European Medicines Agency
Evaluation of Medicines for Human Use

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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
APRIL 2006 PLENARY MEETING
MONTHLY REPORT

The Committee for Medicinal Products for Human Use (CHMP) held its April plenary meeting from 24-27 April 2006.

Centralised procedure

Initial applications for marketing authorisation

The CHMP adopted positive opinions on eight initial marketing authorisation applications at this meeting:

- **Acomplia** and **Zimulti** (rimonabant) from Sanofi-Aventis, for use as adjunct to diet and exercise for the treatment of obese patients or overweight patients with associated risk factors, such as type 2 diabetes or dyslipidaemia. EMEA review for Acomplia began on 18 May 2005 with an active review time of 202 days, EMEA review for Zimulti began on 15 September 2005 with an active review time of 85 days.
- **Avaglim** (rosiglitazone/glimepiride), from SmithKline Beecham plc, for the treatment of type 2 diabetes mellitus. EMEA review began on 15 June 2005 with an active review time of 204 days.
- **Baraclude** (entecavir), from Bristol-Myers Squibb Pharma EEIG, for the treatment of chronic hepatitis B. EMEA review began on 18 October 2004, with an active review time of 210 days.
- **Nexavar** (sorafenib tosylate), from Bayer Healthcare AG, for the treatment of advanced renal cell carcinoma in patients who have failed prior interferon-alpha or interleukin-2 based therapy or are considered unsuitable for such therapy. EMEA review began on 28 September 2005, with an active review time of 177 days. Nexavar is the **twenty-sixth orphan medicinal product** to receive a positive CHMP opinion.
- **RotaTeq** (rotavirus vaccine), from Sanofi Pasteur MSD, for the prevention of rotavirus gastroenteritis in infants from 6 weeks of age. EMEA review began on 18 May 2005, with an active review time of 190 days.
- **Tysabri** (natalizumab), from Elan Pharma International Ltd, for the treatment of multiple sclerosis. EMEA review began on 21 June 2004, with an active review time of 176 days.

The CHMP also adopted the first positive opinion on the granting of a **conditional marketing authorisation** under new EU rules on conditional approvals that came into force at the beginning of April 2006:

- **Sutent** (sunitinib malate), from Pfizer Ltd, for the treatment of unresectable and/or metastatic malignant gastrointestinal stromal tumours (GIST) after failure of imatinib mesylate treatment due to resistance or intolerance, and advanced and/or metastatic renal cell carcinoma (MRCC) after failure of interferon alfa or interleukin-2 therapy. EMEA review began on 28 September 2005, with an active review time of 177 days. Sutent is the **twenty-seventh orphan medicinal product** to receive a positive CHMP opinion.

  A conditional marketing authorisation means that further evidence on the medicinal product is awaited. In the case of Sutent, this relates to the product's effect in terms of progression-free survival in patients

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with MRCC, for which a study is being conducted. The European Medicines Agency will review new information within one year and update the product information as necessary.

Summaries of opinion for these medicinal products are available on the EMEA website: http://www.emea.eu.int. Further information will be included in the European Public Assessment Report (EPAR) once the European Commission has granted final approval.

Extensions of indication and other recommendations

The Committee adopted positive opinions on the extension of indication of medicinal products that are already authorised in the European Union:

- **Betaferon** (interferon beta –1b), from Schering AG, to extend its indication to add the early form of multiple sclerosis. Betaferon was first authorised in the European Union on 21 November 1996 and is currently indicated for the treatment of patients with relapsing remitting multiple sclerosis and two or more relapses within the last two years, and the treatment of patients with secondary progressive multiple sclerosis with active disease, evidenced by relapses.

- **Herceptin** (trastuzumab), from Roche Registration Ltd, to extend its indication to include adjuvant treatment of early (invasive, non-metastatic) breast cancer over-expressing HER2 following surgery, chemotherapy (neo-adjuvant or adjuvant) and radiotherapy (if applicable). Herceptin was first authorised in the European Union on 28 August 2000 and is currently authorised for the treatment of patients with metastatic breast cancer, either as monotherapy for patients who have undergone at least two chemotherapy regimens or in combination with paclitaxel or docetaxel for the treatment of patients who have not received chemotherapy for their metastatic disease.
  This is the first accelerated assessment of an extension of indication by the European Medicines Agency under new EU legislation introduced in November 2005, with the application submitted in February 2006. A separate question and answer document relating to the new extension of indication is available here.

- **Humira** (adalimumab), from Abbott Laboratories, for the extension of indication to include treatment of adults with severe active ankylosing spondylitis who have had an inadequate response to conventional therapy. Humira was first authorised in the European Union on 8 September 2003 and is currently indicated for rheumatoid and psoriatic arthritis.

New contraindication

The Committee recommended that the following medicinal products used to treat erectile dysfunction should be contraindicated in patients suffering from vision loss in one eye because of non-arteritic anterior ischemic optic neuropathy (NAION):

- **Cialis** (tadalafil), from Lilly ICOS Limited (first authorised in the EU on 12 November 2002)

- **Levitra** and **Vivanza** (vardenafil), from Bayer AG (first authorised in the EU on 4 March 2003)

- **Viagra** (sildenafil), from Pfizer Limited (first authorized in the EU on 14 September 1998)

The Committee also recommended that the same contraindication is added for **Revatio** (sildenafil), from Pfizer limited, used for the treatment of patients with pulmonary arterial hypertension classified as WHO functional class III. Revatio was first authorised in the EU on 28 October 2005.

