of two under discussion in this case, that allowed the applicant to begin and, more importantly, continue to see a return on their investment.

30. The applicants have sought to distinguish the facts of the present application from those presented in *Novartis*. They contend that, in *Novartis*, the same product dossier was submitted to, and accepted by both *SwissMedic* and the EMA. However, in the present application, the dossier that was ultimately accepted by the EMA differed from that accepted by *SwissMedic* in 2004, and therefore the MAs in the EU and Switzerland were granted on different facts. They argued that the data provided for the MA application for IRESSA in Switzerland was not sufficient to support an MA application for IRESSA in the EU, and that it was not until further data was gathered that there was enough information regarding the efficacy of IRESSA to permit the granting of an MA by the EMA.

    Marketing Authorisation History for IRESSA

31. Given the significance which the applicant attaches to the differences between the *SwissMedic* and EMA approach, I have examined in detail the papers on file which relate to the marketing authorisation history for IRESSA. The applicant has outlined a timeline of the marketing authorisation history and I have summarised this information in Table 1 below. This is discussed in more detail in the following paragraphs.

[13] see para 39-42 .

SwissMedic Marketing Authorisation

32. The application for an authorisation to market IRESSA was submitted to *SwissMedic* on 2 March 2004[14]. The medicinal product was indicated for adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with progression after at least two rounds of chemotherapy. This was based upon the data obtained from two Phase II studies that showed an association with tumour shrinkage and that the drugs were generally well tolerated. The MA was granted by *SwissMedic* as it was "*deemed to meet an unmet medical need*" on the condition that a number of post-MA studies, including data from the Phase III ISEL clinical trial, were submitted. I particularly note this latter point – *SwissMedic* deemed that further work was necessary to maintain or confirm the authorisation.

33. The first Phase III clinical study (the ISEL trial) showed that the increase in survival rate was statistically insignificant. The Swiss MA was suspended by *SwissMedic* because the clinical trial data and availability of other treatment options no longer justified IRESSA's broad use as a third line therapy in patients with NSCLC (see applicants letter dated 10 December 2009). However, the data did show that individual patents benefit from IRESSA. The suspension was put in place until the applicant was able to properly identify the patient population that would respond to IRESSA, and they were able to put in place a validated test method for identifying this patient population[15].

34. The applicant has stated, in their letter of 10 December 2009, that even before the suspension of this MA in Switzerland, sales in Liechtenstein, i.e. within the EEA, were "*non-existent*". Data for sales in Switzerland and Liechtenstein combined is only available. Although they do not have separate data for sales in Liechtenstein, the applicant indicates that it can be confirmed that no packs containing IRESSA were delivered by the applicant to Liechtenstein in the period before suspension of the MA (March 2004 to November 2005). While it cannot be excluded entirely that no packs containing IRESSA were delivered by a wholesaler to Liechtenstein, this does appear to be very unlikely, in the applicants view. Since the suspension of the MA by *SwissMedic*, all requests to use IRESSA must be approved individually by *SwissMedic* and the medicinal product is delivered directly to the treating physician. The applicant has received no requests to deliver IRESSA to patients in Liechtenstein. Thus, the applicant suggests that it is not very likely that there were sales of IRESSA in Liechtenstein before suspension. This appears to me to be on the basis that requests for continued treatment would have had to be made directly to the appropriate approval authority in Switzerland or Liechtenstein.

35. I can accept this argument only so far. The key question for me is - was IRESSA lawfully available in Liechtenstein? If so, it could be purchased or used, even if, in fact, it was not. The product must first be available for sale and use before it can be bought and used and there may be a little time between the two. However, in this

[14] I note that the *SwissMedic* application was originally in German; I have based my assessment upon the English translation provided by the applicant (which I acknowledge with gratitude).

[15] Even though the *SwissMedic* MA was suspended, as of December 2009, IRESSA was available in Switzerland for patients already benefitting from it or with no alternative treatment options under a special permit for compassionate use (see letter from applicant dated 10 December 2009).

day and age, it is normal for a company who is providing a new medical treatment to promote it and encourage its use as soon as possible after marketing approval is gained in the respective market. The applicant has not indicated that no resources were devoted to promoting the product after its approval, for example, amongst medical practitioners. It appears to me that the applicant can only be certain regarding the situation after suspension of the MA in Switzerland and not while it was in force. However, while I am prepared to accept that the applicant is in a position to know if IRESSA was supplied directly by it to Switzerland and Liechtenstein, I am not sure if it is possible to exclude the possibility that IRESSA was made available via an indirect source, such as a wholesaler. I do not think that it is possible to exclude the possibility that IRESSA was not used by patients in Liechtenstein in the 20 months between approval and suspension of the MA by *SwissMedic.* I note that at this time, unlike the situation today, an approval in Switzerland automatically provided approval in Liechtenstein, so that the medicinal product could be used without delay in Liechtenstein[16] for all of this period. It is not clear to me that a request for treatment of patients in Liechtenstein post the suspension would be made to *SwissMedic* but I accept that I do not know enough about the procedures and arrangements in place in CH and LI to be certain one way of another.

