European Medicines Agency
Evaluation of Medicines for Human Use

London, 4th August 2006
EMEA/296185/2006

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

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

Centralised procedure

Initial applications for marketing authorisation

The CHMP adopted five positive opinions on initial marketing authorisation application at this meeting:

- **Champix** (varenicline), from Pfizer Limited. The approved indication is cessation of smoking in adults. EMEA review began on 23 November 2005 with an active review time of 175 days.
- **Gardasil** (human papillomavirus (types 6, 11, 16 and 18) recombinant vaccine), from Sanofi Pasteur MSD, and **Silgard** (human papillomavirus (types 6, 11, 16 and 18) recombinant vaccine), from Merck Sharpe & Dohme, indicated for prevention of cancer, precancerous or dysplastic lesions and genital warts caused by the human papillomavirus. EMEA review began on 28 December 2005 with an active review time of 177 days.
- **Luminity** (perflutren), from Bristol-Myers Squibb Pharma Belgium Sprl, indicated for use in patients in whom non-contrast echocardiography was suboptimal and who have suspected or established coronary artery disease. EMEA review began on 21 February 2005 with an active review time of 207 days.
- **Suboxone** (buprenorphine and naloxone), from Schering-Plough Europe, indicated for substitution treatment for opioid drug dependence, within a framework of medical, social and psychological treatment. EMEA review began on 26 October 2005 with an active review time of 196 days.

The CHMP adopted two negative opinions on initial marketing authorisation applications at this meeting:

- **Valdoxan** (agomelatine) and **Thymanax** (agomelatine), from Les Laboratoires Servier. Both medicinal products were intended for the treatment of major depressive disorder. EMEA review began on 28 March 2005 with an active review time of 207 days.
  A separate question and answer document with more detailed information about the negative opinion is available.

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

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Extensions of indication and other recommendations

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

- **Abilify** (aripiprazole), from Otsuka Pharmaceutical Europe Ltd, to extend the indication to add rapid control of agitation and disturbed behaviours in schizophrenic patients when oral therapy is not appropriate. This indication concerns a new route of administration, Abilify 7.5 mg/ml solution for injection. Abilify was first authorised in the European Union on 4 June 2004. It is currently indicated for the treatment of schizophrenia.

- **Glivec** (imatinib), from Novartis Europharm Ltd, to extend its indication to add treatment of dermatofibrosarcoma protuberans (DFSP) and the treatment of adult patients with Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL). Glivec was first authorised in the European Union on 11 November 2001. It is currently indicated for the treatment of patients with Philadelphia chromosome positive chronic myeloid leukaemia (Ph+ CML) and for the treatment of adult patients with Kit (CD 117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumours (GIST).

- **Invanz** (ertapenem), from Merck Sharp & Dohme Ltd, to extend its indication to add prophylaxis of surgical site infection following elective colorectal surgery in adults. Invanz was first authorised in the European Union on 18 April 2002. It is currently indicated for the treatment of intra-abdominal infections, community acquired pneumonia, acute gynaecological infections and diabetic foot infections of the skin and soft tissue.

- **Lyrica** (pregabalin), from Pfizer Limited, to extend its indication to add the treatment of central neuropathic pain in adults. Lyrica was first authorised in the European Union on 6 July 2004. It is currently indicated for the treatment of peripheral neuropathic pain in adults, as adjunctive therapy for the treatment of epilepsy in adults with partial seizures with or without secondary generalisation and for the treatment of General Anxiety Disorder (GAD) in adults.

- **Plavix** (clopidogrel), from Sanofi Pharma Bristol-Myers Squibb SNC, and **Iscover** (clopidogrel), from Bristol-Myers Squibb Pharma EEIG, to extend its indication (in combination with acetylsalicylic acid) in the prevention of atherothrombotic events in patients suffering from acute coronary syndromes, to include patients suffering from ST segment elevation acute myocardial infarction who are eligible for thrombolytic therapy. Plavix was first authorised in the European Union on 15 July 1998 and is currently indicated for prevention of atherothrombotic events in patients suffering from myocardial infarction, ischaemic stroke or established peripheral arterial disease and, in combination with acetylsalicylic acid, for the treatment of patients suffering from non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction).

