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

Steps taken after granting the Marketing Authorisation

- On 29 February 1996, Roche Registration Ltd submitted two applications for a Type I variation in accordance with Commission Regulation (EC) No. 542/95. The scope of the variations related to minor changes of the manufacturing process of the finished medicinal products. On 25 March 1996, the EMEA approved the variations. These variations did not require any amendments to the Commission Decision.
- The Marketing Authorisation Holder submitted to the EMEA on 4 October 1996 two applications for a Type II variation in accordance to Article 6 of Commission Regulation (EC) No. 542/95. The procedure started 15 October 1996. The scope of the variations related to the introduction of an additional package size of 300 capsules for CellCept 250 mg and an additional package size of 150 tablets for CellCept 500 mg respectively. The CPMP, during its meeting on 15-17 November 1996, considered both type II variations to be acceptable and adopted a positive Opinion for both type II variations on 20 November 1996, and the corresponding Commission Decisions were issued on 13 May 1997.
- The Marketing Authorisation Holder submitted on 12 November 1996 another application for a Type II variation related to the addition of "colitis" as an adverse event into the SPC. The procedure started on 19 November 1996. The CPMP considered this Type II variation acceptable and agreed on the revised SPC and the Package Leaflet. The CPMP adopted therefore on 19 December 1996 a positive Opinion on the Type II variation, and the corresponding Commission Decision was issued on 2 May 1997.
- On 16 April 1997, the Marketing Authorisation Holder submitted an application for a Type I variation in accordance with Commission Regulation (EC) No. 542/95. The procedure started on 25 April 1997. The scope of the variation related to the extension of the shelf-life for both CellCept 250 mg capsules and500 mg tablets from two years to three years. On 23 May 1997, the EMEA issued the Notification. This variation required amendments to be incorporated into the relevant sections of the Commission Decision, and the corresponding Commission Decision was issued on 14 July 1997.
- On 4 July 1997 the Marketing Authorisation Holder submitted an application for two Type I variations in accordance with Commission Regulation (EC) No. 542/95. The procedures started on 24 July 1997. The scope of the variations related to a tightening of the specifications for the active substance and a minor change in the manufacturing process of the active substance. The EMEA considered the variations to be acceptable and issued on 20 August and 9 September, respectively, positive notifications for the Type I variations. These variations did not require any amendments to the Commission Decision.
- On 7 July 1997, the Marketing Authorisation Holder submitted an application for a Type II variation in accordance with Art. 6 of Commission Regulation (EC) No. 542/95. The procedure started on 25 July 1997. The scope of the variation related to the extension of the approved indication to include prophylaxis of acute transplant rejection in patients receiving allogenic cardiac transplant, in combination with cyclosporine and corticosteroids. The CPMP, during its April 1998 plenary meeting, considered the variation acceptable and issued on 22 April 1998 a positive opinion on the Type II variation. The corresponding Commission Decision was issued on 17 August 1998.
- On 4 July 1997, the Marketing Authorisation Holder submitted several applications for Type I variations in accordance with Art. 6 of Commission Regulation (EC) No. 542/95. The procedures started on 24 July 1997. The scope of the variations related to minor changes in the specification and test methods of the active substance for 250 mg capsules and 500 mg tablets. On 20 August 1997, the EMEA issued the Notifications, which did not require an amendment to the Commission Decision.
- On 28 August 1997 the Marketing Authorisation Holder submitted an application for a Marketing Authorisation for CellCept powder for concentrate for solution for infusion falling

within the scope of Part B of the Annex of the Council Regulation (EEC) 2309/93. The procedure started on 29 September 1997. The CPMP, during its May 1998 plenary meeting, considered the application acceptable and issued on 27 May 1998 a positive Opinion for granting a Marketing Authorisation for CellCept 500 mg powder for concentrate for solution for infusion. The corresponding Commission Decision was issued on 20 October 1998.