Summaries of opinions for all these products are available and can be found here. Further information will be included in the EPAR once the European Commission has granted final approval.

Procedures finalised in accordance with Article 20 of Regulation (EC) No 726/2004

- The Committee finalised a review procedure for the centrally authorised vaccines **HBVAXPRO** (recombinant Hepatitis B virus small surface antigen (HbsAg)) and **Procomvax** (haemophilus influenzae b conjugate and Hepatitis B (recombinant) vaccine) both from Sanofi Pasteur MSD. The review procedure for both vaccines was initiated at the request from the European Commission under Article 20 of Regulation (EC) No 726/2004 in order to assess the benefit of HBVAXPRO and Procomvax. The Committee concluded that these medicinal products continue to offer effective protection against Hepatitis B, but recommended some changes to the prescribing information. These changes are not related to the safety profile of the vaccines. Furthermore, there is currently no evidence of decreased effectiveness and consequently there is no need to revaccinate individuals who have received the appropriate dosing in the past. A Questions and Answers document on the review procedure of HBVAXPRO and Procomvax and a press release on this issue can be found on the EMEA website: http://www.emea.eu.int.

- In November 2005, the MAH for **OPTISON** undertook a voluntary recall of the product from the EU/EEA market as a precautionary measure due to serious findings during a FDA inspection of the US manufacturing facility relating to lack of adequate sterility assurance during aseptic manufacture. No quality defects related to these observations have been reported during testing and use of the product. No adverse events reported from the use of this product have been associated to this problem.
  OPTISON is imported into the EU/EEA by a licensed importer located in Norway. As a result of the inspection findings and concerns about the manufacturers compliance with Good Manufacturing Practice (GMP), the Norwegian Medicines Agency, in November 2005, suspended those parts of the manufacturing licence of the importer prohibiting further importation of OPTISON into the EU/EEA. The MAH and the manufacturer are currently undertaking an extensive corrective action plan to restore GMP compliance at the site of manufacture.
  In April 2006, the European Commission (EC) subsequently asked CHMP in accordance with Article 20 (2) of Regulation (EC) No 726/2004 to evaluate if any further regulatory action is necessary. The CHMP concluded that the regulatory action hitherto taken by the Norwegian Medicines Agency and the commitments and corrective actions agreed with the MAH were adequate. There is no need for further action with respect to the Marketing Authorisation for OPTISON pending the future lifting of the suspension of the manufacturing authorisation.

Lists of Questions

The Committee adopted nine Lists of Questions on initial applications (seven under the mandatory scope and two under the optional scope).

Detailed information on the centralised procedure

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**. The list of medicinal products for which marketing authorisations have been granted by the European Commission since the CHMP plenary meeting in February 2006 is provided in **Annex 3.**

Applications for marketing authorisation for orphan medicinal products

Details of those orphan medicinal products that have been subject of a centralised application for marketing authorisation since March 2006 are provided in **Annex 4**.

Referral procedures

Start of referral procedures

The Committee started a large number of arbitration and referral procedures for medicinal products authorised through the mutual recognition procedure this month.

Arbitrations under Article 29 of the Community code on human medicinal products (Directive 83/2001/EC as amended) are initiated by one or more Member States in cases where an agreement cannot be reached in the context of the mutual recognition procedure. Procedures were started for the following products:

- **Doxazosin Retard 'Arrow' 4 mg prolonged release tablets** (doxazosin as mesylate), from Arrow Generics Ltd
- **Doxazosin Retard 'Winthrop' 4 mg prolonged release tablets (**doxazosin as mesylate), from Winthrop Pharmaceuticals UK Ltd
- **Alendros 70** (alendronate sodium trihydricum), from Zentiva a.s.
- **Glucomed 625 mg tablet** (glucosamine hydrochloride), from Navamedic AS.

The Committee started referral procedures for a number of generic medicinal products containing **cetirizine dihydrochloride** because of concerns over their bioequivalence. The procedures were initiated by the Netherlands under Article 36 of the Community code on human medicinal products (Directive 83/2001/EC as amended) for the following products and associated tradenames: Cetirizine dihydrochloride-APEX 10mg, Cetirizine dihydrochloride Copyfarm 10mg, Cetirizine dihydrochloride Dermapharm 10mg and Cetirizine dihydrochloride Nordic Drugs 10 mg film-coated tablets. Article 36 procedures are initiated where a Member State considers that there are public health issues relating to a product that may require regulatory action.

Finalised referral procedures

The Committee finalised 4 arbitration procedures for **Seretide Diskus, Viani Diskus, Seretide Evohaler** and **Viani Evohaler** from GlaxoSmithKline. The arbitrations for these fixed dose combinations of the long acting beta agonist salmeterol and the inhaled corticosteroid fluticasone propionate used in the treatment of asthma were made by the marketing authorisation holder in September 2005. The Committee recommended that the products could be tried for a short period of time as initial maintenance therapy in adults and adolescents with moderate asthma for whom rapid control of asthma is essential, after which a decision should be taken whether or not to continue treatment with the product. The arbitration was made under Article 6(13) of Commission Regulation (EC) No 1084/2003. Marketing authorisation holders initiate these types of arbitrations where a type II variation in the mutual recognition procedure is rejected by the Member States.

