STEPS TAKEN AFTER GRANTING THE MARKETING AUTHORISATION

For procedures finalised after 01 February 2004 please refer to module 8B**.**

- The MAH submitted in accordance with Commission Regulation (EC) No. 542/95 an application for a Type I variation relating to the filling process, which will be carried out at an alternative site - Sächsische Serumwerke, Dresden, Germany. The EMEA adopted a positive opinion on 23 July 1997 and no amendments to the Annexes of the Community Marketing Authorisation were required.

- The MAH submitted in accordance with Commission Regulation (EC) No. 542/95 an application for a Type II variation relating to an additional presentation, where separate sterile needles are included with the pre-filled syringes (without needle). This new presentation applies to all package sizes. The EMEA adopted a positive opinion on 23 July 1997. The Commission Decision amending the Community Marketing Authorisation was adopted on 17 November 1997.

- The MAH submitted in accordance with Commission Regulation (EC) No. 542/95 an application for a Type I variation relating to the monograph, in which the set limit for unbound hepatitis A antigen has been modified in line with the performance of the ELISA used to test for the completeness of adsorption. The EMEA adopted a positive opinion on 24 September 1997 and no amendments to the Annexes of the Community Marketing Authorisation were required.

- The MAH submitted in accordance with Commission Regulation (EC) No. 542/95 an application for a Type I variation relating to the new Manufacturing Authorisation Holder, SmithKline Beecham Biologicals Manufacturing S.A, located in Wavre Belgium, which performs labelling and packaging of the medicinal product. The EMEA notified the European Commission and the MAH on 31 October 1997 that the variation is accepted.

- The MAH submitted in accordance with Article 10(3) of Council Directive No. 92/27/EE, a notification of a change to an aspect of the Package Leaflet not connected to the Summary of Product Characteristics. The EMEA notified the European Commission and the MAH on 29 October 1998 that the change is accepted. The Commission Decision amending the Community Marketing Authorisation was adopted on 22 December 1998.

- The MAH submitted in accordance with Commission Regulation (EC) No. 542/95 an application for a Type I variation relating to an extension of shelf-life of the finished product from 24 months to 36 months at 2 – 8 ˚C. The EMEA notified the European Commission and the MAH on 6 November 1998 that the variation is accepted. The Commission Decision amending the Community Marketing Authorisation was adopted on 26 January 1999.

- The MAH submitted in accordance with Commission Regulation (EC) No. 542/95 an application for a Type I variation relating to a new subcontracted packaging site located in Mayenne, France. The EMEA notified the European Commission and the MAH on 31 December 1998 that the variation is accepted.

- The MAH submitted in accordance with Commission Regulation (EC) No. 542/95 an application for a Type I variation relating to the introduction of a new HAB in-house reference vaccine. The EMEA adopted a positive opinion on 25 March 1999 and no amendments to the Annexes of the Community Marketing Authorisation were required.

- The MAH submitted in accordance with Commission Regulation (EC) No. 542/95 an application for a Type I variation to replace of the pre-filled glass syringe with one which consists of a longer barrel and a longer plunger rod. The EMEA notified the European Commission and the MAH on 24 June 1999 that the variation is accepted.

- The MAH submitted an application for a Type I variation in accordance with Commission Regulation (EC) No. 542/95 for the the scale up of the hepatitis B component of Twinrix Adult. The EMEA adopted a positive opinion on 29 July 1999 and no amendments to the Annexes of the Community Marketing Authorisation were required.

- The MAH submitted an application for a Type I variation in accordance with Commission Regulation (EC) No. 542/95 for the to the implementation of a new working seed for hepatitis B component of Twinrix Adult. The EMEA adopted a positive opinion on 29 July 1999 and no amendments to the Annexes of the Community Marketing Authorisation were required.

- The MAH submitted in accordance with Commission Regulation (EC) No. 542/95 an application for a Type I variation for an additional packaging site located in Germany (Bönen), in addition to the packaging sites located in Belgium (Rixenart, Wavre) and France (Mayenne). The EMEA notified the European Commission and the MAH on 31 May 2000 that the variation is accepted.

