STEPS TAKEN AFTER GRANTING THE MARKETING AUTHORISATION

For procedures finalised after 30 November 2004 please refer to module 8B.

- In accordance with Article 3 of Commission Regulation (EC) No 2141/96 of 7 November 1996, Sequus Pharmaceutical Inc. submitted on 17 September 1996 to the EMEA an application for the transfer of Marketing Authorisation to SP Europe. On 22 November 1996 the CPMP adopted a positive Opinion on the transfer and the Commission Decision was issued on 18 February 1997.
- On 18 February 1997 SP Europe submitted a Type I variation application in accordance with Article 4 of Commission Regulation (EC) No. 542/95 of 10 March 1995. The scope of the variation related to the change of the manufacturing site responsible for the importation of the medicinal product, the packaging and the batch release of the finished medicinal product within the EEA. On 18 March 1997 the CPMP approved the variation. This variation required amendments in the relevant sections of the Commission Decision and the EPAR. The European Commission amended the Decision on 7 May 1997.
- On 18 February 1997 SP Europe submitted a Type II variation application in accordance with Article 6 of Commission Regulation (EC) No. 542/95 of 10 March 1995. The scope of the variation related to the update in the SPC and PL subsequent to new clinical data from clinical trial 30-11. On 16 April 1997 the CPMP approved the variation. The variation required amendments in the relevant sections of the Commission Decision and the EPAR. The European Commission amended the Decision on 29 July 1997.
- On 7 March 1997 SP Europe submitted another Type I variation application related to the change of its address. On 18 March 1997 the EMEA approved the variation. This variation required amendments in the relevant sections of the Commission Decision and the EPAR. The European Commission amended the Decision on 7 May 1997.
- On 27 August 1997 the Marketing Authorisation Holder submitted six applications for a Type I variation relating to changes in the test procedures of the medicinal product. The procedure started on 16 October 1997. The variations were approved by the EMEA on 13 November 1997 and did not require any amendments to the Commission Decision. Changes were introduced in the chemical and pharmaceutical documentation of the dossier.
- On 11 June 1998 SP Europe submitted another Type I variation application related to a change in the manufacturer of the active substance. The procedure started on 19 June 1998. This variation was approved by the EMEA on 3 July 1998 and did not require any amendments to the Commission Decision. Changes were introduced in the chemical and pharmaceutical documentation of the dossier.
- On 5 February 1999 the Marketing Authorisation Holder submitted an application for a Type II variation for an update of the Summary of Product Characteristics, Labelling and Package Leaflet to include the following: 1) a change of the declaration of the active substance from *doxorubicin HCl (pegylated liposomal)* to *pegylated liposomal doxorubicin hydrochloride* in order to emphasize the importance of the formulation, 2) a warning not to use Caelyx interchangebly with other formulations of doxorubicin hydrochloride, 3) a warning not to use in-line filters as Caelyx vesicles can clog the filter pores. The procedure started on 26 February 1999. This variation was approved by the EMEA on 22 April 1999 and the Commission adopted the decision on 26 July 1999.
- Pursuant to Article 6 of Commission regulation (EC) No. 542/95 of 10 March 1995, the Marketing Authorisation Holder submitted to the EMEA on 7 December 1999 an application for a Type II variation for an update of the Summary of Product Characteristics according to results included in the Fifth Periodic Safety Update covering the period from 22 June 1998 to 20 June 1999. The CPMP during its February 2000 meeting concluded by consensus by that although no new safety signals arose to alter the overall risk/benefit profile of Caelyx, the wording in section 4.8 Undesirable Effects stating that no local necrosis following extravasation has been observed to date should be removed and the section amended accordingly since at least

one case of local necrosis had been reported in the course of the Fifth Periodic Safety Update. This Opinion was forwarded in all all-official languages of the European Union to the European Commission, which adopted the corresponding Decision on 29 May 2000.

- Pursuant to Article 6 of Commission regulation (EC) No. 542/95 of 10 March 1995, the Marketing Authorisation Holder submitted to the EMEA on 29 November 1999 an application for a Type II variation for a new line extension i.e: the treatment of advanced ovarian cancer in women who have failed a first-line platinum-based chemotherapy regimen. The CPMP, during its June 2000 plenary meeting, considered the changes acceptable and issued on 29 June 2000 a favourable Opinion by consensus on the Type II variation. This Opinion was forwarded, in all official languages of the European Union, to the European Commission, which adopted the corresponding Decision 24 October 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 the name of a manufacturer of the active substance	I/0015	I	26.01.00	22.02.00
Change in specifications of active substance	I/0016	I	18.02.00	25.02.00
Update of Summary of Product Characteristics and Package Leaflet	II/0017	II	29.03.01	05.07.01
Extension of shelf-life as foreseen at time of authorisation	I/0018	I	26.02.01	27.04.01
Renewal	R/0019	R	26.04.01	24.09.01
Minor change in the manufacturing of the medicinal product	I/0020	I	20.12.10	21.01.02
Minor change in the manufacturing of the medicinal product	I/0021	I	10.12.01	21.01.02
Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	N/0022	N	14.01.02	19.02.02
Extension of indication (breast cancer)	II/0023	II	17.10.02	10.01.03
Minor change in the manufacturing of the medicinal product (ETC autoclave)	I/0024	I	15.05.02	17.05.02
Minor change in the manufacturing of the medicinal product	I/0025	I	15.05.02	17.05.02
Minor changes in manufacture of the medicinal product and change in or addition of manufacturing site(s) for part or all of the manufacturing process	I/0026	I	17.01.03	24.01.03
Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	N/0027	N	21.02.03	17.03.03
Minor changes in manufacture of the medicinal product	I/0028	I	01.07.03	08.07.03
Synthesis or recovery of non-pharmacopoeial excipients in the medicinal products	I/0029	I	11.07.03	15.07.03
Change in synthesis or recovery of non-pharmacopoeial excipient (when descr. in dossier)	IB/0030	IB	12.03.04	-
Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	N/0031	N	12.05.04	-

[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.