The European Agency for the Evaluation of Medicinal Products
Evaluation of Medicines for Human Use

10 July 2002
EMEA/CPMP/2749/02/Corr

COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS
25-27 JUNE 2002 PLENARY MEETING
MONTHLY REPORT

The Committee for Proprietary Medicinal Products (CPMP) held its 83rd plenary meeting from 25 to 27 June 2002.

Product related issues

Centralised procedures

No opinions on initial marketing authorisation applications were adopted at this meeting. However, the Committee noted the withdrawal of an initial marketing authorisation application and adopted one opinion by consensus on a "line extension" application (Part B) (in accordance with Annex II of Commission Regulation (EC) No. 542/95, as amended). The CPMP also noted the withdrawal of one "line extension" application (Part B) (in accordance with Annex II of Commission Regulation (EC) No. 542/95, as amended).

Two Lists of Questions (2 Part B) on "line extension" applications (in accordance with Annex II of Commission Regulation (EC) No 542/95 as amended) related to two active substances (1 Part A and 1 Part B) were adopted.

The CPMP noted the withdrawal of the Marketing Authorisation for **Triacelluvax** (Combined diphtheria, tetanus and acellular pertussis vaccine), indicated for active immunisation of children from 6 weeks up to 7 years of age against diphtheria, tetanus and pertussis from Chiron S.p.A. (See Public Statement EMEA/15519/02).

An overview of centralised procedures since 1995 is given in **Annex 1**. The list of medicinal products for which marketing authorisations have been granted by the European Commission since the CPMP plenary meeting in May 2002 is provided in **Annex 2**. The post-authorisation centralised procedures finalised during this meeting are summarised in **Annex 3**.

Referrals

Referral under Article 29(2) of Directive 2001/83/EC (previously known as Article 10(2) of Council Directive 75/319/EEC, as amended)

The CPMP adopted one positive opinion by majority vote for **Actilyse** (alteplase) from Boerhringer Ingelheim Pharma KG. The arbitration procedure was referred to the EMEA under the mutual recognition procedure by Germany on 25 January 2001. The CPMP opinion will now be forwarded to the Commission.

Referral under Article 30 of Directive 2001/83/EC (previously known as Article 11 of Council Directive 75/319/EEC, as amended)

Following a referral initiated by France under Article 30 of Directive 2001/83/EC, the CPMP adopted by consensus an opinion for **Motilium** (domperidone) from Janssen Research Foundation which will lead to the European harmonisation of the Summary of Products Characteristics.

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 84 16
E-mail: mail@emea.eu.int http://www.emea.eu.int

Referral under Article 31 of Directive 2001/83/EC (previously known as Article 12 of Council Directive 75/319/EEC, as amended)

Following a referral under Article 31 of Directive 2001/83/EC initiated by Italy in March 2002, the CPMP reassessed the efficacy and safety of sibutramine containing medicinal products (Reductil, Meridia, Reduxade, Sibutral and associated invented names) and adopted a positive opinion by consensus, recommending the maintenance of the Marketing Authorisations with amendments to the Summary of Product Characteristics. The CPMP will continue to keep sibutramine containing medicinal products under review, including the follow-up to the clinical trial previously requested by the CPMP in November 2000.

Scientific Advice procedures

The CPMP was informed of the outcome of the discussions of the Scientific Advice Review Group (SciARG) meeting, which was held on Monday 24 June 2002. For further details, please see **Annex 4**.

EMEA PROCEDURAL ANNOUNCEMENT

Companies intending to submit Scientific Advice requests in August 2002 should notify the EMEA Secretariat formally (scientificadvice@emea.eu.int) by 5 July 2002.

Invented Name Review Group

The invented Name Review Group (NRG) held its 30th meeting on Monday 24 June 2002 and the conclusions of the group were subsequently adopted by the CPMP.

Non-product related issues

CPMP Working Parties and Ad Hoc Groups

- The **CPMP Working Parties Chairpersons** meeting chaired by Dr. D. Brasseur was held on 26 June 2002 to consolidate comments on the Annex 1 of Directive 2001/83/EEC prior to their transmission to the Commission.
- The **Paediatric Expert Group (PEG)**, chaired by Dr D. Brasseur met on 28 June 2002 to discuss amongst other topics, Paediatric initiatives in various Member States, evaluation of medicinal products in neonates, maturation of the immune system (consequence for the evaluation of medicinal products in children) and pharmacovigilance in children.

Organisational Matters

- The next meeting on **ORGAnisation Matters** will be held on 22 July 2002.

Mutual Recognition procedure

The June MRFG meeting was the final meeting under the Spanish Presidency. Denmark will take over the Chairmanship as of 1st July 2002. Mrs Joan Boye will be the next chairperson and should be contacted in case of questions regarding the MRP.