EMA Marketing Authorisation

36. The applicants argue that the EMA assessors were not sufficiently convinced by the Phase II data, which was the basis of the approval by *SwissMedic,* to approve an MA on that basis alone. Instead, they granted an extension to the time period for evaluating the application, a so-called clock-stop, to allow the results from the first Phase III study – the ISEL trial – to be submitted. The applicants withdrew the MA application to the EMA in January 2005 after discussions with the rapporteurs for the Committee for Medicinal Products for Human Use (CHMP)[17] and the EMA. The applicant concluded that the EMA did not consider that the results available would meet the approval requirements for a MA.

37. The MA application was re-submitted in May 2008 including further results from the second Phase III study which indicated that IRESSA was effective in treating adult patients with NSCLC who needed further chemotherapy and had already received platinum-based chemotherapy. This prompted additional questions from the CHMP rapporteurs, which resulted in the submission by the applicant of the results of a third Phase III study in June 2009. This indicated that the patients with NSCLC that respond to IRESSA had activating mutations of the EGFR-TK domain[18]. The EMA

[16] Since 2006, the so called 'negative list' procedure has been in force for marketing authorisations in Switzerland and Liechtenstein, which means that medicinal products approved in Switzerland may not be approved for use in Liechtenstein until up to 12 months later.

[17] The Committee for Medicinal Products for Human Use (CHMP) is responsible for preparing opinions for the European Medicines Agency on all questions concerning medicines for human use. The opinions are prepared by members of the committee acting as rapporteurs, for further details see http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000094.jsp&mid=WC0b01ac0580028c79&jsenabled=true.

[18] EGFR-TK = Epidermal Growth Factor Receptor – Tyrosine Kinase domain, see Section 5.1 of the EU marketing authorisation EU/1/09/526/001 for further details

Table 1: The marketing authorisation history for Gefitinib / IRESSA at *SwissMedic* and at EMA

	Date	***MA***	***Data***	***Indication applied for***	***Outcome***
SWISSMEDIC	*March 2004*	MA application to *SwissMedic*	2 x Phase II IDEAL clinical trial results	(1) Use as 3rd line therapy (i.e. after 2 rounds of chemotherapy) to treat adults with non-small cell lung cancer (=NSCLC)	MA Granted 2 March 2004 – meets an unmet medicinal need; Phase III clinical trial to be completed. *IRESSA* available in CH and LI
	November 2005	*SwissMedic* suspend MA	Phase III clinical trial #1(ISEL trial)		MA suspended 25 November 2005 as Phase III data shows that increased survival rate is statistically insignificant
	July 2008	AZ apply to lift MA suspension at *SwissMedic*	Phase III clinical trial #2 (INTEREST trial)	(2) Treatment of NSCLC in patients who have already received chemotherapy	IRESSA found to be more effective than docetaxel.
	July 2009	AZ response to questions from *SwissMedic*	Phase III clinical trial #3 (IPASS trial)	As (2) but, in addition, as 1st line therapy for NSCLC in patients who have activating mutations of the EGFR-TK	Decision awaited
EMA	*February 2003*	MA application to EMA	2 x Phase II IDEAL clinical trial results	(1) Treatment of NSCLC in patients who have already received platinum - containing and docetaxel chemotherapy	Data not sufficient to approve MA. Clock on application stopped to wait for Phase III clinical trial results
	January 2005	AZ withdraw application to EMA	Phase III clinical trial #1(ISEL trial)		MA withdrawn by AZ after consultation with CHMP at EMA
	May 2008	AZ resubmit MA application to EMA	Phase III clinical trial #2 (INTEREST trial)	(2) Treatment of NSCLC in adults who have already received platinum chemotherapy	IRESSA found to be more effective than docetaxel in terms of improving survival rates
	November 2008	AZ response to questions from CHMP	Phase III clinical trial #3 (IPASS trial)	(3) Treatment of NSCLC in adults who have activating mutations of the EGFR-TK	
	26 June 2009		3 x Phase III Clinical trials completed		EMA grant MA

approved the marketing authorisation on the basis of all this data (i.e., all the phase II and phase III clinical data) which was granted in June 2009.

