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

25 September 2001
CPMP/2936/01

COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS
18 – 20 SEPTEMBER 2001 PLENARY MEETING

TECHNICAL MEETING REPORT

The Committee for Proprietary Medicinal Products (CPMP) held its 74th plenary meeting from 18 – 20 September 2001.

At the beginning of the meeting, a minute's silence was observed by the Committee with respect to the recent tragic events in the United States.

The CPMP welcomed Dr Frits Lekkerkerker as a new member from the Netherlands, succeeding Dr Hans van Bronswijk. On behalf of the CPMP, the CPMP Chairman expressed his thanks to Dr van Bronswijk's contribution to the work of the Committee.

Product related issues

Centralised procedures

The CPMP adopted two positive opinions by consensus on "line extension" applications (in accordance with Annex II of Commission Regulation (EC) No 542/95 as amended) related to one active substance (Part A).

An appeal procedure under Article 8 of Council Regulation (EEC) No 542/95 was initiated and a new Rapporteur and Co-Rapporteur were appointed.

The Committee adopted an Opinion by consensus recommending the renewal of the suspension of the Marketing Authorisation for Tasmar (tolcapone) for another year (see updated EMEA Press Release (CPMP/2457/98 rev.2)).

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 last CPMP plenary meeting in July 2001 is provided in **Annex 2**. The post-authorisation centralised procedures finalised during this meeting are summarised in **Annex 3**.

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 18 September 2001. For further details, please see **Annex 4**.

Other product related issues

The Committee further discussed its scientific review of cardiovascular risks of third generation combined oral contraceptives. Communication on the outcome is foreseen for October 2001.

Referrals

Referral under Article 15(a) of Council Directive(EC) No 75/319, as amended

The CPMP initiated a Community-level review on the risk-benefit of cerivastatin containing medicinal products authorised through the mutual recognition procedure, following a referral by Portugal under Article 15a of Council Directive 75/319/EEC, as amended. A Rapporteur and Co-Rapporteur were assigned and the review procedure has been started.

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.eudra.org http://www.emea.eu.int

Referral under Article 12 of Council Regulation (EC) No 75/319, as amended

The CPMP received a Referral under Article 12 of Council Regulation (EC) No 75/319, as amended by the Marketing Authorisation Holder, Aventis-Behring, for Beriate (human blood coagulation factor VIII). A Rapporteur and Co-Rapporteur were assigned and the review procedure has been started.

Referral under Article 7(5) of Commission Regulation (EC) No 541/95 as amended

The Committee received a Referral for Arbitration under Article 7(5) of Commission Regulation (EC) No 541/95/EEC. A Rapporteur and Co-Rapporteur were appointed and the review procedure has been started.

Following referral under Article 7(5) initiated by the United Kingdom in October 2000, the CPMP adopted an opinion by majority vote for Cerazette, recommending the refusal of the variation.

Inspection

GCP Inspections

GCP inspections have been carried out for 10 centralised procedures, to date, involving investigator sites, Marketing Authorisation Holder/Sponsor/Clinical Research Organisation facilities and laboratories in Europe and United States. The inspection program has been based on a combination of random surveillance and triggered inspections. The CPMP and the Ad Hoc Meeting of Good Clinical Practice Inspection Services are working together to develop and expand this inspection program.

Non-product related issues

CPMP Working Parties and Ad Hoc Groups

The Committee heard reports from the Pharmacovigilance, Biotechnology, Safety and Efficacy CPMP Working Parties and from the Ad-Hoc Working Group on Blood Products.

The 2nd meeting of the Chairpersons' CPMP Working Parties was held on Tuesday 18 September 2001 where common work programmes and mandates were discussed.

The Committee was informed of the outcome of the meeting of the CPMP Expert Group on Pharmacogenetics held on 4 July 2001 under the Chairmanship of Dr Abadie. It was agreed that the group, following comments from Interested Parties and European Learned Societies would re-convene a meeting in autumn to finalise a proposal to the CPMP on the scientific basis and regulatory use of pharmacogenetics terminology.

