STEPS TAKEN AFTER GRANTING THE MARKETING AUTHORISATION

For procedures finalised after 1 January 2005 please refer to module 8B.

- The Marketing Authorisation Holder, Roche Registration Ltd applied for a Type I variation to introduce an additional manufacturer of the active substance with consequential changes an increase in the batch size of the active substance and minor changes in the manufacturing process of the active substance and medicinal product. The application was submitted on 11 June 1998. The procedure for this variation followed a Type II timetable and started on 26 June 1998. An inspection report for the additional manufacturer, Genentech, Inc was issued on 16 October 1998. A positive opinion was adopted by the CPMP on 22 October 1998. This variation did not require any amendments to the Annexes of the Commission Decision.
- The Marketing Authorisation Holder, Roche Registration Ltd, requested an Urgent Safety Restriction on 26 November 1998 in order to include provisional changes in the Summary of Product Characteristics and Package Leaflet following spontaneous reports of adverse reactions. The Urgent Safety Restriction Procedure was finalised on 27 November 1998. The Press Release on Reports of Adverse Reactions and new recommendations for use was published on 30 November 1998. The same information has been communicated through a "Dear Doctor Letter" to EU-haematologists and oncologists.
- The marketing Authorisation Holder, Roche Registration Ltd applied for a Type II variation to introduce the changes in the Summary of Product Characteristics and Package Leaflet following the previous Urgent Safety Restriction of 26 November 1998. The application was submitted on 3 December 1998. The procedure for this variation followed a Type II timetable and started on 16 December 1998. A positive opinion was adopted by the CPMP on 22 February 1999. The Commission Decision on this variation was adopted on 18 June 1999.
- The Marketing Authorisation Holder, Roche Registration Ltd, submitted on 27 January 1999 the first PSUR covering the period 1 December 1997 - 30 November 1998. The CPMP discussed the PSUR on 22 February 1999 and concluded that further amendments to the Summary of Product Characteristics and Package Leaflet were needed. The Marketing Authorisation Holder, Roche Registration Ltd, submitted on 22 April 1999 an application for a Type II variation to introduce changes to the Summary of Product characteristics and the Package Leaflet following the assessment of the 1st PSUR. The procedure started on 26 April 1999. A positive opinion was adopted on 19 May 1999. A Commission Decision on this variation was adopted on 22 September 1999.
- The marketing Authorisation Holder, Roche Registration Limited applied for a Type II variation to introduce changes in the specifications for the sterile bulk. The application was submitted on 7 July 1999. The procedure for this variation started on 30 July 1999. A positive opinion was adopted by the CPMP on 17 November 1999. This variation did not require any amendments to the Annexes of the Commission Decision.
- The marketing Authorisation Holder, Roche Registration Limited applied for a Type II variation to introduce changes in the Summary of Product Characteristics and Package Leaflet following the assessment of the 2nd PSUR. The application was submitted on 25 August 1999. The procedure for this variation started on 27 August 1999. A positive opinion was adopted by the CPMP on 22 September 1999. A Commission Decision on this variation was adopted on 8 February 2000.
- The Marketing Authorisation Holder, Roche Registration Limited applied for a Notification of a Type I variation to introduce changes in the qualitative composition of immediate packaging material. The procedure for this variation started on 15 October 1999. The Head of Evaluation of Medicines for Human Use Sector signed a positive notification on 18 April 2000. This variation did not require any amendments to the Annexes of the Commission Decision.

- The Marketing Authorisation Holder, Roche Registration Limited applied for a Type I variation No 1 and a consequential application for a Type I variation No 15 of Annex I (type II procedure applicable) for the addition of Roche Basel as a filling site of Mabthera vials and consequential minor changes to the manufacturing procedure. The application was submitted on 11 October 1999 and the procedure for this variation started on 22 October 1999. A positive opinion was adopted by the CPMP on 12 April 2000. This variation did not require any amendments to the Annexes of the Commission Decision.

- The Marketing Authorisation Holder, Roche Registration Limited applied for a Notification of a change to an aspect of the Patient Leaflet not connected to the Summary of Product Characteristics to introduce changes affecting the Package Leaflet (Annex IIIB), section "Other information". This notification was submitted on 19 November 1999. The procedure for this notification started on 24 November 1999. The Head of Evaluation of Medicines for Human Use Sector signed a positive notification on 23 February 2000. The Commission Decision on this notification was adopted on 3 May 2000.

