STEPS TAKEN AFTER GRANTING THE MARKETING AUTHORISATION

For procedures finalised after 1 June 2002 please refer to module 8B.

- The Marketing Authorisation Holder submitted on 9 May 1997 an application for a Notification of a Type I variation (Extension of shelf life as foreseen at time of authorisation), pursuant to Article 4 of Commission Regulation (EC) No. 542/95 of 10 March 1995, as amended. The procedure started on 14 May 1997. The Head of the Human Medicines Evaluation Unit signed a positive notification on 13 June 1997 (EMEA/H/C/102/I/01) and the European Commission granted a Commission Decision on 27 August 1997.
- The MAH also submitted a notification to the EMEA in order to introduce changes to the Labelling not connected to the Summary of Product Characteristics, pursuant Article 10(3) of Council Directive No. 92/27/EEC of 31 March 1992. The notification was signed by the Head of Human Medicines Evaluation Unit on 17 June 1997 and forwarded to the European Commission (EMEA/H/C/102/N/02).
- Pursuant to Article 4 of Commission Regulation (EC) No. 542/95 of 10 March 1995, as amended, the Marketing Authorisation Holder submitted to the EMEA on 29 August 1997 an application for two Type I variations (narrowing of the range of specifications of the active substance and narrowing of the range of the specifications and a change of method of testing for a release specification of the finished medicinal product-related respectively to items No 14 & 17 of Annex I to the Regulation). The procedure started on 26 September 1997. Supplementary information was supplied by the MAH on 13 November 1997 and a positive opinion (EMEA/H/C/102/I/03-04) was adopted by the CPMP on 18 November 1997. This variation did not require any amendment to the Community Marketing Authorisation.
- The Marketing Authorisation Holder submitted on 3 September 1997 an application for a Type II variation (additional manufacturing site), pursuant to Article 6 of Commission Regulation (EC) No 542/95 of 10 March 1995, as amended. The procedure started on 26 September 1997 and a positive opinion (EMEA/H/C/102/II/05) was adopted by the CPMP on 18 November 1997. This variation did not require any amendment to the Community Marketing Authorisation.
- The Marketing Authorisation Holder submitted on 11 September 1997 an application for a type II variation (change in summary of product characteristics, section 4.4 Special Warnings and Special Precautions for Use and changes related to the package leaflet, section 8 Instructions for Proper Use) pursuant to Article 6 of Commission Regulation (EC) No. 542/95 of March 1995, as amended. The procedure started on 26 September 1997 and supplementary information was supplied by the MAH on 16 December 1997, 29 January 1998, 26 February 1998 and 14 April 1998. A positive opinion (EMEA/H/C/102/II/06) was adopted by the CPMP on 22 April 1998 and the European Commission granted a Commission Decision on 17 August 1998.
- The MAH submitted to the EMEA on 19 September 1997 an application for a Type I variation (additional manufacturing site for the active substance) pursuant to Article 4 of Commission Regulation (EC) No 542/95 of 10 March 1995, as amended. The procedure started on 26 September 1997 and supplementary information was supplied by the MAH on 24 October and 10 November 1997. A positive opinion was adopted by the CPMP on 18 November 1999. (EMEA/H/C/102/I/07)
- The Marketing Authorisation Holder submitted on 15 April 1998 an application for a type II variation (change in summary of product characteristics and to the package leaflet, following the conclusions of the PSUR) pursuant to Article 6 of Commission Regulation (EC) No. 542/95 of March 1995, as amended. The procedure started on 24 April 1998. A positive opinion (EMEA/H/C/102/II/08) was adopted by the CPMP on 24 June 1998 and the European Commission granted a Commission Decision on 23 October 1998.

