



### Summary of CMD(h) Activities in 2006

The CMD(h) has agreed to publish on the website, for transparency reasons, a summary of the main activities carried out by the CMD(h) and its sub-groups/working groups in 2006.

### MRP/DCP statistics in 2006

Statistics regarding new applications in the MRP and DCP in 2006 according to the 5-level classification will be published on the website.

The statistics will also include information on the referrals to the CMD(h), addressing the referrals to the CMD(h) per type of procedure (MRP vs DCP), per type of product, per legal basis, per grounds and per outcome.

### List of medicinal products for SPC harmonisation – Outcome of consultation with Interested Parties

The CMD(h) has considered, at the meeting of the sub-group on harmonisation of SPCs, the comments received from Interested Parties on the list of medicinal products for SPC harmonisation, published on the website for an eight week period for public consultation.

The CMD(h) concluded that no change to the initial list was required and noted that responses addressing comments on individual products will be sent to the relevant Interested Parties.

The final list of products for SPC harmonisation will be sent to the EC, as foreseen in Article 30(2) of Directive 2001/83/EC, as amended.

The EC or a Member State, in agreement with the EMEA and taking into account the views of Interested Parties, may refer these products to the CHMP in accordance with Article 30(1) of Directive 2001/83/EC, as amended.

It is envisaged that prior to the start of the Article 30 referral procedures, the respective Marketing Authorisation Holders will be invited for pre-referral meetings.

### Position paper on transparency policy of the CMD(h)

The CMD(h) has agreed to publish a position paper on its current transparency policy, covering CMD(h) press releases, questions and answers, Guidance documents and the MRI-Product Index.

The intention of the CMD(h) is to regularly update this document, when new transparency policies are agreed by the CMD(h).

### Timetables for MRP/DCP applications referred to the CMD(h), in accordance with Article 29(1) of Directive 2001/83/EC, as amended

The CMD(h) has agreed a Guidance document to inform Applicants of the timetables for MRP/DCP applications referred to the CMD(h) for the 60-days referral procedure.

The starting date for the 60 days procedure should, in principle, be no later than 30 days after Day 90 or Day 210 of the Mutual Recognition or Decentralised Procedures, respectively. However, due to the calendars of CMD(h) meetings it might not be possible to comply with the 30-days rule in all situations.

### Questions and Answers on the implementation of the new legislation - Product Information

The CMD(h) has reviewed the currently published Q&As on product information and agreed on two new Q&As:

- 1) To address the need for consultation with target patient groups for medicinal products to be renewed according to the new legislation;
- 2) To address the possibility to justify that a PL complies with the requirements of Article 59 of Directive 2001/83/EC, as amended by referring to results of consultation with target patient groups on other package leaflets.

The revised and new Q&As will be published on the website.

EU Work sharing procedure in the assessment of paediatric data - Best Practice Guide for the preparation of the Public Assessment Report

The CMD(h) has agreed a revised BPG for the preparation of the public assessment report within the framework of the EU work sharing procedure in the assessment of paediatric data, to take account of the comments received from Interested Parties on the draft BPG.

The CMD(h) has also agreed, in line with a comment received from an Interested Party, to publish the template for the Paediatric assessment report.

Best Practice Guide for the exchange of regulatory and administrative information regarding orphan medicinal products between the EMEA and the National Competent Authorities

The CMD(h) has agreed a revised BPG for the exchange of information regarding orphan medicinal products between the EMEA and NCAs, which takes into account Regulation (EC) No 726/2004, that requires, from 20 November 2005, that all marketing authorisations for products designated as orphans are granted by the Community via the centralised procedure. The revised BPG will be published on the website.

Feedback from Applicants on requests for MSs to act as RMS in the MRP & DCP

Applicants are reminded that following acceptance by a MS to act as reference member state for a mutual recognition or decentralised procedure, they should inform the respective MS, in case they have decided to use another MS as RMS for the procedure or about any delay in the submission of the dossier.

Contact e-mail addresses for submission of electronic response documents during MRP & DCP

The CMD(h) has agreed a list to assist Companies identifying a contact e-mail address for submission of electronic response documents for applications for marketing authorisation, variations and renewals in MRP/DCP in each Member State.

The CMD(h) would like to remind Applicants that the names and addresses of the CMD(h) Members should not be used for the submission of response documents.

CMD(h) Contact points/Addresses in MRP/DCP

The CMD(h) has agreed updated lists of the following documents, to include the relevant Contacts, following the accession of Bulgaria and Romania to the EU on 1 January 2007:

- List of CMD(h) Members;
- Contact points for advice on Mutual Recognition and Decentralised Procedures;
- Contact e-mail addresses for submission of translations in the MRP & DCP;
- Contact e-mail addresses for submission of electronic version of the responses to the LoQs for applications referred to the CMD(h).

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 18.12.2006 and 21.12.2006.