The Committee also concluded a referral procedure for **Stamaril** and associated tradenames, from Sanofi Pasteur MSD, with a recommendation to harmonise the product information, in particular the sections dealing with indications and safety aspects, across the European Union. Stamaril is a viral vaccine used for active immunisation against yellow fever in persons over 9 months of age. The marketing authorisation holder made the referral in September 2005 under Article 30 of Directive 2001/83/EC as amended.

CHMP Working Parties

The CHMP was informed of the outcome of the discussions of the Scientific Advice Working Party (SAWP) meeting, which was held on 23 March – 1 April 2006. For further details, please see **Annex 5**.

Documents prepared by the CHMP Working Parties adopted during the April 2006 CHMP meeting are listed in **Annex 6**.

Invented Name Review Group (NRG)

Statistical information on the outcome of the checking of acceptability of proposed invented names for medicinal products processed through the centralised procedure is provided in **Annex 7.**

Upcoming meetings following the April 2006 CHMP plenary meeting:

- The 22st meeting of the CHMP will be held at the EMEA on 29 May-1 June 2006.
- The next Invented Name Review Group meeting will be held at the EMEA on 29 May 2006.
- The seventh CMD(h) (Co-ordination Group for Mutual Recognition and Decentralised Procedures-Human) will be held at the EMEA on 29-30 May 2006.
- The 2nd EMEA/CHMP Workshop on Biomarkers in the Development of New Medicines will be held at the EMEA on 15 December 2006.

Organisational matters

The main topics addressed during the April 2006 CHMP meeting related to:

- Final discussion on the new framework for EMEA Scientific Advice. The Committee adopted the amended SAWP mandate.
- Discussion on the outcome of the assessment of the Community System of Pharmacovigilance in the context of the EC public consultation exercise.

EMEA Implementation of the New EU Pharmaceutical Legislation

The sixteenth CHMP/EMEA Implementation Task Force (CEITAF) meeting took place on Monday 24 April 2006.

The following documents were adopted by the CHMP and will be transmitted to the European Commission:

- Guideline on the procedure for accelerated assessment pursuant to article 14(9) of Regulation (EC) No 726/2004.
- Reflection Paper on the Implementation of the review: CHMP/CVMP Opinions on any scientific matter.

Follow-on discussion took place on the following topics:

- Criteria for the appointment of CHMP Rapporteur/Co- Rapporteur.

- Guideline on the scientific application and the practical arrangements necessary to implement Commission Regulation (EC) No 507/2006 on the conditional marketing authorization for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004. This EMEA guideline detailing the scientific application and the practical arrangements necessary to implement Commission Regulation (EC) No 507/2006 will be further discussed with the CHMP next month and thereafter will be sent to the European Commission. An Interested Parties' external consultation is expected to take place thereafter.

  Please note that Conditional Marketing Authorisations can already be granted (please see Sutent, summary of opinion: http://www.emea.eu.int.) since the Commission Regulation (EC) No 507/2006 is in force since 30th April 2006 (date of publication of the EU Official Journal). Applicants are advised to contact the EMEA Product Team Leader in order to discuss/address such aspects as early as possible and in any case at Pre-submission meetings.

Mutual Recognition procedure and Decentralised procedures-Human

The CHMP noted the report from the sixth CMD(h) (Co-ordination Group for Mutual Recognition and Decentralised procedures-Human) held on 24-25 April 2006. For further details, please see **Annex 8**.

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

PRE-AUTHORISATION: MARKETING AUTHORISATION APPLICATIONS

Activity	Dec 2005/2006[1]							1995 onwards
	Optional Scope			Mandatory scope			Total	Overall total
	NAS	Significant innovation	Interest of Patients	Biotech	Indications	Orphans		
Applications for MA submitted[2]	**5**	**4**	**0**	**10**	**3**	**3**	**25**	**515**
Positive opinions[3]	**10**	**1**	**0**	**4**	**0**	**4**	**19**	**345[4]**
Negative opinions[5]	**1**	**0**	**0**	**1**	**0**	**0**	**2**	**9[6]**
Withdrawals prior to opinion	**2**	**1**	**0**	**0**	**0**	**2**	**5**	**104**
Marketing authorisation granted by the Commission	**11**	**0**	**0**	**4**	**0**	**2**	**17**	**328**

PRE-AUTHORISATION: SCIENTIFIC SERVICES

Activity (submissions)	Dec 2005/2006	1995 onwards
Compassionate use applications	**0**	**0**
Art. 58 applications	**0**	**2**
Consultation for medical devices[6]	**0**	**4**
PMF	**1[7]**	**8[7]**
VAMF	**0**	**0**

[1] Starting point for operation of the new eligibility criteria to the centralised procedure
[2] Number of accelerated reviews requested and number of accelerated reviews granted (3/0)
[3] Subdivided by conditional and exceptional (0/0)
[4] [4] 345 positive Opinions corresponding to 273 substances
[5] In case of Re-examination under Art. 9(2) of Regulation (EC) No. 726/2004, the opinion will not be counted twice.
[6] 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 derivates of human blood or plasma and Directive 2001/104/EC
[7] A correction has been made to reflect the total number of adopted PMF Evaluation Reports (not including the PMF annual updates)