- The Marketing Authorisation Holder, Roche Registration Limited applied for a Type I variation No 12 of Annex I (type II procedure applicable) to change the seed-train of the manufacturing process of the active substance. The application was submitted on 7 March 2000. The procedure for this variation started on 17 March 2000. A positive opinion was adopted by the CPMP on 24 May 2000. This variation did not require any amendments to the Annexes of the Commission Decision.

- The Marketing Authorisation Holder, Roche Registration Limited applied for a Type I variation No 15 of Annex I (type II procedure applicable) for a minor change in the manufacture of the medicinal product: use of silicon oil for the vial stoppers. The application was submitted on 4 April 2000. The procedure for this variation started on 14 April 2000. A positive opinion was adopted by the CPMP on 28 June 2000. This variation did not require any amendments to the Annexes of the Commission Decision.

- The marketing Authorisation Holder, Roche Registration Limited applied for a Type II variation to introduce changes in the Summary of Product Characteristics and Package Leaflet to include new safety information, following the 3rd PSUR. In addition, the SPC and PL have been amended in line with the latest EMEA/QRD templates. The application was submitted on 4 December 2000. The procedure for this variation started on 15 December 2000. A positive opinion was adopted by the CPMP on 1 March 2001. A Commission Decision on this variation was adopted on 27 June 2001.

- The Marketing Authorisation Holder, Roche Registration Limited applied for a Notification of a change to an aspect of the Labelling not connected to the Summary of Product Characteristics to apply for an harmonisation of the presentation of the name of the medicinal product and to bring the text of the outer carton and vial label in line with the latest QRD templates. This notification was submitted on and started on 31 July 2001. The Head of Post-Authorisation Evaluation of Medicines for Human Use Unit signed a positive notification on 10 August 2001. The Commission Decision on this notification was adopted on 03 October 2001.

- The marketing Authorisation Holder, Roche Registration Limited applied for a Type II variation for an extension of the indication for the treatment of patients with CD20 positive diffuse large B-cell non-Hodgkin's Lymphoma in combination with CHOP chemotherapy. The application was submitted on 14 May 2001. The procedure for this variation started on 1 June 2001. A positive opinion was adopted by the CPMP on 18 October 2001. The Commission Decision on this variation was adopted on 21 March 2002.

- The Marketing Authorisation Holder, Roche Registration Limited applied for a Type I variation to extend the shelf life. The procedure for this variation started on 27 September 2001. The Head of Post-Authorisation Evaluation of Medicines for Human Use Unit signed a positive notification on 15 November 2001. The Commission Decision on this variation was adopted on 19 February 2002

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 or change(s) to the pharmaceutical documentation	II/011	II	10.08.01	N/A
Update of Summary of Product Characteristics and Package Leaflet	II/12	II	01.03.01	27.06.01
Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	N/13	N	10.08.01	03.10.01
Extension of Indication	II/14	II	18.10.01	21.03.02
Update of the SPC based on efficacy and safety data	II/16	II	24.04.02	15.07.02
Renewal	R/17	R	25.04.03	28.07.03
Change in the batch size of finished product	I/18	I	25.04.03	N/A
Minor changes in manufacture of the medicinal product	I/19	I	25.04.03	N/A
Change in test procedure of active substance	I/20	I	25.04.03	N/A
Change in test procedure of active substance	I/21	I	25.04.03	N/A
Withdrawal of the manufacturing authorisation for a site of manufacture	I/22	I	20.06.03	N/A
Change in or addition of manufacturing site(s) for part or all of the manufacturing process	I/23	I	25.06.03	N/A
Quality changes	II/25	II	25.09.03	14.01.04
Replacement of an exipient with a comparable excipient	I/026	I	21.08.03	N/A
Change(s) to the manufacturing process for the active substance	II/27	II	26.02.04	05.03.04
Update of Summary of Product Characteristics	II/28	II	21.01.04	19.03.04
Update of Summary of Product Characteristics	II/29	II	21.01.04	19.03.04
Change(s) to the manufacturing process for the active substance	II/30	II	03.06.04	11.06.04
Extension of Indication	II/31	II	23.06.04	02.08.04
Minor change in labelling or package leaflet not connected with the SPC	N/32	II	08.06.04	-

[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.