The Committee was informed of up-coming Ad Hoc Expert Group meetings:

- The first Ad Hoc Expert Group on sleep disorders, to be chaired by Prof. Christina Sampaio, will be held on 12 November 2001.
- The first meeting of the Ad Hoc Expert Group on Paediatrics, to be chaired by the CPMP Chairman Dr Daniel Brasseur, will be held on 21 September 2001.
- The second meeting of the Ad Hoc Working Group on Comparability of Biotechnology Products (Pre-Clinical and Clinical issues), to be chaired by Dr Markku Toivonen, will be held on 5 October 2001.
- The Ad Hoc Gene Therapy Expert Group meeting, to be chaired by Dr Lincoln Tsang, will be held on 12 October 2001.
- The Ad-Hoc Working Group on Anti-HIV Medicinal Products meeting, to be chaired by Dr Per Nilsson, is scheduled to take place on 29 November 2001.

An overview of guidance documents adopted during the meeting or released for consultation to Interested Parties is attached as **Annex 5**.

Organisational Matters

The 7th meeting of the CPMP Ad Hoc Group on Organisational Matters (ORGAM) was held on 17 September 2001 and the following topics were discussed:

- Accelerated Review procedure: A revised document on "Accelerated evaluation of products indicated for serious diseases (life threatening or heavily disabling diseases) (CPMP/495/96 rev.1) was adopted by the CPMP and will be published together with this report (**see Annex 6**).
- Improvement of the internal CPMP review "work": An electronic template on comments of Assessment Reports was adopted by CPMP.
- Revision of the status and composition of the Scientific Advice Review Group (SciARG): Further discussions took place on the above and will continue at the October 2001 ORGAM meeting.
- Rapporteur and Co-Rapporteur appointment: A discussion on the timing of Rapporteur/ Co-Rapporteur appointment and the frequency of such appointment took place and the following was confirmed/agreed upon:

PROCEDURAL ANNOUNCEMENT

Appointment of Rapporteur/Co-Rapporteur will, as of October 2001, take place **every month**. Applicants should therefore send in their letter of intent including their proposed choice of Rapporteur/Co-Rapporteur i.e. 3 to 4 CPMP Members' names, **at the latest 2 weeks prior to the monthly CPMP plenary meetings** (attention of CPMP Chairman, Dr Daniel Brasseur and Mr Tony Humphreys, EMEA Head of Sector Regulatory Affairs and Organisational Support). Applicants are reminded to announce any delay in the scheduled submission of the application to Rapporteur/Co-Rapporteur and EMEA as this could have a potential impact on the work schedule of the assessment teams. In such cases there could be, upon CPMP request, a re-appointment of Rapporteur/Co-Rapporteur.

- Review 2001: The group discussed the impact of the European Commission Review 2001 on the future activities of the CPMP.

The Tradename Ad Hoc Review Group (TRAHG) held its 21st meeting on Monday 17 September 2001 and the conclusions of the group were adopted by CPMP.

The first joint CPMP/MRFG Working Group meeting on the Harmonisation of Summary Product Characteristics (SPCs) took place on Monday 17 September 2001. This group is composed of representatives from CPMP, Mutual Recognition Facilitation Group (MRFG), European Commission and the EMEA. At the beginning of the meeting, Dr Tomas Salmonson was elected as Chairman of the newly created group (for further details see MRFG Press Release, which is also annexed to this report as **Annex 7**).

Interested Parties meetings/Workshops

- A meeting between the CPMP Efficacy Working Party and the European Society of Cardiologists took place on Monday 17 September 2001.
- A Joint EFPIA/ EMEA/CPMP Centralised Procedure Performance Indicators meeting will be held on 15 October 2001.

The 75th plenary meeting of the CPMP will be held from 16 to 18 October 2001.

Mutual Recognition procedure

The CPMP noted the report from the Mutual Recognition Facilitation Group (MRFG) which was held on 18 September 2001, which is attached as **Annex 7**.

Noël Wathion
Head of Unit Post-Authorisation
Evaluation of Medicines for Human Use
Tel. (+44 20) 74 18 85 92
This Technical Report and other documents are available on the Internet at the following address:
http://www.emea.eu.int

EMEA CENTRALISED PROCEDURES

	1995-2000			2001			Overall Total
	Part A	**Part B**	**Total**	**Part A**	**Part B**	**Total**	
Scientific Advice	74	122	196	10	33*	43	239
Follow-up to scientific advice	15	11	26	3**	4	7	33

* Including one Protocol Assistance requests.
** Including one Protocol Assistance request.

