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

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COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS
FEBRUARY 2003 PLENARY MEETING
MONTHLY REPORT

The Committee for Proprietary Medicinal Products (CPMP) held its 90th plenary meeting from 18 – 20 February 2003.

Product related issues

Centralised procedures

The Agency's scientific committee, the CPMP, adopted a positive opinion on an initial marketing authorisation application at this meeting for **Aldurazyme** (laronidase), from Genzyme, which is intended for enzyme replacement therapy in mucopolysaccharidosis I (formerly known as Hurler, Hurler-Scheie, Scheie). EMEA review began on 26 March 2002 and the opinion was adopted on 20 February 2003, with an active review time of 209 days.

Aldurazyme was designated an orphan medicinal product on 14 February 2001 and is the ninth orphan medicinal product to receive a CPMP positive opinion for marketing authorisation. A summary of this opinion is available on the EMEA web site: http://www.emea.eu.int.

The Committee adopted an opinion on a "line extension" application (in accordance with Annex II of Commission Regulation (EC) No. 542/95, as amended) (Part A), 3 Lists of Questions on initial marketing authorisation applications (1 Part A and 2 Part B) and 2 Lists of Questions on "line extension" applications (in accordance with Annex II of Commission Regulation (EC) No. 542/95, as amended) (2 Part A).

The Committee also adopted two positive opinions for extensions of indication for the following already authorized medicinal products:

- **Viread** (tenofovir disoproxil fumarate), from Gilead, to include the treatment of previously untreated HIV-1 infected adult patients. The indication approved by the Committee is now as follows: "Viread is indicated in combination with other antiretroviral medicinal products for the treatment of HIV-1 infected adults over 18 years of age. The demonstration of benefit of Viread is based on results of one study in treatment-naïve patients, including patients with a high viral load (> 100,000 copies/ml) and studies in which Viread was added to stable background therapy (mainly tritherapy) in antiretroviral pre-treated patients experiencing early virological failure (< 10,000 copies/ml, with the majority of patients having < 5,000 copies/ml). In deciding on a new regimen for patients who have failed an antiretroviral regimen, careful consideration should be given to the patterns of mutations associated with different medicinal products and the treatment history of the individual patient. Where available, resistance testing may be appropriate". Viread was first authorized in the European Union in February 2002. Further information on this extension will be included in the public assessment report (EPAR) once the European Commission has granted final approval.

- **Remicade** (infliximab), from Centocor, to include the treatment of ankylosing spondylitis in patients who have severe axial symptoms, elevated serological markers of inflammatory activity and who have responded inadequately to conventional therapy. Remicade was first authorised in the European Union in November 2000. Further information on this extension

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will be included in the public assessment report (EPAR) once the European Commission has granted final approval.

An overview of centralised procedures since 1995 is given in **Annex 1**. The post-authorisation centralised procedures finalised during this meeting are summarised in **Annex 2**. No Commission Decision was granted since the January 2003 CPMP plenary meeting.

Referrals

The CPMP concluded its Community-wide review for **Botox** (clostridium botulinum type A neurotoxin complex). The product is already licensed in a number of EU Member States and the review relates only to an application for a new indication for the treatment of primary axillary hyperhidrosis (excessive sweating). The CPMP considers that there is a positive benefit-risk balance based on currently available information and recommended the approval of the new indication. The referral was made by Germany and Italy to the EMEA in October 2002.

The Committee heard an appeal from Aventis Behring GmbH for **Beriate P** (human coagulation factor VIII). The Committee revised its opinion adopted in October 2002, and now recommends that the summary of product characteristics, in particular the warning on transmissible agents may be brought in line with the June 2000 core SPC for human plasma derived medicinal products. The Committee noted that the work on the revision of the warning on transmissible agents to be included in the SPCs for human plasma derived factor VIII products is well advanced.

The Committee also heard an appeal concerning its October 2002 opinion relating to a number of generic medicines containing **felodipine**. Following the hearing from the companies involved, the CPMP recommends that its Opinion of 17 October 2002 should be revised, and that the Marketing Authorisations for felodipine-containing medicinal products should be suspended and not revoked.