- **Remicade** (infliximab), from Centocor B.V., to change the indication of infliximab from third to second-line therapy in patients with severe, active Crohn's Disease. Remicade was first authorised in the European Union on 13 August 1999. It is currently indicated for the treatment of rheumatoid arthritis, Crohn's disease, ankylosing spondylitis, psoriatic arthritis, psoriasis and ulcerative colitis.

The Committee adopted a negative opinion on the extension of indication of a medicinal product that is already authorised in the European Union:

- **Tarceva** (erlotinib), from Roche Registration Limited. The indication applied for related to the addition of first-line treatment of locally advanced, unresectable or metastatic pancreatic cancer in combination with gemcitabine. Tarceva was first authorised in the European Union on 19 September 2005. It is currently indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer.
  A separate question and answer document with more detailed information about the negative opinion is available.

Summaries of opinions for all these products are available and can be found here.

The Committee also adopted a positive opinion on a "line extension" application (under the optional scope) (in accordance with Annex II of Commission Regulation (EC) No. 1085/2003).

Lists of Questions

The Committee adopted eight Lists of Questions on initial applications (six 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 June 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 the June 2006 CHMP plenary meeting are provided in **Annex 4**.

Referral procedures

- The Committee started a referral procedure for **bicalutamide 150 mg**-containing medicinal products. The procedure was initiated by Belgium following suspension of Casodex (bicalutamide) 150 mg, from AstraZeneca, due to efficacy and safety concerns, in particular concerns over heart problems, regarding the use of the medicinal product in the treatment of early prostate cancer. The procedure was initiated under Article 31 of the Community code on human medicinal products (Directive 2001/83/EC as amended).

- The Committee started a referral procedure for **Ciprofloxacine Hikma 200 mg/100 ml** (ciprofloxacine lactate), from Hikma Farmaceutica, Portugal, because of disagreements among the Member States regarding the dosages used to treat complicated urinary tract infections. The procedure was initiated under Article 29 of the Community code on human medicinal products (Directive 2001/83/EC as amended).

- The Committee also started a referral procedure for **Alendronat Hexal 10 mg** (alendronate), from Hexal A/S, Sweden, because of disagreements among the Member States regarding the indication for the treatment of osteoporosis in men. The procedure was initiated under Article 29 of the Community code on human medicinal products (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 3-5 July 2006. For further details, please see **Annex 5**.

Documents prepared by the CHMP Working Parties adopted during the July 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 July 2006 CHMP plenary meeting:

- The 25th meeting of the CHMP will be held at the EMEA on 18 - 21 September 2006.
- The next Invented Name Review Group meeting will be held at the EMEA on 18 September 2006.
- The 10th CMD(h) (Co-ordination Group for Mutual Recognition and Decentralised Procedures) will be held at the EMEA on 18 - 19 September 2006.

Organisational matters

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

- Adoption of the Mandate, Objectives and Rules of Procedures for the EMEA Human Scientific Committees Working Party with Patients and Consumers Organisations.
- Discussions of EMEA/CHMP experience on products containing cells.
- Referrals / arbitrations and their legal, regulatory and scientific implications.

EMEA Implementation of the New EU Pharmaceutical Legislation

The 19th CHMP/EMEA Implementation Task Force (CEITAF) meeting took place on Monday 24 July 2006.

The following guideline is released for 2 months consultation on the EMEA website:

- Principles to be applied for the deletion of commercially confidential information for the disclosure of EMEA documents.

The following document was revised to reiterate that proposals for conditional approval have to be accompanied by explanatory reasons addressing the fulfilment of the requirements set out in Article 4 of Commission Regulation (EC) No 507/2006. This was agreed by the CHMP and will be transmitted to the European Commission:

- 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.

