STEPS TAKEN AFTER GRANTING THE MARKETING AUTHORISATION

For procedures finalised after 1 September 2004 please refer to module 8B.

- On 10 September 1998 the marketing authorisation holder submitted a request pursuant to Article 10(3) of Council Directive 92/27/EEC in order to change the package leaflet with regard to the address of the local representative for Optison in the Netherlands. A Notification (N01) was duly prepared, and the revised Decision was issued by the Commission on 19 November 1998.
- On 5 October 1998 the Marketing Authorisation Holder submitted to the EMEA an application for a Type I variation in accordance with Commission Regulation (EC) No. 542/95 of 10 March 1995, as amended. The scope of this variation was to include Mallinckrodt Medical Imaging Ireland as an additional site for the labelling and packaging of Optison bulk material. This variation was approved by the EMEA on 5 November 1998 and did not require any amendments to the Commission Decision
- On 5 October 1998 the Marketing Authorisation Holder submitted to the EMEA two applications for Type I variations in accordance with Commission Regulation (EC) No. 542/95 of 10 March 1995, as amended, arising from the marketing authorisation holder's Follow Up Measure commitments. I/03 was a request to add a limit test for albumin aggregates into the product specification rejected on grounds of insufficient supporting data). I/04 related to a test with limits for content of octafluoropropane in the product. Following an extension of the procedure for additional data, this variation was approved on 18 December 1998 and did not require any amendments to the Commission Decision
- An application to amend the contact addresses in the package leaflet was approved by Notification under Article 10(3) of Council Directive 92/27/EEC, on 18 May 1999. A revised Commission Decision was issued 29 June 1999.
- On 31 March 1999 the Marketing Authorisation Holder submitted to the EMEA an application for a Type I variation in accordance with Commission Regulation (EC) No. 542/95 of 10 March 1995, as amended. The scope of this variation was a change in in-process controls applied during the manufacture of the product. This variation was approved by the EMEA on 4 May 1999 and did not require any amendments to the Commission Decision.
- On 21 April 1999 the Marketing Authorisation Holder submitted to the EMEA an application for a Type I variation in accordance with Commission Regulation (EC) No. 542/95 of 10 March 1995, as amended. The scope of this variation was to register FluoroMed, L.P. as an additional alternative supplier of an intermediate compound used in the manufacture of the active substance. The CPMP at the May 1999 plenary meeting adopted a request for the new site to be inspected. The procedure was therefore extended. This variation was approved by the EMEA on 19 August 1999 and did not require any amendments to the Commission Decision.
- An application to amend the contact addresses in the package leaflet was approved by Notification under Article 10(3) of Council Directive 92/27/EEC, on 27 January 2000.
- On 7 April 2000 the Marketing Authorisation Holder submitted to the EMEA two applications for Type I variations in accordance with Commission Regulation (EC) No. 542/95 of 10 March 1995, as amended. The scope of these variations was a change in the specifications of excipients in the medicinal product and a minor change in the manufacture of the medicinal product. This variations were approved by the EMEA on 8 May 2000 and did not require any amendments to the Commission Decision.
- On 18 April 2000 the Marketing Authorisation Holder submitted to the EMEA an application for a Type II variation in accordance with Commission Regulation (EC) No. 542/95 of 10 March 1995, as amended. The scope of this variation was to update the SPC and the Package Leaflet following the assessment of the 2nd and 3rd PSUR, to include under section 4.8 rare adverse events of allergic type and transient nervous and visual disorders. The CPMP adopted a positive opinion for this variation on 27 July 2000. A revised Commission Decision was issued on 29 November 2000.

- On 25 April 2000 the Marketing Authorisation Holder submitted to the EMEA an application for a Type I variation in accordance with Commission Regulation (EC) No. 542/95 of 10 March 1995, as amended. The scope of this variation was a minor change in the manufacturing process of the active substance. This variation was approved by the EMEA on 26 May 2000 and did not require any amendments to the Commission Decision.
- On 28 April 2000 the Marketing Authorisation Holder submitted to the EMEA an application for a Type I variation in accordance with Commission Regulation (EC) No. 542/95 of 10 March 1995, as amended. The scope of this variation was a change in the specification of the medicinal product. This variation was a consequence to a follow up measure regarding limit for percent polymers and aggregates accepted at the CPMP meeting held in January 2000. This variation was approved by the EMEA on 31 May 2000 and did not require any amendments to the Commission Decision.
- On 17 July 2000 the Marketing Authorisation Holder submitted to the EMEA an application for a Type I variation in accordance with Commission Regulation (EC) No. 542/95 of 10 March 1995, as amended. The scope of this variation was a change in the name of the manufacturing site of the finished product *Optison Molecular Byosistems* Inc to *Mallinckrodt Inc*. This variation was approved by the EMEA on 9 August 2000 and did not require any amendments to the Commission Decision.

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 the medicinal product (either invented name of common name): the MAH applied to change the name of the INN from octafluoropropane to perflutren, following a recommendation from the WHO INN Committee.	I/0016	I	14.05.01	--
Minor change in labelling or package leaflet not connected with the SPC (Art. 10.3 Notification)	N/0017	N	05.06.01	08.10.01
Change in the contact details of the local representatives on the package leaflet in all official languages.	N/0018	N	13.03.02	18.04.02
Transfer of MAH	T/0019	T	26.03.02	29.04.02
Bulk finished product manufacturing change	II/0020	II	19.09.02	20.11.02
Transfer of the manufacturing site for outer packaging and batch release	I/0021	I	15.01.03	17.03.03
Renewal	R/0022	R	20.02.03	15.05.03
Addition of new plasma sources	II/0023	II	25.09.03	26.09.03
Update of Summary of Product Characteristics and Package Leaflet	II/0024	II	23.06.04	12.08.04

[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.