- 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 HBsAg specifications and analytical methods. The EMEA adopted a positive opinion on 29 June 2000 and no amendments to the Annexes of the Community Marketing Authorisation were required.

- The MAH submitted an application for a Type I variation in accordance with Commission Regulation (EC) No. 542/95 for the scale-up of the manufacture of the active substance, inactivated hepatitis A virus (HAV), which is one of the active substances of Twinrix Adult. The EMEA adopted a positive opinion on 21 September 2000 and no amendments to the Annexes of the Community Marketing Authorisation were required.

- The MAH submitted an application for a Type II variation in accordance with Commission Regulation (EC) No. 542/95 to add the wording regarding sensitization to thiomersal in medicinal products as agreed by CPMP in July 1999 in section 4.4 of SPC. The EMEA adopted a positive opinion on 19 October 2000 and the amendments to Annexes I and IIIB (Summary of Product Characteristics and Package Leaflet) of the Community Marketing Authorisation were adopted on 13 March 2001.

- The MAH submitted an application for a Type II variation in accordance with Commission Regulation (EC) No. 542/95 for the to the approval of a new MRC-5 Manufacturers Working Cell Bank, in replacement of the currently used MRC-5 Manufacturer Working Cell Bank, for the production of inactivated hepatitis A virus bulk antigen, which is used for the formulation of Twinrix vaccines. The EMEA adopted a positive opinion on 14 December 2000 and no amendments to the Annexes of the Community Marketing Authorisation were required.

- The MAH submitted in accordance with Article 10(3) of Council Directive No. 92/27/EE, a notification of a change to an aspect of the Package Leaflet not connected to the Summary of Product Characteristics. The EMEA notified the European Commission and the MAH on 20 March 2001 that the change is accepted. The Commission Decision amending the Community Marketing Authorisation was adopted on 17 May 2001.

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
Quality change (demonstration of TSE compliance)	II/0018	II	20.09.01	20.10.01
Update of the SPC (sections 4.2 and 5.1) following a new vaccination schedule	II/0019	II	26.04.01	30.08.01
Renewal	R/0020	R	26.07.01	09.11.01
Change in name of manufacturing site	I/0021	I	16.11.01	-
Change in the name of the MAH and manufacturer responsible for batch release	I/0022	I	05.11.01	17.12.01
Change in name of manufacturing site	I/0023	I	16.11.01	-
Update of the SPC (section 4.8 undesirable effects) following a review of the post-marketing surveillance data. (7th PSUR).	II/0024	II	17.01.02	11.04.02
Change(s) to test methods and/or specifications for the finished product	II/0025	II	21.03.02	03.04.02
Amendment of the Package Leaflet to reflect changes in section 4.8 of the SPC, previously approved through the variation EMEA/H/C/112/II/24. In addition, the name and address of the local representatives in Greece, Spain, Italy, Norway and the United Kingdom have been updated.	II/0026	II	27.06.02	24.10.02
Change(s) to manufacturing process for the active substance	II/0027	II	25.07.02	02.09.02
Change(s) to shelf-life of the active substance	II/0028	II	25.07.02	02.09.02
Change(s) to test methods and/or specifications for the active substance	II/0030	II	20.02.03	07.03.03
Change(s) to test methods and/or specifications for the finished product	II/0031	II	25.09.03	03.10.03
Change(s) to manufacturing process for the active substance	II/0032	II	22.10.03	27.10.03
Change(s) to manufacturing process for the active substance	II/33	II	22.10.03	27.10.03
Addition of a manufacturing site for part of the manufacturing process	I/35	I	18.07.03	-
The MAH proposes to amend section 4.4 (Special warnings and special precaution of use) of the Summary of Product Characteristics (SPC) to reflect the factors that may lead to a reduced hepatitis B immunogenicity. The PL has been amended accordingly. In addition, the contacts of the DE, ES, IR, PT and FI local representatives have been amended.	II/0036	II	20.11.03	30.01.04

[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.