Follow-on discussions took place on the following topic:

- Publication of information related to withdrawal or refusal of application.

Final discussions took place on the following topic and both documents were adopted by the CHMP:

- Joint Rapporteur's and Co-Rapporteur's Renewal Assessment Report and CHMP Renewal Assessment Report template.

This was the last CEITAF meeting and a review was made on the CHMP/EMEA/EC achievements with regard to the development of "Pharmaceutical Legislation Review implementation guidelines and documents". Review Implementation topics will now be followed up within the ORGAM (Organisational matters) meeting. Regular updates will continue to be made here until all identified guidelines/documents are finalised further to discussions at the ORGAM/CHMP meeting towards the end of 2006/beginning of 2007.

PROCEDURAL ANNOUNCEMENT

- Bulgaria and Romania Accession to the EU

In view of the potential enlargement of the EU with Bulgaria and Romania on 1st January 2007[1], and the fact that Commission Decision Annexes as of that date will have to contain the 2 additional accession country languages, applicants are advised that for all new applications (including extensions) for which an opinion will be adopted in October 2006, translations of SPC, Annex II, Labelling and PL will also have to be provided in Bulgarian and Romanian.

More detailed guidance on this process, including the requirements for all other regulatory procedures can be found in the EMEA "Practical guidance on the extension of Commission Decision Annexes in the new accession country languages" (http://www.emea.eu.int/pdfs/human/regaffair/12951006en.pdf).

Applicants/MAHs are also reminded of the pre-accession linguistic review process (PALC-II) which aims at ensuring timely availability of checked Bulgarian and Romanian product information in preparation of accession (http://www.emea.eu.int/euenlargement.htm#).

- The publication of individual guidelines adopted this month might be delayed due to an ongoing exercise to improve the presentation of guidelines on the EMEA website.

[1] Accession date to be confirmed by the European Commission in the autumn of 2006. Therefore, this guidance and in particular the timelines for submission of documents, cannot be considered as final and may need to be adjusted accordingly.

Mutual Recognition procedure and Decentralised procedures-Human

The CHMP noted the report from the 9th CMD(h) (Co-ordination Group for Mutual Recognition and Decentralised procedures-Human) held on 24 - 25 July 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[2]							1995 onwards
	Optional Scope			Mandatory scope			Total	Overall total
	NAS	Significant innovation	Interest of Patients	Biotech	Indications	Orphans		
Applications for MA submitted[3]	**16**	**4**	**0**	**14**	**4**	**7**	**45**	**535**
Positive opinions[4]	**16**	**2**	**0**	**6**	**0**	**6**	**30**	**356[5]**
Negative opinions[6]	**3**	**0**	**0**	**2**	**0**	**0**	**5**	**12[6]**
Withdrawals prior to opinion	**2**	**1**	**0**	**1**	**0**	**2**	**6**	**105**
Marketing authorisation granted by the Commission	**17**	**0**	**0**	**7**	**0**	**5**	**29**	**340**

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[7]	**1**	**5**
PMF	**1**	**8**
VAMF	**0**	**0**

[2] Starting point for operation of the new eligibility criteria to the centralised procedure
[3] Number of accelerated reviews requested and number of accelerated reviews granted (3/0)
[4] Subdivided by conditional and exceptional (0/0)
[5] 356 positive Opinions corresponding to 282 substances
[6] In case of Re-examination under Art. 9(2) of Regulation (EC) No. 726/2004, the opinion will not be counted twice.
[7] 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

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

Substance	Intended indications(s)	Accelerated Assessment Requests	
		Accepted	Rejected
Chemical	Maintenance of remission of acute myeloid leukaemia		X

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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)	413	3853
Type II Variations (positive opinions)	397	2579
Type II Variations (negative opinions)	1	8
Annex II Applications (positive opinions)	12	139
Annual Re-assessment (positive opinions)	17	N/A
Opinion for renewals of conditional MA's (positive opinions)	0	0
5 Year Renewals (positive opinions)	39	N/A