Other product related issues

The CPMP adopted a CPMP Position Statement concerning the use of intravenous **fibrinolytics** in diabetic patients indicated for the treatment of acute myocardial infarction. Fibrinolytics are currently contraindicated for use in patients with diabetic haemorrhagic retinopathy in all EU Member States. Following a comprehensive review of clinical trial data, published data and pharmacovigilance databases, the Committee recommends the removal of the contraindications and warnings for the intravenous use of fibrinolytics in diabetic patients or those with diabetic retinopathy. This should aid early administration of these products in acute medical situations. This CPMP Position Statement is available on the EMEA web site: http://www.emea.eu.int.

Non-product related issues

CPMP Working Parties and Ad Hoc Groups

The CPMP was informed of the outcome of the discussions of the Scientific Advice Review Group (SciARG) meeting, which was held on 3 – 4 February 2003. For further details, please see **Annex 3**.

Documents prepared by the CPMP Working Parties and Ad Hoc Groups adopted during the February 2003 CPMP meeting are listed in **Annex 4**.

The Paediatric Expert Group (PEG) meeting, chaired by Dr Brasseur, was held on 24 January 2003. The main topics presented/discussed at this meeting were the following: maturation of the immune system and consequences for the evaluation of medicinal products in children, evaluation of medicinal products in neonates, paediatric formulations of medicinal products in EU and assessment of existing paediatric medicinal products by therapeutic classes.

The Ad Hoc Expert Group on Gene Therapy meeting, chaired by Prof. Chichutek, was held on 23-24 January 2003. The main topics presented/discussed at this meeting were the following: mandate and

the rules of the procedure of the Ad Hoc Expert Group (adopted by the CPMP at the February 2003 plenary meeting), gonadal signalling and germline integration and insertional oncogenesis (non-clinical and clinical models). The CPMP adopted the proposed objectives and scope for the ICH 2nd Gene Therapy and ICH Expert Working Group to be held on 12 November 2003 in Tokyo, Japan.

The Committee agreed on the mandate and rules of the procedure for the newly established EMEA/CPMP Working Group with Patients' Associations. The CPMP appointed Dr Frits Lekkerkerker as Chairman of the Working Group. The EMEA Co-Chair will be Dr Noël Wathion.

Upcoming meetings

- The CPMP Herbal Medicinal Products Working Party was held on 24-25 February 2003.
- The 27th Joint CPMP/CVMP QWP will be held on 1 – 3 April 2003.

Meetings with Interested Parties

The 6th EMEA / IFAPP (International Federation of Associations of Pharmaceutical Physicians) Conference on Biotech products: "Current issues and comparability (non-clinical and clinical consideration" was held at the EMEA on Friday 21 February 2003.

ICH

The ICH meeting was held in Tokyo on 6 – 7 February 2003. For further details of ICH/CPMP documents adopted or released for consultation at this plenary meeting, please see **Annex 4**.

Organisational Matters

The 20th CPMP Organisational Matters meeting took place on Monday 17 February 2003, chaired by Dr D. Brasseur. During the meeting the following principle topics were presented/discussed:

- An annual review of the 2002 Organisational Matters meeting was presented. New topics were identified for the year 2003. Some of these topics concern the preparation in view of the European Union Enlargement (see also next topic), Implementation of the revised Variation Regulation, Development of internal Standard Operating Procedures for centralised and referral procedures and EMEA/CPMP publication policies. The group discussed prioritisation of these topics and sponsors were allocated.
- In preparation of the Enlargement of the European Union, organisational aspects were discussed regarding the nomination of observers from the ten Candidate Countries and their smooth and optimum integration/participation in the EMEA Scientific Committees. The group noted that the effective operational date for the participation of observers of these countries at CPMP and CPMP Working Parties' level is 01 April 2003.
- Therapeutic Advisory Groups: The rules of the procedure and composition of the different groups (Oncology, Diagnostics and Anti-Infectives) were discussed.
- Handling of Confidentiality Issues (conflicts of interest for Members/experts of the EMEA Scientific Committees): It was noted that the current internal procedure is under review in order to further optimise the preparation and evaluation of the information provided from experts.
- Handling of safety concerns: The Group continued its discussion on the handling of safety concerns for centrally authorised products in the post authorisation phase.

The next CPMP Organisational Matters meeting is scheduled to take place on Monday 17 March 2003.