- On 30 September 1997, the Marketing Authorisation Holder submitted an application for a Marketing Authorisation for CellCept 1 g/5 ml powder for oral suspension falling within the scope of Part B of the Annex of the Council Regulation (EEC) 2309/93. The procedure started on 22 October 1997. The CPMP, during its November 1998 plenary meeting, considered the application acceptable and issued on 19 November 1998 a positive Opinion for granting a Marketing Authorisation for CellCept 1g/5ml powder for oral suspension. The corresponding Commission Decision was issued on 26 February 1999.

- On 11 March 1998, the Marketing Authorisation Holder submitted an application for a Type II variation in accordance with Art. 6 of Commission Regulation (EC) No. 542/95. The procedure started on 27 March 1998. The scope of the variation related to the inclusion of several post-marketing experiences, which had been collected in the Periodic Safety Update Reports. In particular the Marketing Authorisation Holder proposed changes in sections 4.4, 4.5, 4.8 and 5.1 of the SPC and the corresponding sections of the Package Leaflet. The CPMP, during its May 1998 plenary meeting, considered the variations acceptable and issued on 27 May 1998 a positive opinion on the Type II variation. The corresponding Commission Decision was issued on 18 September 1998.

- On 25 August 1998, the Marketing Authorisation Holder submitted several applications for Type I variations in accordance with Commission Regulation (EC) No. 542/95. The procedures started on 9 September 1998. The scope of the variations related to the introduction of an alternative manufacturing site and change in batch size for CellCept 250 mg capsules and 500 mg tablets, minor changes in the finished product specification and primary packaging material for 250 mg capsules and 500 mg tablets. On 30 October 1998, the EMEA issued the Notifications, which did not require an amendment to the Commission Decision. The scope of one variation related to a minor change in the composition of the 250 mg capsule shell. On 30 October 1998, the EMEA issued the Notification. This variation required amendments to be incorporated into the relevant sections of the Commission Decision, and the corresponding Commission Decision was issued on 17 December 1998.

- On 10 May 1999, the Marketing Authorisation Holder submitted an application for a Type II variation in accordance with Art. 6 of Commission Regulation (EC) No. 542/95. The procedure started on 21 May 1999. The scope of the variation related to the inclusion of several post-marketing experiences, which have been collected in the Periodic Safety Update Reports. In particular the Marketing Authorisation Holder proposed changes in sections: 2, 4.4, 4.5, 4.8 5.2, and 6.4 of the SPC and to the relevant sections of the Package Leaflet. Furthermore changes were proposed to section 4.2 and minor changes were proposed to sections 2, 6.1, 6.2 and 6.3. The SPC, labelling and Package Leaflet have been updated according to the new QRD recommendations/templates. The CPMP, during its July 1999 plenary meeting, considered the variations acceptable and issued on 30 July 1999 a positive opinion on the Type II variation. The corresponding Commission Decision was issued on 8 December 1999.

- On 4 June 1999, the Marketing Authorisation Holder submitted an application for a Type I variation for the powder for oral suspension in accordance with Commission Regulation (EC) No. 542/95. The procedure started on 9 June 1999. The scope of the variation related to a change in the manufacture of the medicinal product. On 4 August 1999, the EMEA issued the Notification, which did not require an amendment to the Commission Decision.

- On 4 October 1999, the Marketing Authorisation Holder submitted an application for a Type II variation (24) in accordance with Art. 6 of Commission Regulation (EC) No. 542/95. The procedure started on 22 October 1999. The scope of the variation related to the extension to the therapeutic indications of the product to include prophylaxis of acute transplant rejection in patients receiving allogenic hepatic transplants. In addition, the SPC and Package Leaflet were updated according to the new QRD templates. The CPMP during its July 2000 plenary meeting

considered the variation acceptable and issued on 27 July 2000 a positive opinion on the Type II variation. The corresponding Commission Decision was issued on 9 November 2000.

- On 10 February 2000 the Marketing Authorisation Holder submitted an application for a Type I variation in accordance with Art. 4 of Commission Regulation (EC) No. 542/95. The procedure started on 15 February 2000. The scope of the variation related to the deletion of the Roche Colarado, Boulder site (formerly Syntex Chemicals, Boulder), as it is no longer used for the manufacture of the active substance. The EMEA considered this variation to be acceptable and issued on 7 March 2000 a positive notification, which did not require an amendment to the Commission Decision.