	1995-2000			2001			Overall Total
	Part A	**Part B**	**Total**	**Part A**	**Part B**	**Total**	
Applications submitted	97	182	279	23	25	48	327
Withdrawals	12	37	49	1	7	8	57
Positive CPMP opinions	64	112	176	9	10	19	195[1]
Negative CPMP opinions[2]	1	3	4	0	1	1	5[3]
Marketing authorisations granted by the Commission	56	95	151	15	24	39	190[4]

	1995-2000			2001			Overall Total
	Part A	**Part B**	**Total**	**Part A**	**Part B**	**Total**	
Variations type I	265	551	816	127	199	326	1142
Positive opinions, variations type II	159	224	383	95	105	200	583
Negative opinions, variations type II	0	2	2	1	1	2	4
Extensions (Annex II applications)	34	20	54	2	5	7	61

[1] 195 positive opinions corresponding to 153 substances
[2] In case of appeal the opinion will not be counted twice
[3] 5 negative opinions corresponding to 4 substances
[4] 190 marketing authorisations corresponding to 145 substances

MEDICINAL PRODUCTS GRANTED A COMMUNITY MARKETING AUTHORISATION UNDER THE CENTRALISED PROCEDURE SINCE JULY 2001 PRESS RELEASE

Brand name	Liprolog
INN	insulin lispro
Marketing Authorisation Holder	Eli Lilly and Company Ltd
ATC code	A10AB04
Indication	Diabetes mellitus
CPMP Opinion date	25/04/2001
Date of Commission Decision	01/08/2001

Brand name	INOmax
INN	nitric oxide
Marketing Authorisation Holder	AGAAB
ATC code	R07AX
Indication	Treatment, in conjunction with ventilatory support and other appropriate agents, of newborns ≥ 34 weeks gestation with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, in order to improve oxygenation and to reduce the need for extracorporeal membrane oxygenation.
CPMP Opinion date	29/03/2001
Date of Commission Decision	01/08/2001

Brand name	Replagal
INN	Agalsidase beta
Marketing Authorisation Holder	TKT Europe-5S AB
ATC code	A16AB03 (pending)
Indication	Long-term enzyme replacement therapy in patients with a confirmed diagnosis of Fabry Disease (α-galactosidase A deficiency).
CPMP Opinion date	29/03/2001
Date of Commission Decision	03/08/2001

Brand name	Fabrazyme
INN	agalsidase alfa
Marketing Authorisation Holder	Genzyme B.V.
ATC code	A16AB04 (pending)
Indication	Long-term enzyme replacement therapy in patients with a confirmed diagnosis of Fabry disease (α-galactosidase A deficiency).
CPMP Opinion date	29/03/2001
Date of Commission Decision	03/08/2001

OUTCOME OF THE SEPTEMBER 2001 CPMP MEETING IN RELATION TO CENTRALISED APPLICATIONS IN THE POST-AUTHORISATION PHASE

Opinions for Type I Variation applications following Type II procedure	
Number of Opinions	**Outcome**
2	Positive by consensus

Opinions for Type II Variation applications	
Number of Opinions	**Outcome**
11 (SPC/PL update)	Positive by consensus
29 (Pharmaceutical Aspects)	Positive by consensus

Opinion for Annual Re-Assessment applications		
Name of Medicinal Product (INN) MAH	**Outcome**	**Comments**
Vitravene (fomivirsen)	Positive by consensus	----

Opinion for Renewal applications		
Name of Medicinal Product (INN) MAH	**Outcome**	**Comments**
Hycamtin (topotecan) – SmithKline Beecham plc	Positive by consensus	----
CEA-Scan (arcitumomab) – Immunomedics Europe	Positive by consensus	----

OUTCOME OF THE AUGUST WRITTEN PROCEDURE and SEPTEMBER 2001 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	Impaired glucose tolerance	X				X

In addition to the adoption of the above final Scientific Advice letter, adopted via written procedure in August 2001, three new requests for Scientific Advice of which one was a follow-up request were accepted by the Committee .

In September 2001, no final Scientific Advice letters were adopted. The Committee accepted three new requests for Scientific Advice and two follow-up Scientific Advice requests.