PROCEDURAL ANNOUNCEMENT

The Standing Committees on medicinal products for human use and on veterinary medicinal products issued, in the meeting of 10 February 2003, a favourable opinion by qualified majority to the adoption by the European Commission of a draft Commission Regulation amending Council Regulation (EC) n° 297/95 on the fees payable to the European Agency for the Evaluation of Medicinal Products (EMEA). The Regulation will modify the amount of the fees by increasing all fees, except the annual fee, by 16%. The annual fee is adjusted by 26%. The Regulation is being finalised and will be submitted to the Commission for final adoption soon. The new Regulation shall enter into force on the day following its publication in the Official Journal of the European Communities. The table containing the new amount of fees can be found in the following web site page:http://pharmacos.eudra.org/F2/pharmacos/docs/Doc2003/FeeLevel2003.pdf.

Mutual Recognition procedure
The CPMP noted the report from the Mutual Recognition Facilitation Group (MRFG) meeting held on 17 February 2003. For further details, please see **Annex 5.**

The 91st plenary meeting of the CPMP will be held from 18 – 20 March 2003.

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

EMEA CENTRALISED PROCEDURES

	1995-2002			2003			Overall Total
	Part A	Part B	Total	Part A	Part B	Total	
Scientific Advice	97	205	302	5	8	13	315
Follow-up to Scientific Advice	23	27	50	-	1	1	51
Protocol Assistance	5	8	13	2	1	3	16
Follow-up to Protocol Assistance	3	1	4	-	-	-	4

	1995-2002			2003			
	Part A	Part B	Total	Part A	Part B	Total	
Applications submitted	127	239	366	1	8	9	375
Consultation for Medical Device[1]	0	1	1	0	0	0	1
Withdrawals	20	53	73	1	1	2	75
Positive CPMP opinions[2]	92	155	247	1	0	1	248[3]
Negative CPMP opinions[4]	1	4	5	0	0	0	5[5]
Marketing authorisations granted by the Commission	88	146	234	0	2	2	236[6]

	1995-2002			2003			Overall Total
	Part A	Part B	Total	Part A	Part B	Total	
Variations type I	585	1132	1717	27	74	101	1818
Positive opinions, variations type II	405	511	916	26	18	44	960
Negative opinions, variations type II	1	6	7	0	0	0	7
Extensions (Annex II applications)	44	44	88	1	0	1	89

[1] Consultation in accordance with Council Directive 93/42/EEC concerning medical devices as amended by Directive 2000/70/EC as regards medical devices incorporating stable derivatives of human blood or plasma and Directive 2001/104/EC.
[2] 1 positive opinion corresponding to 1 Orphan Medicinal Product
[3] 247 positive opinions corresponding to 185 substances
[4] In case of appeal, the opinion will not be counted twice
[5] 5 negative opinions corresponding to 4 substances
[6] 234 marketing authorisations corresponding to 175 substances

OUTCOME OF THE FEBRUARY 2003 CPMP MEETING IN RELATION TO CENTRALISED APPLICATIONS IN THE POST-AUTHORISATION PHASE

Opinions for Type II Variation applications	
Number of Opinions	**Outcome**
2 Extensions of indication	2 Positive opinions by consensus
17 SPC changes	17 Positive opinions by consensus
10 Quality changes	10 Positive opinions by consensus

Opinions for Annual Re-Assessment applications		
Name of Medicinal Product (INN) MAH	**Outcome**	**Comments**
Remicade (infliximab) Centocor 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**
Optison (perflutren) Amersham Health A/S	Positive opinion by consensus	---

OUTCOME OF THE FEBRUARY 2003 CPMP MEETING IN RELATION TO SCIENTIFIC ADVICE PROCEDURES

Substance	Intended indications(s)	Topic				
		Type of Request		Pharma-ceutical	Pre-Clinical	Clinical
		New	Follow-up			
Biological	Multiple sclerosis	**X**				**X**
Chemical	Psoriasis	**X**				**X**
Biological	Parkinson's disease	**X**			**X**	**X**
Chemical	Hyperlipidaemias	**X**			**X**	**X**
Chemical	Prevention of organ rejection in transplantation	**X**				**X**
Chemical	Intestinal microsporidiosis	**X** (Protocol Assistance)		**X**	**X**	**X**
Biological	Mucopolysaccharidosis Type II (MPS II, Hunter Syndrome)	**X** (Protocol Assistance)				**X**
Chemical	Mania	**X**			**X**	**X**

In February 2003, the above-mentioned 6 Scientific Advice letters and 2 Protocol Assistance letters were adopted. The Committee accepted 3 new Scientific Advice requests and 1 new Follow-up Scientific Advice request.

