STEPS TAKEN AFTER GRANTING THE MARKETING AUTHORISATION

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

- The MAH submitted on 20 August 1998 an application to obtain a marketing authorisation in accordance with Annex II of Commission Regulation (EC) No 542/95 of 10 March 1995 (part vi) as amended, falling within the scope of Part A of the Annex of the Council regulation EC No. 2309/93. The procedure started on 21 August 1998, supplementary information was supplied by the MAH on 11 December 1998, the Applicant gave oral explanations on 16 December 1998, and a positive opinion was adopted by the CPMP on 16 December 1998. The European Commission granted a Commission Decision on 29 March 1999 (EMEA/H/C/136/X/01).

- The MAH submitted on 20 August 1998 an application for a Type II variation, pursuant to Article 6 of Commission Regulation (EC) No. 542/95 of 10 March 1995 as amended, in order to apply for a change of the SPC and PIL. The procedure started on 21 August 1998 and a positive opinion was adopted by the CPMP on 22 October 1998. The European Commission granted a Commission Decision on 1 February 1999 (EMEA/H/C/136/II/02).

- Pursuant to Article 13(2) of Council Regulation (EEC) No 2309/93 and part 4G of Annex to Council Directive 75/318/EEC, the MAH provided in the foreseen timeframe the reports of ongoing studies according to the specific obligations stated in the Annex II of the Commission Decision. The MAH submitted to the EMEA the documentation, which formed the basis of the first annual re-assessment of the benefit/risk profile for Rebif. The Rapporteur's annual assessment report was circulated to all CPMP Members on 9 June 1999. During the June 1999 CPMP plenary meeting, the CPMP agreed with the Rapporteur's assessment report and adopted a positive opinion on the annual re-assessment of the specific obligations and the benefit/risk ratio, stating that no amendments of Annexes I and III to the Community Marketing Authorisation are necessary and that the marketing authorisation should remain under exceptional circumstances. The European Commission granted a Commission Decision on 3 December 1999 (EMEA/H/C/136/S/03).

- The MAH submitted on 10 May 1999 an application for a Type I variation No 13 of Annex I to the regulation, pursuant to Article 4 of Commission Regulation (EC) No. 542/95 of 10 March 1995 as amended, in order to apply for a change (scale-up) of the manufacturing process. The procedure started on 21 May 1999 and a positive opinion was adopted by the CPMP on 28 July 1999 (EMEA/H/C/136/I/05). The European Commission granted a Commission Decision on 3 August 1999.

- The MAH submitted on 10 May 1999 an application for a Type I variation No 12 of Annex I to the regulation, pursuant to Article 4 of Commission Regulation (EC) No. 542/95 of 10 March 1995 as amended, in order to apply for minor changes to the manufacturing process. The procedure started on 21 May 1999, supplementary information was supplied by the MAH on 19 July 1999, and a positive opinion was adopted by the CPMP on 22 September 1999 (EMEA/H/C/136/I/06). The European Commission granted a Commission Decision on 5 October 1999.

- The MAH submitted on 25 August 1999 an application for a variation, pursuant to Article 10(3) of Council Directive No. 92/27/EEC of 31 March 1992, as amended in order to apply for a change in the PIL, not connected with the SPC. The procedure started on 31 August, and a positive opinion was adopted by the CPMP on 7 October 1999 (EMEA/H/C/136/N/07). The European Commission granted a Commission Decision on 14 December 1999.

- The MAH submitted on 1 September 1999 an application for a Type I variation, pursuant to Article 4 of Commission Regulation (EC) No. 542/95 of 10 March 1995 as amended, in order to apply for an extension of the shelf life from 12-24 months. The procedure started on 7 September 1999, and a positive opinion was adopted by the CPMP on 7 October 1999

(EMEA/H/C/136/I/08). The European Commission granted a Commission Decision on 14 December 1999.

- The MAH submitted on 9 September 1999 an application for a Type II variation, pursuant to Article 6 of Commission Regulation (EC) No. 542/95 of 10 March 1995 as amended, in order to apply for changes to active substance specifications and test methods. The procedure started on 23 September 1999, and a positive opinion was adopted by the CPMP on 18 November 1999 (EMEA/H/C/136/II/09). The European Commission granted a Commission Decision on 2 December 1999.

- The MAH submitted on 20 October 1999 an application for a Type I variation, pursuant to Article 4 of Commission Regulation (EC) No. 542/95 of 10 March 1995 as amended, in order to apply for a change of name of the manufacturer responsible for batch release. The procedure started on 25 October 1999, and a positive opinion was adopted by the CPMP on 12 November 1999 (EMEA/H/C/136/I/10). The European Commission granted a Commission Decision on 20 January 2000.

- The MAH submitted on 11 February 2000 an application for a Type I variation, pursuant to Article 4 of Commission Regulation (EC) No. 542/95 of 10 March 1995 as amended, in order to apply for a change of to the manufacturing process of the active substance. The procedure started on 18 February 2000, and a positive opinion was adopted by the CPMP on 16 March 2000. (EMEA/H/C/136/I/12). The European Commission granted a Commission Decision on 11 April 2000.