Opinions for Type II Variation applications	
Number of Opinions	**Outcome**
8 Extensions of indication	8 Positive opinions
1 Extensions of indication	1 Negative opinion
41 SPC changes	41 Positive opinions
33 Quality changes	33 Positive opinions

Opinions for Annual Re-Assessment applications		
Name of Medicinal Product (INN) MAH	**Outcome**	**Comments**
Fuzeon (enfuvirtide) Roche Registration Ltd,	Positive Opinion adopted	The Marketing Authorisation will remain under Exceptional Circumstances

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**
Cancidas (caspofungin) Merck Sharp & Dohme	Positive Opinion adopted	Exceptional Circumstances lifted and Additional 5-year renewal
Glivec (imatinib mesilate) Novartis Europharm Ltd	Positive Opinion adopted	Unlimited validity
Norvir (ritonavir) Abbott Laboratories	Positive Opinion adopted	Unlimited validity
Travatan (travoprost) Alcon Laboratories (UK) Ltd	Positive Opinion adopted	Unlimited validity

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

Invented Name	Sutent
INN	sunitinib
Marketing Authorisation Holder	Pfizer Limited
Proposed ATC code	LO1XE04
Indication	Sutent is indicated for the treatment of unresectable and/or metastatic malignant gastrointestinal stromal tumour (GIST) after failure of imatinib mesylate treatment due to resistance or intolerance. SUTENT is indicated for the treatment of advanced and/or metastatic renal cell carcinoma (MRCC) after failure of interferon alfa or interleukin-2 therapy.
CHMP Opinion date	27.04.2006
Marketing Authorisation Date	19.07.2006

Invented Name	Nexavar
INN	Sorafenib
Marketing Authorisation Holder	Bayer HealthCare AG
Proposed ATC code	L01XE05
Indication	Nexavar is indicated for the treatment of patients with advanced renal cell carcinoma who have failed prior interferon-alpha or interleukin-2 based therapy or are considered unsuitable for such therapy.
CHMP Opinion date	27.04.2006
Marketing Authorisation Date	19.07.2006

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

Active substance	**Sponsor/applicant**	**EU Designation Number & Date of Orphan Designation**	**Designated Orphan Indication**
Mecasermin rinfabate (Iplex)	Insmed Europe Ltd	EU/3/06/377 20/06/2006	Treatment of patients with growth hormone (GH) gene deletion have developed neutralizing antibodies to GH
		EU/3/06/378 20/06/2006	Treatment of primary insulin-like growth factor-1 deficiency due to molecular or genetic defects
Abetimus sodium (Riquent)	La Jolla Limited-United Kingdom	EU/3/01/064 20/11/2001	Treatment of lupus nephritis

PRE-AUTHORISATION: SCIENTIFIC ADVICE AND PROTOCOL ASSISTANCE EMEA CENTRALISED PROCEDURES

	1995 - 2005	2006	Overall Total
Scientific Advice	558	97	655
Follow-up to Scientific Advice	94	16	110
Protocol Assistance	107	31	138
Follow-up to Protocol Assistance	26	5	31
	775	149	934

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

Finalised Procedures

Substance	Intended indications(s)	Type of Request				Topic			
		New		Follow-up		Pharmaceutical	Pre-clinical	Clinical	Significant Benefit
		SA	PA	SA	PA				
Biological	Multiple sclerosis	X						X	
Chemical	Pain	X						X	
Chemical	Alzheimer's disease	X						X	
Chemical	Myasthenia gravis		X				X	X	
Chemical	Behavioural disturbances in children and adolescents with pervasive development disorder	X						X	
Chemical	Fibromyalgia	X					X	X	
Chemical	Hypertension in children	X				X		X	