DOCUMENTS PREPARED BY THE CPMP WORKING PARTIES AND AD-HOC GROUPS ADOPTED DURING THE SEPTEMBER 2001 CPMP MEETING

BIOTECHNOLOGY WORKING PARTY

Reference number	Document	Status
CPMP/BWP/3207/00	Note for guidance on Comparability of medicinal products containing biotechnology-derived proteins as active drug substance	Adopted in September 2001
EMEA/CPMP/BWP/2289/01	Points to consider on the Development of live attenuated influenza vaccines	Released for 6 months' consultation in September 2001

SAFETY WORKING PARTY

Reference number	Document	Status
CPMP/SWP/2600/01	Points to consider on the Need for assessment of reproductive toxicity of human insulin analogues	Released for 3 months' consultation in September 2001

EFFICACY WORKING PARTY

Reference number	Document	Status
CPMP/EWP/560/98	Points to consider on Clinical investigation of medicinal products for the treatment of acute stroke	Adopted in September 2001

ACCELERATED EVALUATION OF PRODUCTS INDICATED FOR SERIOUS DISEASES (LIFE THREATENING OR HEAVILY DISABLING DISEASES)

Under Council Regulation (EEC) No. 2309/93, the CPMP has to work under very tight time constraint, in relation to the evaluation of medicinal products to be approved centrally. The maximum time frame is 210 days, excluding clock stops when additional written or oral information is to be provided by the applicant.

This timetable has been further streamlined in the redrafting of chapter 4 of the Notice To Applicants (Volume 2B). In particular, by day 70 the Committee has the first opportunity to consider the initial assessment by the Rapporteur and Co-Rapporteur.

Whereas the legal time frame of 210 days constitutes a maximum applicable to all products evaluated centrally, the CPMP has been confronted with cases where compelling public health reasons may, in exceptional cases, require an even quicker evaluation and management of the application. Experience with such cases have indicated that CPMP has been able to give an opinion within the first evaluation period i.e. by day 120, subject to the quality of the application submitted. This may be achieved in exceptional circumstances preferably by adopting an opinion within the standard first phase timeframe i.e. 120 days, or by prospectively shortening the time to prepare the internal Rapporteur and Co-Rapporteur's Assessment Report (so called "Day-70 Assessment Report").

- In both cases, applicants may be expected to commit to a series of Follow-Up Measure(s) and/or Specific Obligation(s), as appropriate.
- It should be clearly understood that for applications, judged to be premature and/or with major objections identified during the review procedure, the Committee could end up giving a negative opinion, if the benefit/risk assessment is considered to be unfavorable. There could also be the possibility, if a number of objections are identified during the initial review procedure, that the Committee decides that a standard time frame of 210 days should nevertheless be applied.

Recent experience of the CPMP has shown the need to agree on when to accelerate the evaluation of products indicated for serious diseases.

A. Qualification of the medicinal product for an accelerated evaluation:

An accelerated evaluation might be initiated by the CPMP in exceptional cases when a medicinal product is intended to provide an answer to major public health need, defined by three cumulative criteria[1]:

a) the seriousness of the disease (e.g. heavily disabling or life-threatening diseases [such as AIDS, cancer]....) to be treated, and

b) the absence of an appropriate alternative therapeutic approach, and

c) the anticipation of exceptional high therapeutic benefit

When the Rapporteur/Co-Rapporteur consider that a product might meet all the above mentioned criteria, they should ask the Committee to consider an accelerated timetable for the evaluation process and to submit a proposal to that effect at the very beginning of the procedure. When accepting an accelerated evaluation, the CPMP will also take into account the views of other CPMP members as well as the arguments/justifications put forward by the company.

B. Completion of the accelerated evaluation

For the completion of the accelerated evaluation, the quality of the dossier and the clinical data supporting the claim which meets the major public health need should allow the evaluation without any delay due to a formal request for written information.

---

[1] Please note that as for any other medicinal product, medicinal products which have been designated as orphan drug medicinal product might be subject to an accelerated evaluation according to these same above mentioned criteria.

Report from the meeting held on 17 September 2001

General issues

Recommendation for Mutual Recognition Procedure after finalisation of an arbitration procedure with a positive opinion by the CPMP and a positive decision by the European Commission

The MRFG adopted the revision 1 of the above mentioned document that will be published on the Heads of Agencies Website.

Heads of Agencies website

The Heads of Agencies website is under reorganisation and the revision will be available by the end of September.

