STEPS TAKEN AFTER GRANTING THE MARKETING AUTHORISATION

For procedures finalised after 1 September 2003 please refer to module 8B.

- The Marketing Authorisation Holder submitted on 6 May 1997 an application for a Type II variation (change in shelf-life of the active ingredient), pursuant to Article 6 of Commission Regulation (EC) No 542/95 of 10 March 1995, as amended. The procedure started on 16 May 1997 and a positive opinion (EMEA/H/C/105/II/01) was adopted by the CPMP on 23 July 1997. This variation did not require any amendment to the Community Marketing Authorisation.
- The Marketing Authorisation Holder submitted on 26 May 1997 an application for a Type I variation, following a Type II evaluation procedure (additional filtration step in the manufacturing of the finished product), pursuant to Article 4 of Commission Regulation (EC) No. 542/95 of 10 March 1995, as amended. The procedure started on 30 May 1997. Supplementary information was supplied by the MAH on 12 September 1997 and a positive opinion (EMEA/H/C/105/I/02) was adopted by the CPMP on 24 September 1997. This variation did not require any amendment to the Community Marketing Authorisation.
- The Marketing Authorisation Holder submitted on 26 May 1998 an application for a Type I variation No. 15 of Annex I to the regulation (antibiotic-free preculture in the manufacturing 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 30 May 1997, and a positive opinion (EMEA/H/C/105/I/03) was adopted by the CPMP on 23 July 1997. This variation did not require any amendment to the Community Marketing Authorisation.
- The Marketing Authorisation Holder submitted on 26 May 1997 an application for a Type II variation (new formulation), pursuant to Article 6 of Commission Regulation (EC) No. 542/95 of 10 March 1995, as amended. The procedure started on 30 May 1997. Supplementary information was supplied by the MAH on 8 and 31 October 1997, and a positive opinion (EMEA/H/C/105/II/04) was adopted by the CPMP on 19 November 1997. The European Commission granted a Commission Decision on 18 March 1998.
- The Marketing Authorisation Holder submitted to the EMEA on 10 October 1997 an application for a Type II variation (minor change of the manufacturing process of the active ingredient), pursuant to Article 6 of Commission Regulation (EC) No. 542/95 of 10 March 1995, as amended. The procedure started on 24 October 1997. Supplementary information was supplied by the MAH on 9 January 1998 and a positive opinion (EMEA/H/C/105/II/05) was adopted by the CPMP on 25 February 1998. This variation did not require any amendment to the Community Marketing Authorisation.
- The Marketing Authorisation Holder submitted on 5 December 1997 an application for a Notification of a Type I variation (extension of shelf life), pursuant to Article 4 of Commission Regulation (EC) No. 542/95 of 10 March 1995, as amended. The procedure started on 10 December 1997 and supplementary information was provided by the MAH on 9 January 1998. The Head of the Human Medicines Evaluation Unit signed a positive notification on 10 February 1998 (EMEA/H/C/105/I/06) and the European Commission granted a Commission Decision on 15 April 1998.
- The Marketing Authorisation Holder submitted on 4 February 1998 an application for a type II variation (change in summary of product characteristics and 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 26 February 1998 and supplementary information was supplied by the MAH on 8 June 1998. A positive opinion (EMEA/H/C/105/II/07) was adopted by the CPMP on 24 June 1998 and the European Commission granted a Commission Decision on 5 October 1998.
- Boehringer Mannheim GmbH submitted to the EMEA on 10 July 1998 an application for a Type II variation (changes in the specification of active substance; deletion of the two parameters “amino acid analysis” and “residual DNA content”), pursuant to Article 6 of

Commission Regulation (EC) No 542/95 of 10 March 1995, as amended. The procedure started on 24 July 1998. A positive opinion (EMEA/H/C/105/II/08) was adopted by the CPMP on 16 September 1998. This variation did not require any amendment to the Community Marketing Authorisation.

- The MAH submitted to the EMEA on 14 January 1999 an application for the Transfer of the Marketing Authorisation from Boehringer Mannheim GmbH, Germany to Roche Registration Limited, United Kingdom, pursuant to Article 3 of Commission Regulation (EC) No. 2141/96 of 7 November 1996, as amended. The procedure started 15 January 1999. A positive opinion (EMEA/H/C/105/I/09) was signed by the Executive Director at the EMEA on 3 February 1999 and forwarded to the European Commission, which granted a Commission Decision 08 April 1999.
- The Marketing Authorisation Holder submitted on 14 January 1999 an application for a Notification of a Type I variation (change following modification 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 15 January 1999. A positive notification (EMEA/H/C/105/I/10) was signed by the Head of the Human Medicines Evaluation Unit on 3 February 1999 and the European Commission granted a Commission Decision on Decision 08 April 1999.
- The Marketing Authorisation Holder submitted on 17 January 2000 an application for a type II Variation (update of the Summary of Product Characteristics and Package Leaflet following the introduction of an Urgent Safety Restriction), pursuant to Article 1(2) of Commission Regulation (EC) No. 542/95 of March 1995, as amended. The procedure started on 21 January 2000. A positive opinion (EMEA/H/C/105/II/11) was adopted by the CPMP on 16 February 2000 and the European Commission granted a Commission Decision on 29 May 2000.

Subsequent post Marketing Authorisation applications agreed upon are summarised in the table below:

Scope	Application number	Type of modification	Notification/ Opinion issued on	Commission Decision Issued/amended on
Update of summary of product characteristics and package leaflet	II/12	II	16.11.00	22.02.01 (20.03.01)
Change in or addition of manufacturer(s) of active substance	I/II/13	I/II	01.03.01	13.03.01
Quality changes	II/14	II	26.04.01	11.05.01
change in test procedure for determining the content of the two-chain reteplase protein in the bulk drug solution.	I/II/15	I/II	26.04.01	
Renewal of Marketing Authorisation, resulting in changes to the SPC (sections 4.6, 4.8 and 5.3) PL and labelling.	R/16	R	26.07.01	9.11.01
an update of Part II of the dossier, including an extension of the shelf-life of the finished product to 3 years.	II/17	II	13.12.01	27.03.02
a correction of the IPC limit for Specific Amidolytic Activity of the Diafiltrate (IPC Sample 10) of Reteplase.	I/18	I	18.03.03	N/A
change in the Production and In-Process Controls (IPC) of the Raw Material Recombinant Serin-1 Erythrina Trypsin Inhibitor (recSerETI).	I/19	I	25.04.03	N/A
replacement of test kit by manually prepared solutions of ammonium vanadate and ammonium molybdate for routine testing of phosphate.	I/20	I	18.03.03	N/A
deletion of a contraindication in diabetic patients (section 4.3 of the SPC) following the publication of a CPMP position statement concerning the use of iv fibrinolytics in diabetic patients. Section 2 of the PL has been updated accordingly. The MAH took this opportunity to update the contact details of a number of local representatives.	II/21	II	22.05.03	07.08.03
an extension of the shelf-life (from 42 to 60 months) for the intermediates (recSerETI inclusion bodies).	I/22	I	24.06.03	N/A