OUTCOME OF THE APRIL 2006 CHMP MEETING IN RELATION TO ACCELERATED ASSESMENT PROCEDURES

Substance	Intended indications(s)	Accelerated Assessment Requests	
		Accepted	Rejected
N/A	N/A	N/A	N/A

POST-AUTHORISATION: TYPE I AND II VARIATIONS, ANNEX II, RENEWALS AND ANNUAL RE-ASSESSMENT APPLICATIONS

Activity	2006	Overall total 1995 onwards
Type I Variations (positive notifications)	115	3555
Type II Variations (positive opinions)	213	2395
Type II Variations (negative opinions)	0	7
Annex II Applications (positive opinions)	7	134
Annual Re-assessment (positive opinions)	10	N/A
Opinion for renewals of conditional MA's (positive opinions)	0	0
5 Year Renewals (positive opinions)	20	N/A

Opinions for Type II Variation applications	
Number of Opinions	**Outcome**
4 Extensions of indication	4 Positive opinions
34 SPC changes	34 Positive opinions
35 Quality changes	35 Positive opinions

Opinions for Annual Re-Assessment applications		
Name of Medicinal Product (INN) MAH	**Outcome**	**Comments**
Carbaglu (carglumic acid), Orphan Europe SARL	Positive Opinion adopted	Since all specific obligations have now been fulfilled, it was agreed that there were no remaining grounds to keep the Marketing Authorisation under exceptional circumstances. Annex II was revised accordingly.
Renagel (sevelamer) Genzyme B.V	Positive Opinion adopted	Since all specific obligations have now been fulfilled, it was agreed that there were no remaining grounds to keep the Marketing Authorisation under exceptional circumstances. Annex II was revised accordingly

Opinion for renewals of conditional MA's		
Name of Medicinal Product (INN) MAH	**Outcome**	**Comments**
N/A	**N/A**	**N/A**

Opinions for 5 Year Renewal applications		
Name of Medicinal Product (INN) **MAH**	**Outcome**	**Comments**
Bondronat (ibandronic acid) Roche Registration Ltd	Positive Opinion adopted	Unlimited validity
Depocyte (cytarabine) SkyePharma PLC	Positive Opinion adopted	Additional 5-year renewal
HBVAXPRO (recombinant Hepatitis B virus small surface antigen (HbsAg)), Aventis Pharma S.A	Positive Opinion adopted	Additional 5-year renewal

MEDICINAL PRODUCTS GRANTED A COMMUNITY MARKETING AUTHORISATION UNDER THE CENTRALISED PROCEDURE SINCE THE FEBRUARY 2006 CHMP MONTHLY REPORT

Invented Name	Valtropin
INN	Somatropin
Marketing Authorisation Holder	BioPartners GmbH
Proposed ATC code	H01AC01
Indication	Paediatric patients Long-term treatment of children with growth failure due to an inadequate secretion of normal endogenous growth hormone. Treatment of short stature in children with Turner syndrome, confirmed by chromosome analysis. Treatment of growth retardation in pre-pubertal children with chronic renal insufficiency. Adult patients Replacement therapy in adults with pronounced growth hormone deficiency of either
CPMP Opinion date	23.02.2006
Marketing Authorisation Date	24.04.2006

Invented Name	Omnitrope
INN	Somatropin
Marketing Authorisation Holder	Sandoz GmbH
Proposed ATC code	H01AC01
Indication	Children Growth disturbance due to insufficient secretion of growth hormone (GH) and growth disturbance associated with Turner syndrome or chronic renal insufficiency. Growth disturbance (current height standard deviation score (SDS) < -2.5 and parental adjusted SDS < -1) in short children born small for gestational age (SGA), with a birth weight and/or length below -2 standard deviation (SD), who failed to show catch-up growth (height velocity (HV) SDS < 0 during the last year) by 4 years of age or later. Prader-Willi syndrome (PWS), for improvement of growth and body composition. The diagnosis of PWS should be confirmed by appropriate genetic testing. Adults Replacement therapy in adults with pronounced growth hormone deficiency. Patients with severe growth hormone deficiency in adulthood are defined as patients with known hypothalamic pituitary pathology and at least one known deficiency of a pituitary hormone not being prolactin. These patients should

	undergo a single dynamic test in order to diagnose or exclude a growth hormone deficiency. In patients with childhood onset isolated GH deficiency (no evidence of hypothalamic-pituitary disease or cranial irradiation), two dynamic tests should be recommended, except for those having low IGF-I concentrations (SDS < - 2) who may be considered for one test. The cut-off point of the dynamic test should be strict.
CPMP Opinion date	26.01.2006
Marketing Authorisation Date	12.04.2006

Invented Name	Proquad
INN	Measles, Mumps, Rubella and Varicella Vaccine (Live)
Marketing Authorisation Holder	Aventis Pasteur MSD SNC
Proposed ATC code	J07BD54.
Indication	ProQuad is indicated for simultaneous vaccination against measles, mumps, rubella and varicella in individuals from 12 months of age.
CPMP Opinion date	23.02.2006
Marketing Authorisation Date	06.04.2006