38. The applicant considers that the MA approved by the EMA in June 2009 thus required two additional phase III trials which added another 4.5 years to the time to gain approval after the applicant decided the withdraw the application to the EMA. The decision to withdraw the application from the EMA in January 2005 was based on the same data – the results from the first phase III (ISEL) clinical trial - that prompted *SwissMedic* to suspend the MA (they had previously granted) in November 2005. Thus, in their view, the approvals granted by both authorities are thus based on different sets of regulatory data and are for different indications (i.e. specific uses) in the treatment of NSCLC. The EMA approval required a more extensive set of data, and hence was more expensive and time-consuming to obtain.

39. Having reviewed, in depth, the correspondence on file, I find that I am not persuaded by the argument from the applicant that the approval granted by *SwissMedic* was based on a dossier that was not considered sufficient by the EMA. This is, in my view, not the whole story and is an over simplification of the situation. On the assumption that all bodies responsible for approving medicinal products for human use are interested in approving as many of such products as possible that are safe, reliable and effective, I consider that when a body responsible for approving medicinal products is presented with an application for approval which contains a collection of regulatory data, it has two choices. In the first instance, it can approve the product subject to further data to confirm the approval. On this basis, the product is made available for use while this further data is collected. When this data is submitted, depending on the results, this may lead to confirmation or not of the approval. In the second instance, the body responsible for approving medicinal products can indicate, through discussion with the applicant, that approval is unlikely based on the regulatory data provided and that further additional data is likely required. On this basis, the applicant can decide to withdraw the application, collect the further data necessary and then re-submit the application at a later date. Both of these approaches, avoid the authorisation from being refused, and will lead to the applicant having to do additional work to obtain their approval but this is entirely consistent with the overall goal which, as Directive 2001/83/EC indicates[19], is to demonstrate that the potential risks are outweighed by the therapeutic efficacy of the product.

40. It is my view that the same set of regulatory data was submitted initially to the EMA (in February 2003) and to *SwissMedic* (in March 2004). When presented with this data, each of these authorisation bodies had a choice to make if they considered that the data for IRESSA was promising but not sufficient to be approved without reservation. The first choice would be to approve the product for use subject to the completion of additional studies – which was the choice taken by *SwissMedic* – or, the second choice, would be to indicate, through discussion between the applicant and the CHMP assessors, that the evidence was not yet sufficient to gain approval and further studies were required – this was the choice taken by EMA. In response to the latter, the applicant chose to withdraw the application so that it could be resubmitted with additional data at a later date. I note that the *SwissMedic* approval

[19] see, especially recital (7) and also recitals (2), (6), (11)-(15), (35), (39), (40), (53) and (54).

indicated that the approval was made on the basis that IRESSA was "*deemed to meet an unmet medical need*" and so they were prepared to authorise its use in CH while further studies were carried out.

41. Furthermore, I note that the additional Phase III clinical data, collected by the applicant (which provided the basis for the approval by the EMA in June 2009), has also been submitted by the applicant to *SwissMedic* in an effort to lift the suspension of that MA. Thus, it appears to me that the same data is being used by the applicant to gain the approval from the EMA and to re-activate the authorisation granted by *SwissMedic*.

42. I also find it hard to agree with the applicant when he argues that the indication or label, i.e., the specific use, approved by *SwissMedic* is different to that which has been approved by EMA. The original label approved by *SwissMedic* was subject to confirmation, as I have indicated above, which was not forthcoming and the basis of the suspension was that the applicant needed to better identify the population that would benefit from this treatment. This situation is in my view very similar to the one that arose with the EMA, where the discussions between the applicant and the CHMP rapporteurs indicated that the types of patients who would benefit from treatment with this medicinal product needed to be more clearly identified, the so-called personalised medicine approach (based in EGFR screening) referred to by the applicant in their letter of 10 December 2009. From a consideration of the marketing approval history provided by the applicant in the letter of 10 December 2009, I note that the indication approved in the European MA is:

> "*IRESSA is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating mutations of EGFR-TK (see section 5.1)*."

This appears to me to answer exactly the question raised by *SwissMedic* when the MA was suspended until a clearer identification of the patients who would benefit from the treatment (as mentioned above) was provided. I accept that this indication is different, in that it is more specific in terms of relevant patient population, than that approved by *SwissMedic* on 2 March 2004 (subject to additional information), i.e:

> *"IRESSA is indicated as third line therapy in patients with locally advanced and metastatic Non-Small-Cell Lung Cancer (=NSCLC) who show a progression of the disease after receiving at least two chemotherapies."*

Thus, the result with *SwissMedic* was an approval and subsequent suspension while further data was required and the result with the EMA was no approval likely until further data was provided and when this was done, approval was forthcoming. The issue of concern to the applicant is one of time. They consider that they are being penalised unfairly if the date of the MA valid in CH / LI is used because the application at that stage was *de-facto* too early and needed more work before approval. However, this would appear to be the benefit of hindsight given what has happened since the applicant made the initial application to *SwissMedic*.