- On 10 February 2000, the Marketing Authorisation Holder submitted an application for a Type II variation in accordance with Art. 6 of Commission Regulation (EC) No. 542/95. The procedure started on 18 February 2000. The scope of the variation related to changes to the manufacture of the active substance using a new strain of *Penicillium stoloniferum* to increase production. The CPMP, during its June 2000 meeting, considered the variation acceptable and issued on 29 June 2000 a positive opinion on the Type II variation application, which did not require an amendment to the Commission Decision.

- On 28 February 2000, the Marketing Authorisation Holder submitted an application for a Type II variation in accordance with Art. 6 of Commission Regulation (EC) No. 542/95. The procedure started on 17 March 2000. The scope of the variation related to dose recommendations for CellCept, in combination with cyclosporin and corticosteroids, for the prophylaxis of acute allogenic renal transplant rejection in paediatric patients and adolescents. The CPMP during its March 2001 plenary meeting considered the variation acceptable and issued on 29 March 2001 a positive Opinion on the Type II variation application. The corresponding Commission Decision was issued on 16 July 2001.

- On 3 November 2000, the Marketing Authorisation Holder submitted an application for a Type II variation in accordance with Art. 6 of Commission Regulation (EC) No. 542/95. The procedure started on 17 November 2000. The scope of the variation related to the demonstration of compliance with the Commission Directive 1999/82/EC and the Note for Guidance on minimising the risk of transmitting animal spongiform Encephalopathy agents via medicinal products (CPMP/BWP/1230/98 rev. 1). The CPMP, during its April 2001 plenary meeting, considered the changes acceptable and issued on 25 April 2001 a positive Opinion on the Type II variation, which did not require an amendment to the Commission Decision.

- Pursuant to Article 13 of Council Regulation (EEC) No 2309/93 of 22 July 1993, as amended, Roche Registration Limited submitted to the EMEA on 11 October 2000 an application for a renewal of the Marketing Authorisation. The procedure started on 20 October 2000. This renewal required amendments to be incorporated into the relevant sections of the Commission Decision. The CPMP, during its January 2001 plenary meeting, considered the renewal acceptable and issued on 25 January 2001 a positive Opinion, and the corresponding Commission Decision was issued on 03 May 2001.

- On 6 November 2000, the Marketing Authorisation Holder submitted an application for a Type II variation in accordance with Article 6 of Commission Regulation (EC) No. 542/95. The procedure started on 17 November 2000. The scope of the variation related to an update of the SPC (section 4.5, Oral Contraceptives). The CPMP, during its January 2001 plenary meeting, considered the changes acceptable and issued on 25 January 2001 a positive Opinion on the Type II variation application to the terms of the Marketing Authorisation, and the corresponding Commission Decision was issued on 27 April 2001.

- On 6 November 2000, the Marketing Authorisation Holder submitted an application for a Type II variation in accordance with Article 6 of Commission Regulation (EC) No. 542/95. The procedure started on 17 November 2000. The scope of the variation related to an update of the SPC (section 5.3), to reflect the genotoxic potential of mycophenolate mofetil. The CPMP, during its March 2001 plenary meeting, considered the changes acceptable and issued on 29 March 2001 a positive Opinion on the Type II variation application. The corresponding Commission Decision was issued on 16 July 2001.

- On 10 May 2001 the Marketing Authorisation Holder submitted an application for a Type I variation in accordance with Art. 4 of Commission Regulation (EC) No. 542/95. The procedure started on 15 May 2000. The scope of the variation related to a change in the name of the manufacturer of the finished product for CellCept 500 mg powder for concentrate for solution for infusion. The EMEA considered this variation to be acceptable and issued on 18 May 2001 a positive notification for the Type I variation application which did not require an amendment to the Commission Decision.