MRFG meeting dates in 2002

The MRFG has adopted the following meeting dates for the year 2002 which are to be published on the Heads of Agencies website:

Month	Day
January	14
February	18
March	18
April	22
May	28
June	24
July	22
August*	**19**
September	16
October	14
November	18
December	16

*if needed

Meeting schedule

The next MRFG meeting will be held on **15 October 2001**.

ANNEX 1

Joint CPMP / MRFG Working Group on harmonisation of SPCs

Following the decision of the Heads of Agencies at their meeting on the 12 and 13 June 2001 to continue the SPC harmonisation project, the first meeting of the Joint CPMP / MRFG Working Group on the harmonisation of SPCs took place on the 17 September 2001. Representatives of CPMP, MRFG, EMEA and EC participated at this first meeting. The group will discuss the issues outlined by the Heads of Agencies with the aim of finishing and presenting a report to the November Heads of Agencies meeting. Dr. Tomas Salmonson (SE) was elected as chairperson. During the Belgian presidency, Ms. Natacha Grenier should be contacted for questions concerning this item.

Mutual Recognition Monitoring

The MRFG noted that 94 new mutual recognition procedures were finalised during the months of July and August 2001, as well as 292 type I and 69 type II variations.

The status as of 31 August 2001 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
2001	264	122	806	121	318	223	1 var.

97 new procedures (regarding 175 products) started in July and August 2001. The categories of these procedures are as follows:

10 new active substances, including **1** repeat use.

31 known active substances (already authorised in at least one member state), including **6** multiple applications and **4**repeat use.

48 abridged applications including **7** multiple applications and **4** repeat use.

8 line extension applications.

The new procedures started this month relate to 22 full dossiers, 51 generics, 9 bibliographic applications, 3 fixed combination and 12 for different use, route or dose.

The procedures consisted of 93 chemical substances, 2 biological – vaccines, 1 biological – blood product and 1 biological – others [1].

85 of these procedures were prescription-only medicinal products in the reference Member State and 12 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 July and August 2001

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
DE (2)	13
DE (1)	3
DE (2)	4
DE (1)	15
DE (2)	3
DE (1)	7
DE (1)	16
DE (3)	1
DE (2)	15

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
DE (2)	4
DE (3)	16
DE (1)	9
DE (1)	9
DE (1)	9
DE (1)	9
DE (1)	9
DK (1)	11
DK (2)	1
DK (2)	1
DK (2)	1
DK (2)	1
DK (2)	1
DK (2)	1
DK (2)	7
DK (2)	3
DK (1)	15
DK (1)	3
DK (1)	13
DK (1)	4
DK (2)	1
DK (2)	1
DK (2)	2
DK (2)	2
ES (1)	1
ES (1)	4
FI (1)	2
FI (4)	5
FI (5)	12
FI (5)	1
FI (5)	1
FI (5)	1
FI (5)	1
FI (5)	3
FR (4)	1
FR (1)	10
FR (2)	6
FR (2)	3
FR (2)	4
FR (3)	5
FR (1)	16
FR (1)	3
FR (4)	1
IT (1)	9
IT (1)	6
NL (3)	6
NL (1)	6
NL (4)	3
NL (2)	2
NL (2)	8
NL (2)	3
NL (2)	8

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
NL (2)	4
NL (2)	9
NL (4)	16
NL (4)	5
NL (1)	8
NL (1)	1
SE (1)	1
SE (1)	2
SE (1)	8
SE (2)	1
SE (2)	2
SE (1)	16
SE (1)	11
SE (1)	1
UK (1)	16
UK (1)	3
UK (1)	3
UK (1)	4
UK (1)	7
UK (2)	3
UK (1)	13
UK (2)	5
UK (1)	1
UK (1)	7
UK (1)	7
UK (1)	8
UK (1)	1
UK (1)	15
UK (1)	8
UK (3)	3
UK (1)	4
UK (1)	9
UK (1)	16
UK (1)	9
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. Natacha **GRENIER**
Ministry of Public Health
Pharmaceutical Inspectorate
Bd. Bischoffsheim 33, local 411
1000 BRUSSELS - BELGIUM

Phone: + 32 2 227 5516
Fax: + 32 2 221 0355
e-mail: natacha.grenier@afigp.fgov.be

Alternatively, you could visit the **MRFG website** at the EUROPEAN NATIONAL MEDICINES AUTHORITIES WINDOW:

http://heads.medagencies.org/