STEPS TAKEN AFTER GRANTING THE MARKETING AUTHORISATION

For procedures finalised after 9 January 2003 please refer to module 8B.

- The MAH in accordance with Commission Regulation (EC) No. 542/95 submitted an application to introduce an additional pack size of 5 vials of powder and solvent for solution for injection. A favourable opinion was adopted by the CPMP on 17 July 1996, which required an update of the Annexes of the Commission Decision.
- The MAH submitted in accordance with Commission Regulation (EC) No. 542/95 an application for a Type II variation to amend the text of the SPC and PL in the light of the first PSUR data: strengthening the warnings on the injection site necrosis. A favourable opinion on a modified text was adopted by the CPMP on 20 November 1996.
- Pursuant to Article 13(2) of Council Regulation (EEC) No 2309/93 and part 4G of Annex to Council Directive 75/318/EEC, the Marketing Authorisation Holder (MAH) provided in the foreseen timeframe the reports of ongoing studies according to the specific obligations stated in the Annex II of the Decision. The Marketing Authorisation Holder submitted to the EMEA the documentation, which formed the basis of the annual re-assessment of the benefit/risk profile for Betaferon, including an updated expert report summarising the different specific obligations already submitted within the period November 1995- November 1996. The Rapporteur's annual assessment report was circulated to all CPMP Members on 20 January 1997. During the February 1997 plenary meeting, the CPMP agreed with the Rapporteur's assessment report, reviewed the specific obligations of the Marketing Authorisation Holder and finalised the annual risk benefit assessment, which remained unchanged. The marketing authorisation should therefore remain under exceptional circumstances. On this basis a positive opinion was adopted on 18 February 1997 with an updated Annex II and stating that no further amendments of Annexes I and III to the Community Marketing Authorisation were necessary.
- The MAH submitted data showing that the shelf life specification for moisture had been tightened accordingly to the specific obligations set out in the CPMP opinion dated 12 July 1995. The response to this specific obligation has resulted in a type I variation in accordance with Commission Regulation (EC) No. 542/95 for which the CPMP adopted a favourable opinion in its 19 February 1997 plenary meeting.
- The MAH submitted an application for a Type I variation in accordance with Commission Regulation (EC) No. 542/95 to introduce a change in the manufacture of the medicinal product with the addition of a final filtration step. A positive opinion was adopted by the CPMP in its February 1997 plenary meeting.
- The MAH submitted an application for a Type I variation in accordance with Commission Regulation (EC) No. 542/95 to replace the Brain Hearth Infusion (BHI) agar with a soya derived medium to be used in the manufacture of the medicinal product (medium for the growth of the working cell bank). The CPMP adopted a favourable opinion on this variation on 19 March 1997.
- The MAH submitted an application for a Type II variation in accordance with Commission Regulation (EC) No. 542/95, relating to changes in the Summary of Product Characteristics and Package Leaflet, to reflect a better understanding of the safety profile based on the review of the third Periodic Safety Update Report. The CPMP adopted a favourable opinion on this variation on 22 October 1997.
- Pursuant to Article 13(2) of Council Regulation (EEC) No 2309/93 and part 4G of Annex to Council Directive 75/318/EEC, the Marketing Authorisation Holder (MAH) provided in the foreseen timeframe the reports of ongoing studies according to the specific obligations stated in the Annex II of the Decision. The Marketing Authorisation Holder submitted to the EMEA the documentation, which formed the basis of the 2nd annual re-assessment of the benefit/risk profile for Betaferon. The Rapporteur's annual assessment report was circulated to all CPMP

Members on 19 January 1998. During the February 1998 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. Annex II has been amended according to the conclusions reached during the CPMP discussion.

- The MAH submitted an application for a Type I variation in accordance with Commission Regulation (EC) No. 542/95 to introduce the RP-HPLC test into the finished product specification. The updated method is used for quantitative analysis of interferon beta-1b both for final product testing and for stability testing. The CPMP adopted a favourable opinion on this variation on 27 May 1998.

- The MAH submitted an application for a Type I variation in accordance with Commission Regulation (EC) No. 542/95 to obtain approval for Chiron, USA, a second supplier of Betaferon, to replace bovine brain-heart infusion (BHI) with soy peptone in the medium to prepare the Working Cell Banks (WCBs).The CPMP adopted a favourable opinion on this variation on 24 June 1998.

- The MAH submitted an application for a Type II variation in accordance with Commission Regulation (EC) No. 542/95, containing safety-related changes in the Summary of Product Characteristics and Package Leaflet resulting from the 4th and 5th Periodic Safety Update Report assessment by the CPMP. The CPMP adopted a favourable opinion on this variation on 22 July 1998.