The CPMP noted the report from the MRFG meeting held on 24 June 2002. For further details, please see **Annex 6**.

The 84th plenary meeting of the CPMP will be held from 23 to 25 July 2002.

Noël Wathion

Head of Unit
Post-Authorisation Evaluation of Medicines for Human Use
Tel. (+44-20) 74 18 85 92

This CPMP Monthly Report and other documents are available on the Internet at the following address: http://www.emea.eu.int

EMEA CENTRALISED PROCEDURES

	1995-2001			2002			Overall Total
	Part A	**Part B**	**Total**	**Part A**	**Part B**	**Total**	
Scientific Advice	88	164	252	3	20	23	275
Follow-up to scientific advice	18	17	35	1	2	3	38
Protocol Assistance	0	2	2	2	0	2	4
Follow-up to Protocol Assistance	2	0	2	1	0	1	3

	1995-2001			2002			
	Part A	**Part B**	**Total**	**Part A**	**Part B**	**Total**	
Applications submitted	120	215	335	5	13	18	353
Withdrawals	15	45	60	4	4	8	68
Positive CPMP opinions	77	131	208	14	10	24	232[1]
Negative CPMP opinions[2]	1	4	5	0	0	0	5[3]
Marketing authorisations granted by the Commission	71	123	194	3	20	23	217[4]

	1995-2001			2002			Overall Total
	Part A	**Part B**	**Total**	**Part A**	**Part B**	**Total**	
Variations type I	448	806	1254	65	143	208	1462
Positive opinions, variations type II	285	362	647	58	84	142	789
Negative opinions, variations type II	1	6	7	0	0	0	7
Extensions (Annex II applications)	38	36	74	0	4	4	78

[1] 232 positive opinions corresponding to 175 substances
[2] In case of appeal the opinion will not be counted twice
[3] 5 negative opinions corresponding to 4 substances
[4] 217 marketing authorisations corresponding to 166 substances

MEDICINAL PRODUCTS GRANTED A COMMUNITY MARKETING AUTHORISATION UNDER THE CENTRALISED PROCEDURE SINCE MAY 2002 CPMP MONTHLY REPORT

Invented Name	Pegasys
INN	peginterferon alfa-2a
Marketing Authorisation Holder	Roche Registration Ltd
ATC code	L03AB11
Indication	Treatment of chronic hepatitis in adults
CPMP Opinion date	21/03/2002

Invented Name	Tamiflu
INN	oseltamivir
Marketing Authorisation Holder	Roche Registration Ltd
ATC code	J05AH02
Indication	Treatment of influenza
CPMP Opinion date	21/03/2002

OUTCOME OF THE JUNE 2002 CPMP MEETING IN RELATION TO CENTRALISED APPLICATIONS IN THE POST-AUTHORISATION PHASE

Opinions for Type II Variation applications	
Number of Opinions	**Outcome**
5 Extensions of indication	5 Positive opinions by consensus
6 SPC changes	6 Positive opinions by consensus
1 quality changes	1 Positive opinion by consensus

Opinions for Annual re-assessment applications		
Name of Medicinal Product (INN) MAH	**Outcome**	**Comments**
Cystagon (mercaptamine) Orphan Europe SARL	Positive opinion by consensus	Marketing Authorisation to remain under exceptional circumstances
Kaletra (lopinavir/ritonavir), Abbott Laboratories	Positive opinion by consensus	Marketing Authorisation no longer to remain under exceptional circumstances
Benefix (nonacog alfa), Genetics Institute of Europe B.V.	Positive opinion by consensus	Marketing Authorisation to remain under exceptional circumstances

Opinions for Renewal applications		
Name of Medicinal Product (INN) MAH	**Outcome**	**Comments**
Benefix (nonacog alfa), Genetics Institute of Europe B.V.	Positive opinion by consensus	---
Cystagon (mercaptamine), Orphan Europe SARL	Positive opinion by consensus	---
Helicobacter Test INFAI (13C-urea), INFAI	Positive opinion by consensus	---

OUTCOME OF THE JUNE 2002 CPMP MEETING IN RELATION TO SCIENTIFIC ADVICE PROCEDURES

Substance	Intended indications(s)	Topic				
		Type of Request		Pharma-ceutical	Pre-Clinical	Clinical
		New	Follow-up			
Chemical	Generalized Anxiety Disorder		**X**			**X**
Chemical	Treatment of atrial fibrillation Treatment and prevention of venous thromboembolism	**X**				**X**
Biological	Multiple Sclerosis	**X**			**X**	**X**
Chemical	Congestive heart failure	**X**				**X**
Chemical	Hepatocellur carcinoma		**X** (Protocol assistance)			**X**

In June 2002, the above-mentioned 5 final Scientific Advice letters were adopted. The Committee accepted 3 new Scientific Advice requests, 1 follow-up Scientific Advice requests and 1 request for Protocol Assistance.

