STEPS TAKEN AFTER THE MARKETING AUTHORISATION

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

- On 18 December 1998, the Marketing Authorisation Holder (MAH) applied for a Type I Variation in accordance with Commission Regulation (EC) 542/95, as amended. The MAH applied for an additional alternative manufacturer for one step of the manufacturing process of the active substance. On 20 January 1999, the EMEA issued a Notification that the variation is accepted and does not require any amendment to the Community Marketing Authorisation..
- On 06 January 1999, the Marketing Authorisation Holder (MAH) applied for a Type I Variation in accordance with Commission Regulation (EC) 542/95, as amended. The MAH applied for an alternative manufacturer of the active substance. On 05 February 1998, the EMEA issued a Notification as the variation is accepted and does not require any amendment to the Community Marketing Authorisation.
- On 18 January 1999, the Marketing Authorisation Holder (MAH) applied for two Type I Variation in accordance with Commission Regulation (EC) 542/95, *as amended*. The MAH applied for an increase of the size of the batch of the finished product and a change of the manufacturing site for all of the manufacturing process of the medicinal product. on 19 February 1999, the EMEA issued two Notifications that the variations are accepted and do not require any amendment to the Community Marketing Authorisation.
- Between 1 June and 21 December 1999, the EMEA issued Notifications for the approval of four type I variations concerning;
  - change in specification of starting material or intermediate used in the manufacture of the active substance,
  - change in supplier of an intermediate compound used in manufacture of the active substance,
  - change in the manufacture of the medicinal product,
  - minor change in manufacturing process of the active substance.

  These variations did not require any amendment to the Commission Decision.
- Between 26 February 1999 and 22 December 1999, the Marketing Authorisation Holder requested to introduce changes to aspects of the labelling not connected to the Summary of Product Characteristics, by means of three Notifications under Article 10(3) of Directive 92/27/EEC. Following EMEA's Notifications on 26 March, 11 November 1999 and 18 January 2000, the European Commission amended the Decision (Annex III B) on 7 May 1999, 3 February 2000 and 24 March 2000, respectively.
- On 13 April 2000, the Marketing Authorisation Holder submitted a type II variation application in accordance with Article 6 of Commission Regulation (EC) No.542/95 of 10 March 1995, as amended. The Marketing Authorisation Holder applied for an update of the SPC and PL accordingly to recently approved changes for the monotherapy product and post-marketing data. On 27 July 2000, the CPMP approved the variation. The variation required amendments in annex I and III B of the Commission Decision. The European Commission amended the Decision on 16 November 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
Change in test procedure for starting material/intermediate used in manuf. of active substance	I/13	I	21.11.00	-
Update of Summary of Product Characteristics and Package Leaflet	II/14	II	14.12.00	23.04.01
Changes to comply with supplements to pharmacopoeias	I/15	I	20.03.01	-
Change following modification(s) of the manufacturing authorisation(s)	I/16	I	04.04.01	-
Minor change of manufacturing process of the active substance	I/17	I	26.04.01	-
Update of Summary of Product Characteristics and Package Leaflet	II/18	II	20.09.01	10.04.02
Change in pack size for a medicinal product	I/19	I	13.07.01	08.10.01
Change in pack size for a medicinal product	I/20	I	13.07.01	08.10.01
Change in pack size for a medicinal product	I/21	I	20.09.01	19.02.02
Change in pack size for a medicinal product	I/22	I	20.09.01	19.02.02
Change in the name and/or address of the marketing authorisation holder	I/23	I	20.09.01	-
Replacement of an excipient with a comparable excipient	I/24	I	12.10.01	26.02.02
Change following modification(s) of the manufacturing authorisation(s)	I/25	I	22.12.01	08.03.02
Change in test procedure for starting material/intermediate used in manuf. of active substance	I/26	I	10.04.02	02.05.02
Extension of shelf-life as foreseen at time of authorisation	I/27	I	20.02.02	18.04.02
Change in test procedure for starting material/intermediate used in manuf. of active substance	I/28	I	10.04.02	20.04.02
Minor changes in manufacture of the medicinal product	I/29	I	05.06.02	18.06.02
Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	N/30	N	07.06.02	28.06.02
Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	N/31	N	03.12.02	15.01.03
Minor change of manufacturing process of the active substance	I/32	I	19.12.02	17.01.03
Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	N/33	N	17.01.03	07.03.03
Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	N/34	N	04.04.03	16.05.03
Extension of shelf-life or retest period of the active substance	I/35	I	21.03.03	01.04.03
Change in or addition of manufacturer(s) of active substance	I/36	I	23.04.03	25.04.03
Update of Summary of Product Characteristics and Package Leaflet	II/37	II	26.06.03	02.10.03
Minor change of manufacturing process of the active substance	I/38	I	11.06.03	26.06.03
Minor change of manufacturing process of the active substance	I/39	I	12.06.03	26.06.03
Change or addition of a new pharmaceutical form	X/40	X	22.10.03	02.03.04
Renewal	R/41	R	25.09.03	04.12.03
Change in supplier of an intermediate compound used in manufacture of the active substance	I/42	I	31.10.03	12.11.03
Minor change in the manufacturing process of the active substance	I/43	I	10.11.03	-
Update of Summary of Product Characteristics and Package Leaflet	II/44	II	16.09.04	28.10.04
Change in manuf. of active substance without Ph. Eur. certificate - change in manuf. Site	IB/45	IB	14.04.04	-
Update of Summary of Product Characteristics and Package Leaflet	II/46	II	03.06.04	02.08.04
Change in BR/QC testing - repl./add. of batch control/testing site and replacement/add. of manufacturing site: All other manufacturing operations ex. batch release	IB/47	IB	20.04.04	-
Minor change in the manufacturing process of the active substance	IB/48	IB	01.07.04	-
Change in BR/QC testing - repl./add. manuf. responsible for BR - not incl. BC/testing	IA/49	IA	30.06.04	-
Replacement/add. of manufacturing site: Secondary packaging site	IA/50	IA	30.06.04	-

[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 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.

and change in BR/QC testing - repl./add. manuf. responsible for BR - not incl. BC/testing				
Change in manuf. of active substance without Ph. Eur. certificate - change in manuf. Site	IB/51	IB	28.07.04	-
Minor change in the manufacturing process of the active substance	IB/53	IB	10.08.04	-
Change in batch size of active substance or intermediate - up to 10-fold	IA/54	IA	17.09.04	-