Invented Name	Myozyme
INN	Alglucosidase alpha
Marketing Authorisation Holder	Genzyme Europe B.V
Proposed ATC code	A16AB07
Indication	Myozyme is indicated for long-term enzyme replacement therapy (ERT) in patients with a confirmed diagnosis of Pompe disease (acid α-glucosidase deficiency).
CPMP Opinion date	26.01.2006
Marketing Authorisation Date	29.03.2006

Invented Name	Tygacil
INN	Tigecycline
Marketing Authorisation Holder	Wyeth Europa Ltd
Proposed ATC code	Not yet assigned
Indication	Tygacil is indicated for the treatment of the following infections. Complicated skin and soft tissue infections

	Complicated intra-abdominal infections
CPMP Opinion date	23.02.2006
Marketing Authorisation Date	24.04.2006

Invented Name	Preotact
INN	Parathyroid hormone
Marketing Authorisation Holder	Nycomed Danmark ApS
Proposed ATC code	H05AA03
Indication	Treatment of osteoporosis in postmenopausal women at high risk of fractures.
CPMP Opinion date	23.02.2006
Marketing Authorisation Date	24.04.2006

Invented Name	DuoTrav
INN	Travoprost/Timolol
Marketing Authorisation Holder	Alcon Laboratories (U.K.) Limited
Proposed ATC code	S01ED51
Indication	Decrease of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to topical beta-blockers or prostaglandin analogues.
CPMP Opinion date	23.02.2006
Marketing Authorisation Date	24.04.2006

OVERVIEW OF DESIGNATED ORPHAN MEDICINAL PRODUCTS THAT HAVE BEEN THE SUBJECT OF A CENTRALISED APPLICATION FOR MARKETING AUTHORISATION: UPDATE SINCE THE MARCH 2006 CHMP MEETING

Active substance	**Sponsor/applicant**	**EU Designation Number & Date of Orphan Designation**	**Designated Orphan Indication**
3-(4'aminoisoindoline-1'-one)-1-piperidine-2,6-dione (Lenalidomide Celgene Europe)	Celgene Europe Limited	EU/3/03/177 12/12/2003	Treatment of multiple myeloma
Imatinib mesylate (Glivec)	Novartis Europharm Limited	EU/3/05/320 28/10/2005	Treatment of chronic eosinophilic leukaemia and the hypereosinophilic syndrome

OUTCOME OF THE APRIL 2006 CHMP MEETING IN RELATION TO SCIENTIFIC ADVICE PROCEDURES

EMEA CENTRALISED PROCEDURES

	1995 - 2005	2006	Overall Total
Scientific Advice	558	51	609
Follow-up to Scientific Advice	94	6	100
Protocol Assistance	107	17	124
Follow-up to Protocol Assistance	26	2	28
	785	76	861

Substance	Intended indications(s)	Type of Request				Topic			
		New		Follow-up		Pharma ceutical	Pre-clinical	Clinical	Significant Benefit
		SA	PA	SA	PA				
Biological	Acute peripheral arterial occlusion		X			X	X	X	X
Biological	Hypovolemia	X						X	
Chemical	Acute ischemic stroke	X						X	
Chemical	Acute Decompensated Heart Failure (ADHF)	X				X	X	X	
Chemical	Amyotrophic lateral sclerosis	X					X	X	
Chemical	Acute Myeloid Leukemia (AML)	X					X	X	
Biological	Immunisation against pneumococcal infections	X				X		X	
Chemical	Cystic fibrosis		X			X	X	X	X
Biological	Repair of symptomatic cartilaginous defects of the femoral condyle of the knee	X				X	X	X	
Chemical	Systemic lupus erythematosous and lupus nephritis	X				X	X		
Chemical	Paediatric asthma	X					X	X	
Chemical	Reduction of combined risks of total mortalility and non-fatal cardiovascular events	X						X	
Chemical	Contraceptive	X						X	

Substance	Intended indications(s)	Type of Request				Topic			
		New		Follow-up		Pharma ceutical	Pre-clinical	Clinical	Significant Benefit
		SA	PA	SA	PA				
Biological	Chronic Hepatitis B	X				X	X	X	
Total		**12**	**2**	**0**	**0**				

SA: Scientific Advice

PA: Protocol Assistance

The above-mentioned 12 Scientific Advice letters, 2 Protocol Assistance letters, 0 Follow-up Scientific Advice letters and 0 Follow-up Protocol Assistance letters were adopted at the 24 – 27 April 2006 CHMP meeting.

The Committee accepted 14 Initial Scientific Advice Requests, 2 Follow-up Scientific Advice Requests, 2 Initial Protocol Assistance Requests and 2 Follow-up Protocol Assistance Requests started at the SAWP meeting that took place on 29 – 31 March 2006.