Substance	Intended indications(s)	Type of Request				Topic			
		New		Follow-up		Pharmaceutical	Pre-clinical	Clinical	Significant Benefit
		SA	PA	SA	PA				
Chemicals	Hypertension	X						X	
Chemical	Acute coronary syndromes	X						X	
Chemical	Secondary prevention in coronary artery disease	X						X	
Chemicals	Hypertension			X		X			
Chemical	Superficial thrombophlebitis	X						X	
Chemical	Pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension		X			X	X	X	X
Biological	Lipoprotein lipase deficiency				X	X	X	X	
Biological	Type 1 Gaucher Disease	X				X	X	X	
Chemical	Cushing's disease	X					X	X	
Biological	Pneumococcal vaccine			X				X	
Chemical	Prophylaxis of pulmonary fungal infections	X				X	X	X	
Biological	Influenza vaccine	X				X		X	
Chemical	Cystic fibrosis				X			X	
Biological	Rotavirus vaccine	X				X	X	X	
Biological	Sepsis	X						X	
Biological	Anal fistula		X					X	
Biological	Cystic fibrosis		X			X	X	X	X

Substance	Intended indications(s)	Type of Request				Topic			
		New		Follow-up		Pharmaceutical	Pre-clinical	Clinical	Significant Benefit
		SA	PA	SA	PA				
Chemical	Treatment of asthma in children	X						X	
Biological	Malabsorption due to exocrine pancreatic enzyme insufficiency		X			X	X	X	
Chemical	Hepatocellular carcinoma	X						X	
Chemical	Prevention of chemotherapy-induced nausea and vomiting	X						X	
Chemical	Carcinoid and pancreatic neuroendocrine tumors			X				X	
Chemical	Breast cancer	X						X	
Chemical	Prevention of bone loss in postmenopausal women with breast cancer receiving chemotherapy	X					X	X	

SA: Scientific Advice
PA: Protocol Assistance

The above-mentioned 21 Scientific Advice letters, 5 Protocol Assistance letters, 3 Follow-up Scientific Advice letters and 2 Follow-up Protocol Assistance letters were adopted at the 24-27 July 2006 CHMP meeting.

New requests for SA/PA Procedures

The Committee accepted 34 new Requests for which the procedure started at the SAWP meeting held on 3-5 July 2006. The new requests are divided as follows: 20 Initial Scientific Advice, 6 Follow-up Scientific Advice, 7 Initial Protocol Assistance and 1 Follow-up Protocol Assistance.

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

VACCINE WORKING PARTY

Reference number	Document	Status[8]
EMEA/214301/2006	EMEA pandemic influenza crisis management plan for the evaluation and maintenance of pandemic influenza vaccines and antivirals	Adopted
CHMP/VWP/263499/2006	Draft guideline on dossier structure and content for marketing authorisation for influenza vaccines with avian strains with a pandemic potential for use outside of the core dossier context	Released for 1.5 months consultation
CHMP/VWP/244894/2006	Explanatory note on immunomodulators for the guideline on adjuvants in vaccines for human use	Adopted

PHARMACOGENETICS WORKING PARTY

Reference number	Document	Status
EMEA/128517/2006	Reflection Paper on the Use of Pharmacogenetics in the Phamacokinetic Evaluation of Medicinal Products	Released for 3 months consultation

SAFETY WORKING PARTY

Reference number	Document	Status
EMEA/194898/2006	Guideline on Carcinogenicity Evaluation of Medicinal Products for the Treatment of HIV Infection	Released for 6 months consultation

EFFICACY WORKING PARTY

Reference number	Document	Status
CHMP/EWP/267575/2006	Appendix 1 to the Guideline on the Evaluation of Anticancer Medicinal Products in Man	Released for 6 months consultation
CHMP/EWP/83561/2005	Guideline on Clinical Trials in Small Populations	Adopted
CHMP/EWP/270226/2006	Overview of comments received on the Guideline on Clinical Trials in Small Populations	Adopted
CHMP/EWP/40326/2006	Questions & Answers on the Bioavailability and Bioequivalence Guideline	Adopted

[8] Adopted or release for consultation documents can be found at the EMEA website (under "What's new-recent publications" or under Human Medicines-Guidance documents").