- On 11 June 2001 the Marketing Authorisation Holder submitted an application for a Type II variation in accordance with Article 6 of Commission Regulation (EC) No. 542/95. The procedure started on 29 June 2001. The scope of the variation related to an update of section 4.8 (undesirable effects) of the SPC to add information in line with the recommendations outlined by the CPMP in the 11th PSUR assessment report. The CPMP, during its August 2001 plenary meeting, considered the changes acceptable and issued on 23 August 2001 a positive Opinion on the Type II variation application to the terms of the Marketing Authorisation, and the corresponding Commission Decision was issued on 6th December 2001.

- On 3 September 2001 the Marketing Authorisation Holder notified the EMEA of their intention to introduce changes to aspects of the Package Leaflet not connected to the Summary of Product Characteristics in accordance with Article 10(3) of Council Directive 92/27/EEC of 31 March 92. The procedure started on 5 September 2001. Changes were made to the package leaflets to update the leaflets in line with the latest QRD template and to amend details of several of the local representatives of the Marketing Authorisation Holder. The EMEA considered this notification to be acceptable and informed the Commission on 20 September 2001. The corresponding Commission Decision was issued on 12 November 2001.

- On 17 October 2001, the Marketing Authorisation Holder submitted several applications for Type I variations in accordance with Commission Regulation (EC) No. 542/95. The procedures started on 24 October 2001. The scope of the variations related to the introduction of an alternative manufacturing site, deletion of packaging sites, changes to the excipients and excipient specifications and change in batch size for CellCept 250 mg capsules and 500 mg tablets. In addition, minor changes were made to the manufacturing process and in process controls for the 500 mg tablets. On 23 November 2001, the EMEA issued the Notifications, which did not require an amendment to the Commission Decision. The scope of two variations related to a deletion of a batch release site for CellCept 250 mg capsules and 500 mg tablets and a change from printing to engraving for the 500mg tablets. On 23 November 2001, the EMEA issued the Notification. These variations required amendments to be incorporated into the relevant sections of the Commission Decision.

- On 31 October 2001, the Marketing Authorisation Holder submitted several applications for Type I variations in accordance with Commission Regulation (EC) No. 542/95. The procedures started on 8 November 2001. The scope of the variations related to a change to the manufacturing process, new methods of analysis and a change to the packaging sites for CellCept powder for oral suspension. On 30 November 2001 and 19 November 2001, the EMEA issued the Notifications, which did not require amendments to the Commission Decision.

- On 6 November 2001, the Marketing Authorisation Holder submitted an application for Type I variation in accordance with Commission Regulation (EC) No. 542/95. The procedure started on 9 November 2001. The scope of the variations related to an increase in batch size for CellCept 500 mg tablets. On 30 November 2001 the EMEA issued the Notification, which did not require an amendment 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
Update section 5.2, pharmacokinetic properties of the SPC to include details of the pharmacokinetic interaction with Cyclosporin.	II/0036	II	13.12.01	15.05.02
Change in kit procedures of the medicinal product	I/0049	I	30.11.01	
Application to register a larger batch size of 300 kg, in addition to the approved batch size of 150 kg for imprinted tablets.	I/0050	I	30.11.01	
Change in kit procedures of the medicinal product	I/0051	I	04.02.02	
Minor change of of the manufacturing process of the active substance.	I/0053	I	14.08.02	
Change in supplier (see notification)	I/0054	I	14.08.02	
Update sections 4.5 (Interaction with other medicinal products and other forms of interaction), 4.8 (Undesirable effects) and 4.9 (Overdose) of the Summary of Product Characteristics (SPC) in line with the recommendations made in the company Core Safety Information. Changes to the information with regards to interactions between the mycophenolate mofetil and prodrugs of aciclovir and ganciclovir (e.g. valaciclovir and valganciclovir respectively). Additionally, the information regarding the undesirable effects and overdose were updated with regards to the frequency of treatment-related adverse effects in paediatric patients and experience in overdose respectively.	II/0055	II	25.07.02	18.10.02
Minor changes in manufacture of the medicinal product.	I/0056	I	23.08.02	
Change in storage conditions.	I/0057	I	18.10.02	12.02.02
Change in the site of manufacture of the medicinal product, also minor changes in the product manufacturing process reduction of product batch size, change in degradation product assay method, change in primary packaging	II/0058	II	24.07.03	

[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.