DOCUMENTS PREPARED BY THE CPMP WORKING PARTIES AND AD-HOC GROUPS ADOPTED DURING THE JUNE 2002 CPMP MEETING

EFFICACY WORKING PARTY

Following **Efficacy Working Party (EWP)** recommendation, the CPMP agreed that the revision of the CPMP Note for guidance on Harmonisation of requirements for influenza vaccines (CPMP/BWP/214/96), as described in the EWP concept paper CPMP/EWP/1045/01, should be postponed until further information is available. The concept paper will be consequently withdrawn from the EMEA website.

SAFETY WORKING PARTY

Reference number	Document	Status
CPMP/SWP/398/01	Note for Guidance on Photosafety testing	Adopted in June 2002
CPMP/SWP/2592/02	SWP Conclusions and recommendations with regard to the use of genetically modified animal models for carcinogenicity assessment	Adopted in June 2002
CPMP/SWP/2599/02	Position Paper on the Non-clinical safety studies to support clinical trials with a single low dose of a compound	Released in June 2002 for 6 month consultation
CPMP/SWP/4446/00	Note for Guidance on Specification limits for residues of metal catalysts	Released in June 2002 for 6 month consultation

VACCINE EXPERT GROUP

Reference number	Document	Status
CPMP/1100/02	Note for Guidance on Development of vaccinia based vaccines against smallpox	Adopted in June 2002

Report from the meeting held on 24 June 2002

General issues

Legal basis for an application under Article 10 a) iii 1st or 2nd paragraph when the strength or pharmaceutical form of the Reference product differs between RMS/CMS(s)

Abridged applications are made under Article 10.1 a) iii) of Directive 2001/83/EC. The first paragraph of this article concerns products where the particular strength or form of the originator product is authorised in the Member State (MS) to which the application is made. The second paragraph of this article concerns products where the particular strength or form of the originator product is not authorised in the MS to which the application is made.

For abridged applications submitted in an MR procedure, the legal basis (and the dossier) must be the same for the RMS and all CMSs. However it is difficult for applicants to comply with this requirement when the particular strength or form of the originator product is authorised in some but not all the MSs. Where the strength or form is authorised, the first paragraph of Article 10.1 a) iii) applies, while for those CMSs where it is not authorised, the second paragraph of Article 10.1 a) iii) applies. For these types of applications, applicants may follow the guidance given below:

- The legal basis specified **for the MRP** should be Article 10.1 a) iii), without reference to either the first or second paragraphs. The applicant should indicate this in the covering letter. The assessment report from the RMS should also indicate Article 10.1 a) iii) as the legal basis for the MRP.

- In the application form, the applicant should tick the box for Article 10.1 a) iii) **and** also tick either the first paragraph if the originator strength/form is authorised in the MS to which the application is made, or the second paragraph if the strength/form is not authorised in the MS to which the application is made.

- The applicant should submit the same dossier in all MSs, including all information required for an Article 10.1 a) iii) second paragraph application, even if some information is not necessary for particular CMSs as the strength/form is already licensed on their markets.

- The assessment report from the RMS should cover all aspects of the dossier, including the information relevant to the Article 10.1 a) iii) second paragraph application which may not be needed in some CMSs.

Terfenadine containing medicinal products:

Marketing Authorization Holders of Terfenadine containing medicinal products are reminded about the need to submit a Type II variation by 15 July 2002 to introduce certain changes to the SPC, as outlined in the statement below which was part of the April MRFG Press Release:

Medicinal products with terfenadine as active substance have been the subject in 1998 of a Commission Decision on a referral under article 31 of Directive 2001/83/EC, resulting in a harmonised SPC for all Marketing Authorisations of terfenadine-containing medicinal products in the European Community.
Recently, a safety- related Type II variation application has been approved for one of the Marketing Authorisation Holders (MAH), adding a new interaction between terfenadine and carbamazepine in the SPC as follows:

Section 4.4
"Terfenadine should be used cautiously in patients of epilepsy under treatment of carbamazepine (see section 4.5)."

Section 4.5

"A drug interaction between terfenadine and carbamazepine has been reported. It is characterised by increased serum carbamazepine concentrations with possible clinical symptoms of carbamazepine overdosage. Data suggest, that the mechanism is linked to inhibition of hepatic metabolism of carbamazepine (inhibition of CYP3A4 enzyme). Consequently, especially for patients under long-term concomitant treatment, clinical and laboratory monitoring is recommended."