EMEA HUMAN SCIENTIFIC COMMITTEES WORKING PARTY WITH PATIENTS AND CONSUMERS ORGANISATIONS

Reference number	Document	Status
EMEA/208157/2006	Mandate, Objectives and Rules of Procedures	To be adopted by COMP and HMPC in September 2006

INVENTED NAME REVIEW GROUP (NRG)

	July 2006			2006	
	Accepted	Rejected	Pending	Accepted	Rejected
Proposed invented names	7	8	29	69	96
Justification for retention of invented name *	2	2	7	11	19

*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 on 24th and 25th July 2006

Sub-group meeting on Harmonisation of SPCs

There was a meeting of the Sub-Group on harmonisation of SPCs, to discuss the rationale for inclusion of the medicinal products proposed in the list for SPC harmonisation.

The Sub-Group on harmonisation of SPCs agreed to have further discussions in September 2006, with a view to finalising the list of medicinal products for which a harmonised SPC should be drawn up, in accordance with Article 30(2) of Directive 2001/83/EC, as amended.

Guidance on contacts with Representative Organisations

The CMD(h), having in regard the Rules of Procedure, Article 14, has agreed a Guidance document, which defines the scope and conditions of contacts with Representative Organisations.

Interactions with the following CMD(h) Stakeholders: Patients Organisations, Health Care Professionals and Pharmaceutical Industry Organisations are addressed in the Guidance document.

The Guidance on contacts with Representative Organisations will be published on the website.

Question and Answer on Combination packages

The CMD(h) has agreed a Q&A on combination packages, addressing the possibility to apply for a combination package via the MRP or DCP.

In principle, many MS can accept a combination package if there are strong arguments for the provision of a combination package with respect to benefit to public health or where the use of a combination package is more user friendly for the patient or healthcare professional. However, Applicants are advised to consult with the RMS well in advance of any MRP or DCP to clarify the acceptance of the combination package in the relevant MSs.

Harmonisation of the Package leaflet and labelling in the MRP

Applicants are reminded that the harmonisation of the labelling and package leaflet of a medicinal product in the MRP should, in principle, not imply any changes to the content of the Summary of Product Characteristics (SPC).

In case any changes to the SPC are requested with the harmonisation of the package leaflet and labelling, this should be submitted as a type II variation.

Best Practice Guide for the Reference Member State in the Mutual Recognition and Decentralised Procedures

The CMD(h) has agreed an updated BPG for the RMS in the MRP and DCP, mainly to consider the Decentralised procedure and the CMD(h) referral procedure.

Informed consent applications in Mutual Recognition and Decentralised Procedures - Recommendations

The CMD(h) has updated the document 'Informed consent applications in MRP and DCP – Recommendations', mainly to include the new legal references and to consider the possibility to follow the decentralised procedure for informed consent applications.

For information on the dossier requirements for informed consent applications, Applicants are advised to contact the National Competent Authorities.

Applicants are reminded that the CTD format has to be used for the submission of the Module 3 for informed consent applications (when requested).

Extension applications in Mutual Recognition and Decentralised Procedures – Member States Recommendations

The CMD(h) has agreed an updated document 'Extension applications in MRP and DCP – MSs Recommendations', to include the new legal references for the legal basis of the applications and to consider the decentralised procedure and the harmonisation of the labelling and package leaflet.

Best Practice Guide on Break-out sessions for Mutual Recognition and Decentralised Procedures

Further to the publication of the BPG on Break-out Sessions for a one month public consultation with the March 06 CMD(h) press release, the CMD(h) has considered the comments received from Interested Parties and agreed a final updated Best Practice Guide.

In the updated Best Practice Guide it has been clarified that Applicants are allowed to participate in the break-out session to ensure an efficient dialogue with Member States on the outstanding issues.

The CMD(h) would like to thank Interested Parties for the contribution on the revision of the Best Practice Guide on Break-out sessions.