DOCUMENTS PREPARED BY THE CHMP WORKING PARTIES ADOPTED DURING THE APRIL 2006 CHMP MEETING

BIOLOGICS WORKING PARTY

Reference number	Document	Status
CHMP/BWP/298388/ 2005	Guideline on validation of immunoassay for the detection of antibody to human immunodeficiency virus (anti-HIV) in plasma pools	Adopted
CHMP/BWP/51885/2006	Guideline on validation of immunoassay for the detection of Hepatitis B virus surface antigen (HbsAg) in plasma pools	Adopted
CHMP/BWP/145237/ 2006	Revised EU recommendation for the influenza vaccine composition for the season 2006 – 2007	Adopted

BLOOD PRODUCTS WORKING PARTY (BPWP)

Reference number	Document	Status
CPMP/BPWG/575/99 Rev. 1	Revised Guideline on the Clinical Investigation of Human Anti D Immunoglobulin for Intravenous and/or Intramuscular use	Released for 5 months consultation
CPMP/BPWG/574/99 Rev. 1	Revised Guideline on the Core SPC for Human anti-D immunoglobulin for Intramuscular use	Released for 5 months consultation
CPMP/BPWG/319619/ 2005	Revised Guideline on the Core SPC for Human Anti-D Immunoglobulin for Intravenous use	Released for 5 months consultation
CPMP/BPWG/4222/02	Revised core SPC for hepatitis-B immunoglobulin for Intramuscular use	Adopted
CPMP/BPWG/4027/02	Revised core SPCs for hepatitis-B immunoglobulin for Intravenous use	Adopted

EFFICACY WORKING PARTY (EWP)

Reference number	Document	Status
CPMP/EWP/555/95 Rev. 1	Guideline on Haematopoietic Growth Factor	Release for 6 months consultation
CHMP/EWP/147231/ 2006	Concept paper for an addendum to the Note for Guidance on the investigation of Bioavailability and Bioequivalence: Evaluation of Bioequivalence of highly variable drugs and drug products	Release for 3 months consultation

PHARMACOGENETICS WORKING PARTY (PgWP)

Reference number	Document	Status
CHMP/PGxWP/128629/2006	Concept Paper on the Use of Genomics in Cardiovascular Clinical Trials	Adopted
CHMP/PGxWP/128435/2006	Concept Paper on Pharmacogenomic EMEA Experience in Oncology	Adopted
CHMP/PGxWP/20227/2004	Guideline on Pharmacogenetics Briefing meetings	Adopted

PHARMACOVIGILANCE WORKING PARTY (PhVWP)

Reference number	Document	Status
EMEA/83889/2006	CHMP Guideline on the handling of direct Health Care Professional communications on the safe and effective use of Medicinal Products for Human use	Adopted

WORKING PARTY ON SIMILAR BIOLOGICAL (BIOSIMILAR) MEDICINAL PRODUCTS (BMWP)

Reference number	Document	Status
CHMP/BMWP/7241/2006	Concept paper on similar biological medicinal products containing recombinant alpha-interferon - Annex to the guideline on similar biological medicinal products containing biotechnology derived proteins as active substance – (non) clinical issues	Released for 3 months consultation
CHMP/BMWP/81294/2006	Overview of comments on Guideline on Similar Biological Medicinal Products containing biotechnology derived products as active substance: non-clinical and clinical issues	Adopted
CHMP/BMWP/81498/2006	Overview of comments on Guideline on Similar Biological Medicinal Products containing biotechnology derived products as active substance: non-clinical and clinical issues Annex: recombinant G-CSF containing product	Adopted
CHMP/BMWP/127910/2006	Overview of Comments on Guideline on Similar Biological Medicinal Products containing biotechnology derived products as active substance: non-clinical and clinical issues Annex: recombinant human soluble Insulin	Adopted

INVENTED NAME REVIEW GROUP (NRG)

	April 2006			2006	
	Accepted	Rejected	Pending	Accepted	Rejected
Proposed invented names	2	17	39	25	51
Justification for retention of invented name *	2	2	3	3	13

*In case of objections to the proposed invented name(s), the applicant may justify the retention of the proposed invented name using the relevant justification form available on the EMEA website.

Co-ordination Group for Mutual Recognition and Decentralised Procedures - Human

Report from the CMD(h) meeting held from 24th to 26th April 2006

General Issues

Sub-group meeting on Harmonisation of SPCs

There was a meeting of the Sub-Group on harmonisation of SPCs, mainly to consider the initial proposals from Member States for products for which a harmonised SPC should be drawn up.

The Sub-group considered also the number of products that may be referred to the CHMP for arbitration and future cooperation with Interested Parties.

The Sub-Group agreed to meet with Interested Parties as needed.

The CMD(h) Sub-Group on harmonisation of SPCs will continue its work with a view to laying down a list of medicinal products for which a harmonised SPC should be drawn up, taking into account the proposals from all Member States, in accordance with Article 30(2) of Directive 2001/83/EC, as amended.

List of Guidance documents in the Mutual Recognition Procedure under revision & Publication and consultation of MRFG/CMD(h) Guidance documents on the implementation of the new legislation

The CMD(h) has updated the lists of Guidance documents in the MRP under revision & Publication and consultation of Guidance documents on the implementation of the new legislation, to reflect the current status of the documents under revision/preparation by the CMD(h), in accordance with the new legislation.

Urgent Safety Restriction – Member States' Standard Operating Procedure

The CMD(h) has considered the comments received from Interested Parties on the Urgent Safety Restriction – Member States' Standard Operating Procedure. The updated SOP, agreed by the CMD(h) and PhVWP, will be published on the website.

Best Practice Guide EU Work Sharing Procedure in the Assessment of Paediatric Data

The CMD(h) has updated the Best Practice Guide for the EU Work sharing procedure in the assessment of paediatric data, mainly with regard to the content of the application and to give further clarification on the role of the Rapporteur and Co-Rapporteur in the procedure. The updated BPG will be published on the website.

