**STEPS TAKEN AFTER GRANTING THE MARKETING AUTHORISATION**

For procedures finalised after 1 September 2004 please refer to module 8B

- On 12 November 1996, SmithKline Beecham plc submitted to the EMEA an application for a Type II variation in accordance with Article 6 of Commission Regulation (EC) No. 542/95 of 10 March 1995. The scope of the variation was related to the introduction of an additional package size of 1 vial of 5 ml in a cardboard carton. The CPMP during their meeting on 16-18 December 1996 issued a positive Opinion for this Type II variation. The CPMP Opinion was forwarded, in all official languages of the European Union, to the European Commission, which adopted the corresponding Decision on 15 April 1997. This variation required amendments to relevant sections of the previous Commission Decision and the EPAR.
- On 13 August 1997, the Marketing Authorisation Holder submitted a Type I variation in accordance with Commission Regulation (EC) No. 542/95. This variation related to the batch size of the finished product. On 18 September 1997, the EMEA approved this variation, which did not require an amendment to the Commission Decision.
- Following fulfilment by the Marketing Authorisation Holder of pharmaceutical follow-up measures, as agreed by the CPMP during their meeting on 22-25 September 1997, relevant changes to section III.2 of the EPAR have been made.
- On 16 October 1998 the Marketing Authorisation Holder submitted to the EMEA an applications for a Type I variation in accordance with Commission Regulation (EC) No. 542/95 of 10 March 1995, as amended. The scope of the variation was to extend the shelf life. On 20 November 1998, the EMEA approved the variation. The variation required amendments to the Annex I (Summary of Product Characteristics) of the Commission Decision. The European Commission amended the Decision on 27 January 1999.
- On 26 October 1998, the Marketing Authorisation Holder submitted a Type I variation in accordance with Commission Regulation (EC) No. 542/95 of 10 March 1995, as amended. This variation related to a change in specifications of the active substance. On 27 November 1998, the EMEA approved this variation, which did not require an amendment to the Commission Decision.
- On 9 November 1998, the Marketing Authorisation Holder submitted to the EMEA an application for a Type II variation relating to section 4.8 Undesirable effects as well as for the amendment of details in accordance with the updated EMEA/QRD template for product information. The Package Leaflet was amended in line with the SPC. The CPMP, during its December plenary meeting, considered the changes acceptable, and adopted on 17 December 1998 a favourable opinion on the Type II variation. The corresponding Commission Decision was issued on 26 April 1999.
- In accordance with Article 10(3) of Council Directive 92/27 EEC of 31 March 1992, the EMEA issued on 12 April 1999 a Notification for amendments of the addresses of the local representatives included in the package leaflet as applied by the Marketing Authorisation Holder. The Commission amended the Commission Decision on 1 July 1999.
- On 9 April 1999, the Marketing Authorisation Holder submitted two Types I variations in accordance with Commission Regulation (EC) No. 542/95 of 10 March 1995, as amended. One of these variations related to a change in manufacture of the medicinal product and the other related to a change in the specifications of the medicinal product. On 7 May 1999, the EMEA approved the two variations, none of which required an amendment to the Commission Decision.
- On 9 July 1999, the Marketing Authorisation Holder submitted to the EMEA an application for a Type II variation relating to an additional presentation of an already authorised strength. The presentations applied for are a 1 mg vial in packs of 1 vial and 5 vials. The CPMP, during its October plenary meeting, considered the presentation acceptable, and adopted on 21 October

1999 a favourable opinion on the Type II variation. The variation required amendments to the Annex I (Summary of Product Characteristics) and Annex III (Labelling and Package Leaflet) of the Commission Decision. The European Commission amended the Decision on 16 March 2000.