Update of Guideline on dossier requirements for Type IA and IB notifications – Practical information on notifications 7, 8, 14 and 15

Applicants are informed that the Guideline on dossier requirements for Type IA and IB notifications has been updated and is published in Notice to Applicants, Volume 2C – Regulatory Guidelines http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-2/c/var_type_1a1b_guideline_06-2006.pdf

Notifications submitted as of 1 October 2006 have to comply with the Guideline on dossier requirements for Type IA and IB notifications.

Information on MR procedures for new active substances

A mutual recognition procedure for a medicinal product containing human normal immunoglobulin has been finalised on 08.06.2006. Please find below information on the Invented name, INN, MAH, Indication, Procedure number and Day 90.

Invented Name (RMS)	Gamunex 10%
INN	Human normal immunoglobulin
Marketing Authorisation Holder	Bayer Vital GmbH
Indication	Replacement therapy in: *Primary immunodeficiency syndromes such as:* - Congenital agammaglobulinaemia and hypogammaglobulinaemia - common variable immunodeficiency - severe combined immunodeficiency - Wiskott-Aldrich syndrome *Multiple myeloma or chronic lymphocytic leukaemia with severe secondary hypogammaglobulinaemia and recurrent infections,* *Children with congenital AIDS and recurrent severe bacterial infections.* Immunomodulation in: *Idiopathic thrombocytopenic purpura (ITP) in adults and children at high risk of bleeding or to correct the platelet count prior to surgery,*

	Guillain-Barré syndrome, *Kawasaki disease (in conjunction with acetylsalicylic acid therapy).* Allogeneic bone marrow transplantation.
Procedure number	DE/H/0473/001/MR
Day 90	08.06.2006

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 6 and 10 July 2006.

Name of the product in the RMS	Uvadex
Active substance	methoxasalen
Pharmaceutical form	Solution for haemofiltration
Procedure number	UK/H/397/01/E/01
CMS	AT, DE (wave 1) BE, CZ, DK, EL, ES, FI, FR, HU, IT, NL, NO, PL, PT, SE (wave 2)
Legal basis	Article 8.3, Directive 2001/83/EC – Full dossier
Grounds for referral to CMD(h)	One CMS was concerned at the evidence supporting dose and irradiation conditions for photoactivation and characterisation of photoactivated cells in relation to clinical efficacy. CMS were reassured by clarification from the company along with a commitment to completion of further characterisation studies.
Day 60	06.07.06
Outcome	Agreement reached

Name of the product in the RMS	Ciprofloxacin Hikma
Active substance	ciprofloxacin
Pharmaceutical form	Solution for infusion
Procedure number	NL/H/679/01/MR
CMS	AT, DE, IE, IT, UK
Legal basis	Art 10.1, Directive 2001/83/EC - Generic
Grounds for referral to CMD(h)	The procedure highlighted differences in approved indications, posology and contra-indications between national 'brand leader' SPCs. Specifically, the referring CMSs objected to the RMS approved posology for complicated urinary tract infections, UTI (200-400 mg twice daily) and considered that the maximum recommended daily dose (1200mg) should be decreased to 800mg daily.

	In the absence of data in favour or against the different options under discussion a consensus could not be reached on the posology. Consensus was reached on the other grounds of referral, which means that the indications treatment of osteomyelitis and complicated skin infections was accepted by all Member States, like as the contraindication for the concomitant use with tizanidine, and the inclusion of a special warning for use in patients with pre-existent significant renal disorders. All CMD members were of the opinion that the organisms listed in the breakpoints and susceptibility table should be relevant to the indications exclusively. It was decided to add this point to the request for an article 29(4) referral as a remark.
Day 60	06.07.06
Outcome	Referred to CHMP for arbitration