Informal CMD(h) meeting

An informal CMD(h) meeting will be held in Vienna on 18-19 May 2006. The meeting will be mainly focused on Member States experience with the new legislation, including the new decentralised procedure, referrals to CMD(h) and the work within the CMD(h).

The transparency requirements of the new legislation, consultation with target patient groups, usage patents and harmonisation of package leaflets will also be on the Agenda for the meeting.

Information on applications referred to the CMD(h) in accordance with Article 29(1) of Directive 2001/83/EC, as amended

Please find below information on the Name of the products in the RMS, active substances, pharmaceutical forms, procedure numbers, CMS, legal basis, grounds for referral to CMD(h), Day 60 and outcome of the procedures, for the referrals to the CMD(h) finalised on 31 March 2006.

Name of the product in the RMS	Fostimon 75, 150 IU/ml
Active substance	urofollitropin
Pharmaceutical form	Powder and solvent for solution for injection
Procedure number	FR/H/282/01-02
CMS	AT, BE, CY, DE, DK, ES, FI, IE, LU, NL, NO, PT, SE, UK
Legal basis	Article 8(3), Directive 2001/83/EC – Full dossier
Grounds for referral to CMD(h)	Efficacy in the claimed indications and safety (immunogenicity).
Day 60	31.03.06
Outcome	Agreement Reached

Name of the product in the RMS	Glucomed
Active substance	Glucosamine hydrochloride
Pharmaceutical form	Tablet
Procedure number	SE/H/560/01
CMS	AT, BE, CY, CZ, DE, DK, EE, EL , ES, FI, FR, HU, IE, IS, IT, LT, LU, LV, NL, NO, PL, PT, SK, UK
Legal basis	Article 10.1(a)(ii), Directive 2001/83/EC - Bibliographic
Grounds for referral to CMD(h)	Different interpretation of the submitted quality data and existing bibliographic data concerning safety and efficacy.
Day 60	31.03.06
Outcome	Referred to CHMP for arbitration

Name of the product in the RMS	Alendros 70
Active substance	alendronic acid
Pharmaceutical form	Tablet
Procedure number	CZ/H/115/01
CMS	EE, HU, LT, LV, PL, SK
Legal basis	Article 10.1(a)(iii), Directive 2001/83/EC - Generic
Grounds for referral to CMD(h)	Different views on the clinical consequences of deviation from the existing bioequivalence guideline.
Day 60	31.03.06
Outcome	Referred to CHMP for arbitration

Name of the product in the RMS	Doxazosin NM Pharma
Active substance	Doxazosin mesylate
Pharmaceutical form	Prolonged release tablet
Procedure number	SE/H/465/01
CMS	CZ, HU, NL, PL, SI, SK
Legal basis	Article 10.1(a)(iii), Directive 2001/83/EC - Generic
Grounds for referral to CMD(h)	Different views on the clinical consequences of deviation from the existing bioequivalence guideline.
Day 60	31.03.06
Outcome	Agreement reached

Name of the product in the RMS	Doxazosin Retard "Arrow"	Doxazosin "Winthrop"
Active substance	Doxazosin mesylate	
Pharmaceutical form	Prolonged release tablet	
Procedure number	DK/H/431/01/E/01	DK/H/694/01/E/01
CMS	PT, SI, UK (wave 2) NO, SE, DE (wave 1)	DE, ES, HU, NL, PL, SK, UK (wave 2) CZ (wave 1)
Legal basis	Article 10.1(a)(iii), Directive 2001/83/EC - Generic	
Grounds for referral to CMD(h)	1. Different views on the clinical consequences of deviation from the existing bioequivalence guideline. 2. One CMS for Doxazosin Retard "Arrow" raised concerns over the indication "Essential Hypertension". Agreement was reached in the CMD(h) on the wording of the indication.	
Day 60	31.03.06	
Outcome	Referred to CHMP for arbitration	

Name of the product in the RMS	Ramipril Capsules 1.25, 2.5, 5, 10 mg
Active substance	ramipril
Pharmaceutical form	Capsule, hard
Procedure number	UK/H/830/01-04
CMS	BE, DE, IT, MT, NL, PT, SE
Legal basis	Article 10.1(a)(iii), Directive 2001/83/EC - Generic
Grounds for referral to CMD(h)	1. Difference in approved indications between RMS SPC and CMS, such that the following indications are not included in the UK SPC: • Treatment of manifest non-diabetic glomerular nephropathy • Treatment of incipient diabetic nephropathy (microalbuminuria) in patients with type 2 diabetes mellitus and hypertension The CMS considered that omission of these indications was a public health concern because all information in SPC and PIL for interchangeable generic products should be consistent. 2. One CMS raised concern over interpretation of criteria for extrapolation of results from a bioequivalence study conducted with the 10mg strength capsules to the 1.25mg strength, based on linearity of ramipril/ramiprilat pharmacokinetics over this dose range.
Day 60	31.03.06
Outcome	Agreement reached. Further action in the Sub-group on harmonisation of SPCs.