- The MAH submitted to the EMEA on 15 June 1998 an application for a Type I variation (change of manufacturing site for part or all of the manufacturing process of the medicinal product) pursuant to Article 4 of Commission Regulation (EC) No 542/95 of 10 March 1995, as amended. The procedure started on 15 June 1998. A positive notification was signed by the Head of the Human Medicines Evaluation Unit on 15 July 1998 (EMEA/H/C/102/I/09) and forwarded to the European Commission.
- The Marketing Authorisation Holder submitted on 30 September 1998 an application for a Type I variation No. 14 of Annex I to the regulation (Change in specification of the active substance), pursuant to Article 4 of Commission Regulation (EC) No 542/95 of 10 March 1995, as amended. The procedure started on 7 October 1998, and the Head of the Human Medicines Evaluation Unit signed a positive notification on 06 November 1998 (EMEA/H/C/102/N/10). This variation did not require any amendment to the Community Marketing Authorisation.
- The Marketing Authorisation Holder submitted on 30 September 1998 an application for a Type I variation No. 17 of Annex I to the regulation (Change in specification of the medicinal product), pursuant to Article 4 of Commission Regulation (EC) No 542/95 of 10 March 1995, as amended. The procedure started on 7 October 1998, and the Head of the Human Medicines Evaluation Unit signed a positive notification on 06 November 1998 (EMEA/H/C/102/N/11). This variation did not require any amendment to the Community Marketing Authorisation.
- The Marketing Authorisation Holder submitted on 30 September 1998 an application for a Type I variation (change in shelf-life of the active ingredient), pursuant to Article 4 of Commission Regulation (EC) No 542/95 of 10 March 1995, as amended. The procedure started on 7 October 1998 and a positive notification (EMEA/H/C/102/N/12) was signed by the Head of the Human Medicines Evaluation Unit on 06 November 1998. This variation did not require any amendment to the Community Marketing Authorisation.
- The Marketing Authorisation Holder submitted on 30 September 1998 an application for a type II variation (change in summary of product characteristics and to the package leaflet, following the conclusions of the second and third PSUR) pursuant to Article 6 of Commission Regulation (EC) No. 542/95 of March 1995, as amended. The procedure started on 23 October 1998. A positive opinion (EMEA/H/C/102/II/13) was adopted by the CPMP on 25 February 1999 and the European Commission granted a Commission Decision on 18 June 1999.
- The Marketing Authorisation Holder also submitted evidence of compliance with the specific obligations pursuant to Article 13(2) of Council Regulation No. 2309/93, as amended and Part 4G of the Annex to Council Directive 75/318/EEC, allowing re-assessment of the benefit/risk profile of the medicinal product. A positive opinion (EMEA/H/C/102/S/14) was adopted by the CPMP on 22 October 1998.
- The Marketing Authorisation Holder submitted evidence of compliance with the specific obligations pursuant to Article 13(2) of Council Regulation No. 2309/93, as amended and Part 4G of the Annex to Council Directive 75/318/EEC, allowing re-assessment of the benefit/risk profile of the medicinal product. A positive opinion (EMEA/H/C/102/S/15) was adopted by the CPMP on 21 October 1999.
- The Marketing Authorisation Holder submitted on 12 October 1999 an application for a type II variation (change in summary of product characteristics and to the package leaflet, following the conclusions of the fourth PSUR) pursuant to Article 6 of Commission Regulation (EC) No. 542/95 of March 1995, as amended. The procedure started on 22 October 1999. A positive opinion (EMEA/H/C/102/II/16) was adopted by the CPMP on 18 November 1999 and the European Commission granted a Commission Decision on 09 March 1999.
- The MAH submitted to the EMEA on 10 December 1999 an application for a Type I variation (change of manufacturing site for part or all of the manufacturing process of the medicinal product) pursuant to Article 4 of Commission Regulation (EC) No 542/95 of 10 March 1995, as amended. The procedure started on 17 December 1999. The Head of the Human Medicines Evaluation Unit signed a positive notification on 14 January 2000 (EMEA/H/C/102/I/17). This variation did not require any amendment to the Community Marketing Authorisation.

- The Marketing Authorisation Holder submitted on 26 January 2000 an application for a Type II variation (additional supplier of Human Serum Albumin), pursuant to Article 6 of Commission Regulation (EC) No 542/95 of 10 March 1995, as amended. The procedure started on 18 February 2000 and a positive opinion (EMEA/H/C/102/II/18) was adopted by the CPMP on 13 April 2000. This variation did not require any amendment to the Community Marketing Authorisation.
- The Marketing Authorisation Holder submitted on 17 May 2000 an application for a Type I variation No. 1 of Annex I to the regulation (Change in the content of the manufacturing authorisation), pursuant to Article 4 of Commission Regulation (EC) No 542/95 of 10 March 1995, as amended. The procedure started on 22 May 2000. A positive notification (EMEA/H/C/102/I/19) was signed by the Head of the Human Medicines Evaluation Unit on 20 June 2000 and forwarded to the European Commission.
- The Marketing Authorisation Holder submitted on 19 July 2000 an application for a Type II variation (new vial presentation), pursuant to Article 6 of Commission Regulation (EC) No 542/95 of 10 March 1995, as amended. The procedure started on 28 July 2000 and a positive opinion (EMEA/H/C/102/II/20) was adopted by the CPMP on 21 September 2000. The European Commission granted a Commission Decision on 22 January 2001.
- The Marketing Authorisation Holder submitted evidence of compliance with the specific obligations pursuant to Article 13(2) of Council Regulation No. 2309/93, as amended and Part 4G of the Annex to Council Directive 75/318/EEC, allowing re-assessment of the benefit/risk profile of the medicinal product. A positive opinion (EMEA/H/C/102/S/21) was adopted by the CPMP on 21 September 2000 and the European Commission granted a Commission Decision on 29 December 2000.
- The MAH submitted to the EMEA on 19 July 2000 an application for a Type I variation (change of manufacturing site for part or all of the manufacturing process of the medicinal product) pursuant to Article 4 of Commission Regulation (EC) No 542/95 of 10 March 1995, as amended. The procedure started on 26 July 2000. A positive notification (EMEA/H/C/102/I/23) was signed by the Head of Sector of the Human Medicines Evaluation Unit on 17 August 2000. This variation did not require any amendment to the Community Marketing Authorisation.

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
Extension of the indication	II/0022	II	16.01.02	07.05.02
Update of Summary of Product Characteristics and Package Leaflet following the 5th PSUR	II/0024	II	01.03.01	08.06.01
Quality changes	II/0025	II	01.03.01	13.03.01
Quality changes	II/0026	II	27.06.01	03.07.01
Update of Summary of Product Characteristics following the outcome of a dose comparison study	II/0027	II	25.07.01	03.12.01
Annual Reassessment	S/0029	S	15.11.01	08.03.02
Renewal	R/0030	R	17.01.02	07.05.02

[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 10(3) of Council Directive 92/27/EEC of 31 March 1992.

[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.