- The MAH submitted on 16 May 2000 an application for a Type II variation, pursuant to Article 6 of Commission Regulation (EC) No. 542/95 of 10 March 1995 as amended, in order to apply for changes in the SPC and PL, based on the results of the extension study in RRMS. The procedure started on 26 May 2000, and a positive opinion was adopted by the CPMP on 19 October 2000 (EMEA/H/C/136/II/13). The European Commission granted a Commission Decision on 22 January 2001.

- Pursuant to Article 13(2) of Council Regulation (EEC) No 2309/93 and part 4G of Annex to Council Directive 75/318/EEC, the MAH provided in the foreseen timeframe the reports of ongoing studies according to the specific obligations stated in the Annex II of the Commission Decision. The MAH submitted to the EMEA the documentation, which formed the basis of the second annual re-assessment of the benefit/risk profile for Rebif. The Rapporteur's annual assessment report was circulated to all CPMP Members on 26 June 2000. During the July 2000 CPMP plenary meeting, the CPMP agreed with the Rapporteur's assessment report and adopted a positive opinion on the annual re-assessment of the specific obligations and the benefit/risk ratio, stating that no amendments of Annexes I and III to the Community Marketing Authorisation are necessary. Since all specific obligations stated in Annex II of the Commission Decision have been fulfilled, the CPMP recommended that the Marketing Authorisation for Rebif was released from the status "under exceptional circumstances"(EMEA/H/C/136/S/14).

- The MAH submitted on 13 July 2000 an application for a Type I variation No 12 of Annex I to the regulation, pursuant to Article 4 of Commission regulation (EC) No. 542/95 of 10 March 1995, as amended, in order to apply for minor changes to the active substance production process. The procedure started on 28 July 2000, and a positive opinion was adopted by the CPMP on 21 September 2000 (EMEA/H/C/136/I/16). The European Commission granted a Commission Decision on 16 October 2000.

- The MAH submitted on 13 July 2000 an application for a Type II variation, pursuant to Article 6 of Commission regulation (EC) No. 542/95 of 10 March 1995, as amended, in order to apply for an amendment in the specifications of the active substance. The procedure started on 28 July 2000, and a positive opinion was adopted by the CPMP on 21 September 2000 (EMEA/H/C/136/II/17). The European Commission granted a Commission Decision on 16 October 2000.

- The MAH submitted on 28 July 2000 an application for a Notification of a Type I variation, pursuant to Article 4 of Commission regulation (EC) No. 542/95 of 10 March 1995, as amended, in order to apply for minor changes to the active substance production process. The procedure started on 4 August 2000, and a positive opinion was signed on 1 September 2000 (EMEA/H/C/136/I/18). The European Commission granted a Commission Decision on 12 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
Extension of Indication	II/11	II	25.07.01	21.11.01
Change in or addition of manufacturer(s) of active substance	I/15	I	14.12.00	20.03.01
Change in or addition of manufacturing site(s) por part or all of the manufacturing process	I/II/19	I/II	14.12.00	20.12.00
Changes to comply with supplements to pharmacopoeias	I/20	I	28.02.01	13.03.01
Change in storage conditions	I/21	I	11.06.01	
Change(s) to the manufacturing process for the active substance	X-22	X	17.10.02	16.01.03
Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	N-24	N	21.08.01	03.10.01
Change in supplier of an intermediate compound used in manufacture of the active substance	I/25	I	09.08.01	07.09.01
Change in the name and/or address of the marketing authorisation holder	I/26	I	26.07.01	18.09.01
Change in or addition of manufacturing site(s) for part or all of the manufacturing process	I/27	I	17.08.01	07.09.01
Extension of shelf-life or retest period of the active substance	I/28	I	21.09.01	
Change(s) to the manufacturing process for the active substance	II/29	II	15.11.01	28.11.01
Update of Summary of Product Characteristics and Package Leaflet	II/30	II		17.05.02
Change in the batch size of finished product	I/31	I	01.02.02	11.02.02
Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	N/32	N	11.03.02	02.04.02
Change(s) to the test method(s) and/or specifications for the finished product	II/33	II	25.07.02	31.07.02
Change in the procedure of active substance	I/34	I	25.07.02	31.07.02
Change in the supplier of an intermediate compound used in manufacture of active substance	I/35	I	22.08.02	10.09.02
Minor change of manufacturing process of the active substance	I/36	I	22.08.02	10.09.02
Change in specification of starting material/intermediate used in manuf. of the active substance	I/37	I	11.12.02	13.12.02
Update of Summary of Product Characteristics and Package Leaflet	II/38	II	19.03.03	25.06.03
Minor change in the package leaflet not connected with the SPC	N/39	N	27.01.03	04.03.03
Renewal	R/40	R	19.03.03	04.06.03
Change(s) to the test method(s) and/or specifications for the active substance	II/42	II	22.05.03	27.05.03
Change in container shape	I/43	I	20.08.03	18.09.03
Change(s) to the test method(s) and/or specifications for the active substance	II/44	II	22.10.03	30.10.03
Replacement/add. of manufacturing site: Secondary packaging site	I/45	I	01.12.03	-
Change in in-process controls applied during the manufacture of the product	I/46	I	01.12.03	-
Change in in-process controls applied during the manufacture of the product	I/48	I	20.10.03	-
Update of Summary of Product Characteristics and Package Leaflet	II/49	II	17.12.03	23.02.04

[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.