Name of the product in the RMS	Lamotrigine 25, 50, 100, 200mg
Active substance	lamotrigine
Pharmaceutical form	Tablets
Procedure number	UK/H/827/01-04
CMS	BE, CZ, DE, DK, EL, HU, IE, PL, SI
Legal basis	Article 10.1(a)(iii), Directive 2001/83/EC - Generic
Grounds for referral to CMD(h)	Difference in approved indications between innovator SPC in RMS and CMS, such that the indication for bipolar disorder is not included in the RMS SPC. One CMS considered that omission of this indication was a potential serious risk to public health because all of the information in the SPC and PIL for interchangeable generic products should be consistent.
Day 60	31.03.06
Outcome	Agreement reached. Further SPC activity proposed.

NEW APPLICATIONS

Mutual Recognition Procedure

The CMD(h) noted that **82** new Mutual Recognition Procedures were finalised during the month of March 2006. **7** Mutual Recognition Procedures for new applications were referred to CMD(h) in this period. **7** Mutual Recognition Procedures for new applications were referred to CHMP in this period.

The status as of 31th March of procedures under Mutual Recognition is as follows:

Year	Procedures from New applications finalised	Procedures from New applications in process	Procedures referred to CMD(h)	Agreement reached in the CMD(h)	Arbitrations referred to CHMP
2006	152	103	32 N.A.	11	7

60 Mutual Recognition Procedures (regarding **128** products) started in March 2006. The categories of these procedures are as follows:

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

9 known active substances (already authorised in at least one member state), including **1** repeat use.

32 abridged applications including **2** multiple applications and **3** repeat use.

16 line extension applications.

The new procedures started related to **11** full dossiers, **39** generics, **5** hybrid applications, **2** fixed-combinations and **3** bibliographic applications.

The procedures consisted of **56** chemical substances and **4** biological blood products.

59 of these procedures were prescription-only medicinal products in the reference Member State and **1** procedure was classified as Non-prescription (including OTC) medicinal product[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 in Mutual Recognition procedure started in March 2006.

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
CZ (3)	4
CZ (2)	2
CZ (1)	4
DE (1)	10
DE (1)	15
DE (1)	5
DE (3)	1
DE (4)	9
DE (4)	9
DE (4)	9
DE (4)	5
DK (1)	17
DK (1)	3
DK (1)	8
DK (2)	6
DK (2)	2
DK (2)	4

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
DK (4)	1
DK (2)	16
DK (2)	1
DK (2)	8
DK (1)	8
DK (1)	3
FI (2)	8
FI (2)	4
FI (2)	1
FI (2)	1
FI (2)	9
FI (2)	11
FI (1)	3
FI (2)	5
FI (2)	1
FI (2)	1
FI (1)	8
FR (1)	17
FR (1)	12
HU (4)	5
IT (2)	4
NL (2)	3
NL (3)	4
NL (3)	4
NL (3)	5
NL (2)	4
NL (2)	4
NL (6)	2
NL (6)	4
NL (6)	2
NO (2)	2
PT (1)	3
SE (2)	3
SE (1)	6
SE (3)	9
UK (4)	23
UK (1)	1
UK (2)	8
UK (1)	4
UK (1)	18
UK (1)	7
UK (1)	2
UK (1)	2

Decentralised Procedure

The status as of 31th March of procedures under Decentralised Procedure is as follows:

Year	Procedures from New applications finalised	Procedures from New applications in process	Procedures referred to CMD(h)	Agreement reached in the CMD(h)	Arbitrations referred to CHMP
2006	--	86	--	--	--

25 Decentralised Procedures (regarding **45** products) started in March 2006. The categories of these procedures are as follows:

18 abridged applications including **8** multiple applications.

5 known active substances (already authorised in at least one member state), including **2** multiple applications.

2 line extension applications, including **1** multiple applications.

The new Decentralised procedures started related to **5** full dossiers, **11** generics, **2** similar biologicals and **7** hybrid applications.

The procedures consisted of **25** chemical substances[3].

All of these procedures were prescription-only medicinal products in the reference Member State[4].

3. As considered by RMS.
4. In this category products are classified as prescription-only or Non-prescription (OTC) products as applied for in the RMS, although the legal status is not part of the Decentralised Procedure.

Number of countries involved in the new applications in Decentralised procedures started in March 2006.

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
DK (3)	14
DK (3)	3
DK (3)	3
DK (2)	12
DK (2)	3
FI (4)	5
FR (2)	24
FR (2)	14
FR (2)	2
NL (1)	18
NL (1)	3
NL (1)	1
NL (1)	1
NL (1)	6
NL (1)	4
NL (1)	4
NL (2)	12
NL (2)	14
NL (2)	5
NL (3)	13
SE (1)	1
SE (2)	3
SE (1)	6
SE (1)	2
SE (1)	1

VARIATIONS AND RENEWALS

Mutual Recognition and Decentralised Procedures

The CMD(h) noted that **377** type IA variations, **234** type IB variations and **167** type II variations were finalised during the month of March 2006. **32** renewals were finalised in this period.

The status as of 31th March of variations and renewals under Mutual Recognition is as follows:

Year	Procedures from Type IA variations finalised	Procedures from Type IB variations finalised	Procedures from Type II variations finalised	Renewals finalised	Arbitrations referred to CHMP
2006	992	532	420	77	- -

All documents mentioned in this press release can be found at the CMD(h) website at the European Medicines Authorities Windows under the heading *Press Releases.*

Information on the above mentioned issues can be obtained from the chair of the CMD(h):

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