Was the authorisation in Switzerland compliant with Directive 2001/83/EC?

43. In their letter of 22 March 2011, the applicants note that according to Article 3(b) of the Regulation, the MA must be compliant with Directive 2001/83/EC[5]. They refer to the decision of CJEU in case C-127/00, *Hassle*, in this regard also[20]. They expand on this later in that letter, where they attempt to distinguish the facts of the present case from the facts presented in *Novartis*.

44. I note that the correspondence between the examiner and the applicant which refers to the question of compliance with Directive 2001/83/EC was based on the AG Opinions in the *Synthon* and *Generics* cases and the CJEU decisions in these cases were not delivered until July 2011 shortly before the applicant's final letter dated 13 October 2011. In this latest response, the Applicant pointed out that these two cases were decided on the basis of a failure under Article 2 and not on the basis of Article 13 as proposed by the referring UK courts. The CJEU found that if products were placed on the market in the EU on the basis of a procedure that did not meet the requirements of Directive 65/65/EEC in terms of testing of safety & efficacy, they were outside the scope of the Regulation and thus were not entitled to SPC protection at all. Thus, I agree that these cases are not relevant for the purpose of deciding the present case. The procedure used by Switzerland to approve medicinal products in Switzerland and consequently in Liechtenstein is deemed to be compliant with Directive 65/65/EEC (and its successor directives including Directive 2001/83/EC)[21].

45. The applicant argues that, in *Novartis,* the factual situation was different because the dossiers approved by *SwissMedic* and the EMA, in that case, were for the same label and supported by the same regulatory data. As such the MA granted by *SwissMedic* would inherently have been Directive 2001/83/EC compliant. The applicants state that this was not the case for IRESSA because the dossiers approved by *SwissMedic* and the EMA in this instance were not for the same label and were not supported by the same regulatory data. Thus, they consider that the MA granted in Switzerland for IRESSA was not Directive 2001/83/EC compliant. I take this to mean that they consider that the approval granted by *SwissMedic* did not apply the same high threshold in determining the benefits v risks ratio as the EMA. I think this argument does not take sufficient account of the fact that *SwissMedic* was not unconditional and the treatment was approved on the basis of an "*unmet medical need*". However, I do note that the EMA did not take the same view based on the same data.

46. As indicated above, I do not consider that the differences between the facts of the present case and those in *Novartis* are as significant as the applicant has argued and so provide the basis to ignore the existence of the earlier MA valid in LI for the

[20] See para 58 of case C-127/00, *Hassle AB v Ratiopharm GmbH*

[21] see paras 5 and 11 of CJEU decision, C-207/03 & C-252/03, *Novartis & others*. Para 5, quoting from the relevant part of the EEA agreement, confirms that for the purposes of Article 3(b) and those other articles in the Regulation that refer to Article 3(b): "*an authorisation to place the product on the market granted in accordance with the national legislation of the EFTA State shall be treated as an authorisation granted in accordance with Directive 65/65/EEC …"*

purposes of Article 13. *Novartis* in my view makes clear that the arrangements put in place in LI and CH on the basis of the regional arrangements between these two states to authorise medicinal products are equally valid in legal terms as approvals made in LI directly under Directive 65/65/EEC[22]. The decision also indicates (as mentioned above) that LI may apply Swiss technical regulations and standards deriving from its regional union in relation to products covered by the Regulation[23]. All this indicates to me that *Novartis* confirms the relevance of MAs issued by *SwissMedic* for the purposes of Article 13 of the Regulation because of their validity in LI.

47. In my view, one cannot ignore the legal interpretation of the Regulation applied by the Court in that case. The question asked in *Novartis* is clear: is the date of granting of an MA in Switzerland the first authorisation to place a medicinal product on the market for the purpose of Article 13 of the Regulation? The CJEU determined that such an MA is a valid one from a legal point of view to be regarded as the first relevant MA in the EEA for the purposes of Article 13. Once granted by *SwissMedic* it is a relevant MA when recognised in Liechtenstein. Thus I do not consider that an argument based on showing that the decision to grant this MA was not on the same standard or basis as the grant of the MA for the EC, while an interesting one, is not a fruitful one in this instance. Therefore, in view of *Novartis*, if the first authorisation granted on a medicinal product was granted in Switzerland and was recognised in Liechtenstein, then for the proper application of EC law in this area, this MA is considered to be the first MA granted within the EEA.