- On 1 October 1999, the Marketing Authorisation Holder submitted one Type I variation in accordance with Commission Regulation (EC) No. 542/95 of 10 March 1995, as amended. This variation related to a change in the name and/or address of the Marketing Authorisation Holder. On 19 October 1999, the EMEA approved the variation, which required amendments to annexes I, IIIA and IIIB of the Commission Decision. The European Commission amended the Decision on 22 February 2000.
- In accordance with Article 10(3) of Council Directive 92/27 EEC of 31 March 1992, the EMEA issued on 19 October 1999 a Notification for amendments of the addresses of the local representatives included in the package leaflet as applied by the Marketing Authorisation Holder. The Commission amended the Commission Decision on 22 February 2000.
- On 20 December 1999, the Marketing Authorisation Holder submitted one Type I variation in accordance with Commission Regulation (EC) No. 542/95 of 10 March 1995, as amended. This variation related to a change in in-process controls applied during the manufacturing of the product. On 20 January 2000, the EMEA approved the variation, which did not require an amendment to the Commission Decision.
- On 17 April 2000, the Marketing Authorisation Holder submitted one Type I variation in accordance with Commission Regulation (EC) No. 542/95 of 10 March 1995, as amended. This variation related to a change in in-process controls applied during the manufacturing of the product. On 10 May 2000 EMEA approved the variation, which did not require an amendment to the Commission Decision.
- In accordance with Article 10(3) of Council Directive 92/27 EEC of 31 March 1992, the EMEA issued on the 7 July 2000 and 3 August 2000 a Notification for amendments of the addresses of the local representatives included in the package leaflet as applied by the Marketing Authorisation Holder. The Commission amended the Commission Decision for both notifications on the 25 September 2000.

Subsequent post Marketing Authorisation applications agreed upon are summarised in the table below:

| Scope | Application number | Type of modification[1] | Notification/ Opinion issued on[2] | Commission Decision Issued/amended on |
|---|---|---|---|---|
| Update of the Summary of Product Characteristics on the risk and benefits of prolonged use | II/17 | II | 14.12.00 | 20.03.01 |
| Update of the Summay of Product Characteristics Section 4.8 following the assessment of the 6th PSUR | II/18 | II | | 13.09.01 |
| Change in test procedure of active substance | I/19 | I | 07.06.01 | 05.07.01 |
| Changes to comply with supplements to pharmacopoeias | I/20 | I | 22.06.01 | 05.07.01 |
| 5-year renewal of the Marketing Authorisation | R/21 | R | | 04.02.02 |
| Update of the Summay of Product Characteristics Sections 4.5, 4.8 | II/22 | II | 25.04.02 | 30.07.02 |
| Change in the name of the marketing authorisation holder | I/23 | I | 24.05.02 | 30.07.02 |
| Change in the address of the marketing authorisation holder | I/24 | I | 24.05.02 | 30.07.02 |
| Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification) | N/25 | N | 08.11.02 | 11.12.02 |
| Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification) | N/27 | N | 17.01.03 | 06.02.03 |
| Change in the batch size of finished product | I/29 | I | 12.06.03 | 17.06.03 |
| Change(s) to container | II/30 | II | 24.07.03 | 28.07.03 |
| Change(s) to the manufacturing process for the active substance | II/31 | II | 25.09.03 | 26.09.03 |
| Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification) | N/32 | N | 27.06.03 | 18.07.03 |
| Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification) | N/33 | N | 15.06.04 | - |

[1] In accordance with Commission Regulation (EC) No. 542/95 of 10 March 1995, as amended: **I** refers to a minor variation (Type I variation); **II** refers to a major variation (Type II variation); **I/II** refers to a minor variation following the procedure set out in Article 6, 7 and 8 of the Regulation; **X** refers to an Annex II application.
**T** refers to a transfer of a Marketing Authorisation in accordance with Commission Regulation (EC) No 2141/96 of 7 November 1996.
**N** refers to a notification in accordance with Article 61(3) of Directive 2001/83/EC.

[2] For Notifications and Type I variations, the date of entry into force of the change is the EMEA Notification date. The Commission Decision will be amended accordingly.