- The MAH submitted an application for a Type II variation in accordance with Commission Regulation (EC) No. 542/95, relating to the extension of the indication to include the secondary progressive form of multiple sclerosis. The CPMP adopted a favourable opinion on this variation on 22 October 1998, which required an update of the Annexes of the Marketing Authorisation. The Commission Decision was issued on 26 January 1999.

- The MAH submitted an application for a Type I variation in accordance with Commission Regulation (EC) No. 542/95, relating to a change in the specification of the medicinal product as result from the pharmaceutical follow-up measure to provide a suitable specification for the control of deamidated by-products in the final container product. The EMEA issued a positive notification on 10 December 1998.

- Pursuant to Article 13(2) of Council Regulation (EEC) No 2309/93 and part 4G of Annex to Council Directive 75/318/EEC, the Marketing Authorisation Holder (MAH) provided in the foreseen timeframe the reports of ongoing studies according to the specific obligations stated in the Annex II of the Decision. The Marketing Authorisation Holder submitted to the EMEA the documentation that formed the basis of the 3rd annual re-assessment of the benefit/risk profile for Betaferon. The Rapporteur's annual assessment reports on pharmaceutical specific obligations and follow-up measures were circulated to all CPMP Members on 11 December 1998. The Rapporteur's annual assessment report on the clinical specific obligations and on the 6th periodic Safety Update Report was circulated to all CPMP members on 18 December 1998, 8 January 1999 and 20 January 1999. During the January 1999 CPMP plenary meeting, the CPMP 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. Annex II has been amended according to the conclusions reached during the CPMP discussion. The Commission decision was issued on 11 May 1999.

- The MAH submitted an application for a Type II variation in accordance with Commission Regulation (EC) No 542/95, containing safety-related changes in the Summary of Product Characteristics and Package Leaflet resulting from the 6th Periodic Safety Update. The CPMP adopted a favourable opinion on this variation on 20 May 1999 which required an update of the Annexes I and III of the Marketing Authorisation. The Commission decision was issued on 14 September 1999.

- Pursuant to Article 2(1) of Commission Regulation (EC) No 542/95 of 10 March 1995, as amended, and Annex II (points 3 iv) thereof, the MAH submitted an Annex II application for a new pharmaceutical form of Betaferon, in which the solvent vial is replaced with a pre-filled syringe. The CPMP adopted a favourable opinion on this Annex II application on 23 September 1999 which required an update of the Annexes I, II and III of the Marketing Authorisation. The Commission decision was issued on 3 February 2000.
- The MAH submitted an application for a Type II variation in accordance with Commission Regulation (EC) No. 542/95, relating to an updated of the SPC and PIL. The CPMP adopted a favourable opinion on this variation on 20 May 1999, which required an update of the Annexes of the Marketing Authorisation. The Commission Decision was issued on 14 September 1999.
- Pursuant to Article 13(2) of Council Regulation (EEC) No 2309/93 and part 4G of Annex to Council Directive 75/318/EEC, the Marketing Authorisation Holder (MAH) provided in the foreseen timeframe the reports of ongoing studies according to the specific obligations stated in the Annex II of the Decision. The Marketing Authorisation Holder submitted to the EMEA the documentation that formed the basis of the 4th annual re-assessment of the benefit/risk profile for Betaferon. The Rapporteur's annual assessment reports on the 7th periodic Safety Update Report was circulated to all CPMP Members on 25 October 1999. The Rapporteur's annual assessment reports on the clinical specific obligations and on the clinical and chemical, pharmaceutical and biological follow-up measures were circulated to all CPMP members on 17 December 1999. The CPMP adopted a positive opinion on the annual re-assessment on 19 January 2000, stating that no amendments of Annexes I and III to the Community Marketing Authorisation are necessary. Annex II has been amended according to the conclusions reached during the CPMP discussion. The Commission decision was issued on 11 May 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 specification of excipients in the medicinal product	I/0020	I	17.05.00	
Quality changes	II/0021	II	27.07.00	02.08.00
Quality changes	II/0022	II	21.09.00	29.01.01
Renewal	R/0023	R	16.11.00	03.04.01
Annual re-assessment	S/0024	S	14.12.00	03.04.01
Update of summary of product characteristics and package leaflet	II/0025	II	25.07.01	19.11.01
Change following modification(s) of the manufacturing authorisation(s)	I/0026	I	16.03.01	06.04.01
Changes in manufacture of the medicinal product	I/0027	I	20.09.01	02.10.01
Change in storage conditions	I/0028	I	14.11.02	09.01.03

[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 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.