DOCUMENTS PREPARED BY THE CPMP WORKING PARTIES AND AD-HOC GROUPS ADOPTED DURING THE FEBRUARY 2003 CPMP MEETING

QUALITY WORKING PARTY

Reference number	Document	Status
CPMP/QWP/130/96	Note for Guidance on Chemistry of New Active Substance	Adopted
CPMP/QWP/609/96 rev. 1	Note for Guidance on Declaration of Storage Conditions A: In the product information of Medicinal Products and B: for Active Substances	Adopted
CPMP/QWP/3309/01	Note for Guidance on the use of Near Infrared Spectroscopy by the pharmaceutical industry and the data requirements for new submissions and variations	Adopted
CPMP/QWP/415/03	Concept paper on the development of CPMP Guidance on formulations of choice for the paediatric population	Adopted
CPMP/QWP/419/03	Note for Guidance on excipients, antioxidants and antimicrobial preservatives in the dossier for application for MA of a medicinal product	Released for 6 month consultation

BIOTECH WORKING PARTY

Reference number	Document	Status
CPMP/BWP/2289/01	Points to consider on the development of live attenuated influenza vaccines	Adopted
EMEA/CPMP/BWP/2879/02	CPMP Position Statement on CJD and Plasma-Derived and Urine-Derived Medicinal Products	Adopted

EFFICACY WORKING PARTY

Reference number	Document	Status
CPMP/EWP/252/03	Concept paper on the development of a CPMP Points to consider on clinical investigation of medicinal products in neuropathic pain management	Adopted
CPMP/EWP/49/01	Appendix to the Note for Guidance on the clinical investigation of medicinal products in the treatment of schizophrenia – methodology of clinical trials concerning the development of depot preparations of approved medicinal products in schizophrenia	Adopted

ICH

Reference number	Document	Status
CPMP/ICH/2736/99:	ICH Q1A(R) – Revision of Note for Guidance on stability testing: Stability testing of new active substance and medicinal products	Adopted
CPMP/ICH/420/02	ICH Q1E – Evaluation of stability data	Adopted
CPMP/ICH/421/02	ICH Q1F – Stability data package for registration: climatic Zones III and IV	Adopted
CPMP/ICH/2738/99	ICH Q3B (R) – Impurities in new drug products	Adopted
CPMP/ICH/774/03	ICH E2C – Addendum – Clinical safety data management: periodic safety update reports for marketed drugs	Adopted

Report from the meeting held on 17 February 2003

General issues:

The following new documents will be published on the MRFG website:

- Guidance paper and Templates for the mutual recognition assessment report in the CTD format

Meeting schedule

The next MRFG meeting will be held on 17 March 2003.

Annex 1

Joint CPMP/ MRFG working group on harmonisation of SPCs:

No meeting was held in February.

Mutual Recognition Monitoring

The MRFG noted that 32 new mutual recognition procedures were finalised during the month of January 2003, as well as 164 type I and 39 type II variations.

The status as of 31st January 2003 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
2003	32	97	164	245	39	237	1 N.A.

29 new procedures (regarding 44 products) started in January 2003. The categories of these procedures are as follows:

3 new active substances, classified as repeate use.

10 known active substances (already authorised in at least one member state), including **1** multiple application and **2** repeate use.

11 abridged applications including **3** multiple applications and **2** repeate use.

The new procedures started this month relate to 7 full dossiers, 10 generics, 5 bibliographic applications, 2 fixed combinations and 5 for different use, route or dose.

The procedures consisted of 26 chemical substances, 2 biological- vaccines and 1 biological –other[1].

28 of these procedures were prescription-only medicinal products in the reference Member State and 1 was 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 January 2003

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
DE (1)	1
DK (3)	1
DK (1)	5
DK (1)	3
DK (1)	1
DK (1)	1
DK (1)	1
DK (1)	1
DK (1)	3
DK (1)	1
DK (1)	1
ES (1)	6
ES (1)	4
FI (1)	8
FR (2)	9
FR (2)	14
FR (1)	11
NL (1)	9
NL (1)	1
NL (1)	1
SE (2)	1
UK (5)	1
UK (2)	4
UK (1)	13
UK (1)	14
UK (2)	1
UK (4)	3
UK (1)	5
UK (2)	4

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:

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http://heads.medagencies.org/