Name of the product in the RMS	Alendronat Hexal
Active substance	alendronic acid
Pharmaceutical form	Tablet
Procedure number	SE/H/517/01/E01
CMS	DE, PL (wave 1) BE, DK, EL (wave 2)
Legal basis	Article 10.1, Directive 2001/83/EC – Generic
Grounds for referral to CMD(h)	The indication "Prophylaxis of glucocorticoid-induced osteoporosis" was initially not accepted by one member state, but was accepted during the CMD(h) referral. The indication "Treatment of osteoporosis in men" is not acceptable to two CMS.
Day 60	10.07.06
Outcome	Referred to CHMP for arbitration

NEW APPLICATIONS

Mutual Recognition Procedure

The CMD(h) noted that **60** new Mutual Recognition Procedures were finalised during the month of June 2006. **6** Mutual Recognition Procedures for new applications were referred to CMD(h) in this period. **1** Mutual Recognition Procedure for a new application was referred to CHMP in this period.

The status as of 30th June 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	253	258	43 N.A.	23	15

44 Mutual Recognition Procedures (regarding **94** products) started in June 2006. The categories of these procedures are as follows:

1 new active substance (classified as a multiple application).

7 known active substances (already authorised in at least one member state).

35 abridged applications, including **13** multiple applications and **1** repeat use.

1 line extension application, which is a repeat use.

The new procedures started in June related to **3** full dossiers, **29** generics, **6** hybrid applications and **6** bibliographic applications.

The procedures consisted of **43** chemical substances and **1** biological blood product.

All of these procedures were prescription-only medicinal products in the reference Member State[1].

1. 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 June 2006.

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
CZ (1)	6
DE (3)	1
DE (3)	26
DE (3)	1
DE (1)	1
DE (2)	6
DE (2)	9
DE (7)	10
DE (1)	10
FI (1)	22
FI (1)	16
FI (1)	1
FI (1)	23
FI (1)	4
FI (3)	8
FI (9)	13
FI (3)	2
FI (3)	3
FI (3)	10
FI (1)	11
NL (2)	2
NL (2)	6
NL (2)	4
NL (2)	1
NL (2)	2
NL (2)	1
NL (2)	4
NL (2)	3
NL (2)	2
NL (2)	1
NL (2)	9
NL (2)	1
NL (1)	1
NL (3)	6
NL (2)	1
SE (1)	1
SE (1)	5

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
SE (2)	22
UK (1)	10
UK (2)	17
UK (1)	1
UK (2)	3
UK (2)	16
UK (2)	1

Decentralised Procedure

The status as of 30th June 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	--	202	--	--	--

44 Decentralised Procedures (regarding **75** products) started in June 2006. The categories of these procedures are as follows:

1 new active substance application (first application in the European Community).

43 abridged applications, including **24** multiple applications.

The new Decentralised procedures started related to **1** full dossier and **43** generic applications.

All of these procedures consisted of chemical substances.

All of these procedures were prescription-only medicinal products in the reference Member State[2].

2. 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 June 2006.

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
CZ (2)	2
DE (2)	1
DE (1)	1
DE (1)	1
DE (1)	1
DE (1)	1
DK (5)	11
DK (3)	17
DK (3)	3
DK (5)	1
FI (3)	9
NL (3)	22
NL (1)	23
NL (3)	3
NL (3)	3
NL (2)	6
NL (2)	14
NL (2)	6

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
NL (2)	1
NL (1)	21
NL (1)	16
NL (1)	1
NL (1)	1
NL (1)	1
NL (1)	19
NL (1)	4
NL (1)	10
NL (1)	9
NL (1)	14
NL (1)	5
NL (1)	5
NL (1)	1
NL (1)	1
NL (1)	1
NL (1)	1
NL (1)	1
NL (1)	1
NL (1)	1
NL (4)	11
UK (1)	17
UK (2)	20
UK (2)	20
UK (1)	1
UK (1)	1

VARIATIONS AND RENEWALS

Mutual Recognition and Decentralised Procedures

The CMD(h) noted that **284** type IA variations, **150** type IB variations and **154** type II variations were finalised during the month of June 2006. **26** renewals were finalised in this period.

The status as of 30th June 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	2119	1102	831	148	--

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/