48. The examiner has referred to para 49 of the AG opinion on this case as also supporting this view (see official examination report dated 24 January 2011) because it suggests that the actual material on which the authorisation is based is not the decisive issue, it is the actual date that the authorisation takes effect. The subsequent court judgement in this case, does, in my view, endorse this analysis although this specific paragraph is not referred to explicitly in the judgement.

49. As I referred to briefly above, in reaching their conclusion, the CJEU was concerned with the underlying principal of the Regulation that the maximum period of exclusivity must be 15 years from the grant of the MA. It concluded that if an MA granted in Switzerland and automatically recognised in Liechtenstein, was precluded from being the first relevant MA then the duration of an SPC would have to be calculated from a subsequent authorisation in the EEA and this could result in the 15 year exclusivity period being exceeded in the EEA. This would be contrary to the Regulation. Consequently, if the first MA is granted in Switzerland, and recognised by Liechtenstein, then that is the first valid authorisation to place the product on the market.

50. In this context, the key for the applicant is that this Swiss MA valid in LI was suspended after 20 months and the medicinal product IRESSA could no longer be marketed directly in CH or, by analogy, in LI. The applicant could no longer, following the suspension of the MA, place IRESSA on the market in either country. As such, the medicinal product was no longer legally available in LI. The applicant

[22] see para 28-30 of CJEU decision, C-207/03 & C-252/03, *Novartis & others.*

[23] see para 11 of CJEU decision, C-207/03 & C-252/03, *Novartis & others*

considers that the appropriate first MA in the EEA must be an MA which allows the applicant to start and continue to see a return on its investment. In their opinion, the Court in Novartis (or the AG in his Opinion on this case) did not contemplate the situation, such as the one that has occurred in the present application, where the product authorised is only legally available on a temporary basis and its availability is negated by subsequent events.

51. I do appreciate the situation that the applicant has found themself in and I do have some sympathy with their situation. They have had to commit more time and resources to gain approval and find themselves in a situation where, in their view, they are being unfairly limited in their opportunity to recover the investment they have already made to meet the regulatory requirements. It is clear that in the period between November 2005 and June 2009, the applicant was not able to market IRESSA in the European Community as the EMA approval process was still on-going and was only able to make IRESSA available on an a very limited individual need basis (each to be approved by *SwissMedic*) following the suspension of the MA in CH. They needed to spend time and money to complete additional clinical work in this period in order to gain approval from the EMA. As mentioned already, if the duration of the SPC was calculated on the basis of the European MA, the 15 year maximum exclusivity period would not be exceeded. Also, I note that the additional period of protection available on this basis would not compensate for all of the time-delay experienced by the applicant.

52. Although in this case, the applicants proposed approach would not lead to a period of protection that would exceed the maximum of 15 years[24] allowed under the Regulation, I am not confident that I can simply ignore the existence of the earlier MA valid in LI because the calculation works out on the right side of the limit in this situation. I think it is just as easy to conceive of an example where this would not be the case.

53. As a result, I find that, in dealing with this SPC application, I am not able to set aside the decision in *Novartis* and so cannot avoid taking its conclusion into account when determining the duration of the SPC. The earlier MA granted for IRESSA that is valid in Liechtenstein is relevant in my view as it did make IRESSA legally available in the EEA after 2 March 2004. Although, this MA was subsequently suspended in Switzerland in November 2005, I find that IRESSA was approved for use and legally available on the market in Liechtenstein for at least the 20 month period March 2004 to November 2005.

Conclusion

54. Taking account of all of the above, I find that I must conclude that the marketing authorisation for the medicinal product IRESSA, granted in Switzerland on 2 March 2004, was, due to the regional relationship between both states, a valid authorisation to place the product on the market in Liechtenstein.

[24] This does not take into account the additional 6 months extension to this period of exclusivity now available under Regulation EC/1901/2006 on medicinal products for paediatric use.

55. Given that Liechtenstein is a member state of the EEA, this marketing authorisation is the first authorisation valid within the EEA for the purposes of determining the duration of an SPC under Article 13 of the Regulation.

56. As a consequence, I find that the expiry date, under Article 13, for SPC application SPC/GB/09/059 for Gefitinib, the active ingredient in the medicinal product IRESSA, is 1 March 2019.

57. I remit the application back to the examiner to make the necessary arrangements to grant the SPC in light of the earlier marketing authorisation valid in Liechtenstein.

Appeal

58. 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