In order to maintain a harmonised SPC and to ensure that the same safety-related information is given, all other MAHs of terfenadine-containing medicinal products are hereby requested to apply for an identical change to their SPC. The corresponding variation application should be submitted **not later than 15 July 2002** to the national competent authorities.

MAHs are reminded that for medicinal products, which have been subject of an article 31 referral, a change to the Marketing Authorisation should be submitted via a MR procedure as outlined in Commission Regulation (EC) 541/95, as amended. Therefore, and in order to be able to submit a variation application, the MAH has to choose a Member State as RMS. The RMS will then issue the MR-number to the MAH and assign, where applicable, the CMS(s) for this procedure.

The MRFG will review the situation at their meeting of 22 July 2002 and will consider, in case of a possible non-compliance with this request, whether a new referral procedure should be triggered.

Change in the EU-Presidency

The June MRFG meeting was the one last under the Spanish Presidency. Denmark will take over the Chairmanship as of 1st July 2002. Mrs Joan Boye will be the next chairperson. She should be contacted in case of questions regarding the MRP.

Meeting dates for 2003

The MRFG adopted the meeting dates for 2003, which will be published on the Heads of Agencies Website. Please note that the April 2003 MRFG meeting will take place on **Thursday 24 April 2003.**

Meeting schedule

The next MRFG meeting will be held on **Monday 22 July 2002**.
It was agreed that no MRFG meeting would be held in August 2002.

The MRFG noted that 38 new mutual recognition procedures were finalised during the month of May 2002, as well as 188 type I and 60 type II variations.

The status as of 31st May 2002 of procedures under mutual recognition is as follows:

Year	Procedures from New applications finalised	Procedures from New applications in process	Procedures from Type I variations finalised	Procedures from Type I variations pending	Procedures from Type II variations finalised	Procedures from Type II variations pending	Arbitrations referred to CPMP
2002	156	107	762	214	233	214	1 N.A. 3 Var.

31 new procedures (regarding 51 products) started in May 2002. The categories of these procedures are as follows:

4 new active substances (first authorisation in the European Community after RMS approval) including **2** multiple applications.

11 known active substances (already authorised in at least one member state) including **3** multiple applications and **1** repeat use.

15 abridged applications including **5** multiple applications and **1** repeat use.

1 Line extension application.

The new procedures started last month relate to 14 full dossiers, 8 generics, 1 bibliographic application, 1 fixed combination and 7 for different use, route or dose.

The procedures consisted of 29 chemical substances, 1 biological blood product and 1 biological vaccine[1].

20 of these procedures were prescription-only medicinal products in the reference Member State and 11 were Non-prescription (including OTC) medicinal products[2]

1. As considered by RMS.
2. In this category products are classified as prescription-only or Non-prescription (OTC) products when the RMS has approved them accordingly, although the legal status is not part of the Mutual Recognition Procedure.

Number of countries involved in the new applications procedures started in May 2002

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
DE (2)	1
DE (2)	11
DE (1)	1
DK (2)	1
DK (1)	4
DK (3)	3
DK (3)	1
DK (1)	12
DK (1)	5
DK (1)	3
DK (2)	1
DK (1)	1
FR (2)	2
NL (3)	6
NL (1)	7
NL (1)	7
NL (3)	8
UK (1)	5
UK (1)	2
UK (4)	3
UK (2)	2
UK (1)	13
UK (2)	4
UK (1)	15

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
UK (1)	1
UK (1)	1
UK (1)	2
UK (1)	1
UK (1)	5
UK (1)	1

All documents mentioned in this press release can be found at the MRFG website at the European Medicines Authorities Windows under the heading SOP.

Information on the above mentioned issues can be obtained by the presiding chair of the MRFG:

*Ms. Maria Luisa **GARCIA VAQUERO***
Agencia Española del Medicamento
c/Huertas 75
28014 MADRID - SPAIN

Phone: + 34 91 59615 61
Fax: + 34 91 596 44 92
+ 34 91 596 40 69
e-mail: mgarciav@agemed.es

From 1st of July 2002:

*Ms. Joan **BOYE***
Danish Medicines Agency
Frederikssundsvej 378
DK-2700 Brønshøj

Phone: + 45 44 88 92 54
Fax: + 45 44 94 02 37
e-mail: jbo@dkma.dk

(a) Vice-chair:

*Ms. Pia **NÆSBORG ANDERSEN***
Danish Medicines Agency
Frederikssundsvej 378
DK-2700 Brønshøj

Phone: + 45 44 88 93 70
Fax: + 45 44 94 02 37
e-mail:pna@dkma.dk

*Or you could visit the **MRFG web site** at the EUROPEAN NATIONAL MEDICINES AUTHORITIES WINDOW:*
http://heads.medagencies.org/