<b>Name of the product in the RMS</b>	Ciprofloxacin Mayne 2 mg/ml
<b>Active substance</b>	ciprofloxacin
<b>Pharmaceutical form</b>	Solution for infusion
<b>Procedure number</b>	FI/H/609/01/MR
<b>CMS</b>	AT, BE, DE, DK, IE, IT, LU, NL, NO, SE, UK
<b>Legal basis</b>	Art 10.1, Directive 2001/83/EC - Generic
<b>Grounds for referral to CMD(h)</b>	A serious public health concern was raised by one Member State regarding the following: 1) Should the dosage in the indication "Complicated urinary tract infections" in adults be 100 mg twice daily or 200-400 mg twice daily. 2) Should the maximum daily dose in adults be 800 mg or 1200 mg. 3) Should sections 4.4 and 4.8 of the Summary of Product Characteristics include warnings about ciprofloxacin and QTc prolongation.
<b>Day 60</b>	18.12.06
<b>Outcome</b>	After the written responses by the Applicant and the final discussion in CMD(h), it was concluded that: 1) The dosage in the indication "Complicated urinary tract infections" in adults should be 200-400 mg twice daily.

	<p>2) The maximum daily dose in serious, life threatening and recurrent infections should be 1200 mg.</p> <p>3) The warning about ciprofloxacin and QTc prolongation should be included in sections 4.4 and 4.8 of the Summary of Product Characteristics.</p> <p>All Concerned Member States approved the aforementioned conclusions. Agreement was reached.</p>
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<b>Name of the product in the RMS</b>	Paroxetine 10mg	Paroxetine 20mg	Paroxetine 30mg	Paroxetine 40mg
<b>Active substance</b>	paroxetine			
<b>Pharmaceutical form</b>	Tablet			
<b>Procedure number</b>	NL/H/831/01/MR	NL/H/831/02/MR	NL/H/831/03/MR	NL/H/831/04/MR
<b>CMS</b>	BE, CY, EL, ES, FR, IT, LU, PT	BE, CY, DE, EL, ES, FR, IT, LU, PT	BE, CY, EL, ES, FR, IT, LU, PT	BE, CY, DE, EL, ES, FR, IT, LU, PT
<b>Legal basis</b>	Art 10.1, Directive 2001/83/EC - Generic			
<b>Grounds for referral to CMD(h)</b>	Two CMSs have raised public health objections to the bioequivalence study with the 40 mg strength. The size of biobatch (5.000 units / 40 mg strength) is not in accordance with the Note for Guidance published in 2001, while the biobatch was produced in 2002. The <i>a posteriori</i> justification for deviation to the minimum requirements was not considered acceptable.			
<b>Day 60</b>	18.12.06			
<b>Outcome</b>	<p>It was acknowledged, that there was a deviation of the guidelines. However, according to the RMS, the applicant has adequately argued that the biobatches are representative for the product on full production scale and it is not expected that the bioavailability of the biobatch will differ from a batch of tablets that would have been produced from the full amount of bulk blend.</p> <p>Nevertheless, to finalise the procedure and not to deviate from generally accepted standards, the applicant committed to perform a new BE in line with the European guidelines and to report on the results within 6 months.</p> <p>Agreement reached with a commitment of the applicant.</p>			

<b>Name of the product in the RMS</b>	Finasterid Jacobsen
<b>Active substance</b>	finasteride
<b>Pharmaceutical form</b>	Film coated tablet
<b>Procedure number</b>	SE/H/636/01/MR
<b>CMS</b>	DE, IT, PL, SK, UK
<b>Legal basis</b>	Art 10.1, Directive 2001/83/EC - Generic
<b>Grounds for referral to CMD(h)</b>	A potential serious risk to public health concern was raised by one member state who considered it necessary to include a statement in section 4.6 of the SPC that small amounts of finasteride have been recovered from the semen in subjects receiving finasteride 5 mg/day and since there may be a possibility that a male foetus could be adversely affected if his mother is exposed to such semen, a man treated with finasteride should avoid exposure of his partner to semen, e g by use of a condom, or discontinue finasteride.
<b>Day 60</b>	21.12.06
<b>Outcome</b>	<p>At the CMD(h) meeting the RMS gave a presentation of the procedure. The RMS considered that a condom warning was not scientifically justified, based on two human studies and on a reproductive toxicity study in Rhesus monkeys, and would impose an unnecessary restriction on peoples lives. All member states agreed, except one, who considered the risk to a male foetus not to be negligible and therefore proposed a warning in the SPC.</p> <p>Agreement was reached to refer the scientific question to the Pharmacovigilance Working Party whether exposure to semen from a man treated with finasteride 5 mg/day could risk to cause malformations in a male foetus exposed in utero to such semen. In addition, additional information was included in the SPC sections 5.2 and 5.3 concerning studies</p>

	performed but the condom warning proposed for section 4.6 of the SPC by one member state was not included. The Applicant has committed to follow the outcome of the PhVWP discussion by submitting a Type II variation afterwards if necessary.
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<b>Name of the product in the RMS</b>	Fentanyl-ratiopharm 25, 50, 75, 100 µg/h Matrixpflaster	Fentanyl-ratiopharm 25, 50, 75, 100 µg/h TTS
<b>Active substance</b>	fentanyl	
<b>Pharmaceutical form</b>	Transdermal patch	
<b>Procedure number</b>	DE/H/739/01-04/MR	DE/H/740/01-04/MR
<b>CMS</b>	AT, ES, FR, NL, UK	
<b>Legal basis</b>	Art 10.1, Directive 2001/83/EC - Generic	
<b>Grounds for referral to CMD(h)</b>	<p>The CMD(h) referral was raised by one CMS with regard to a number of concerns regarded as a potential serious risk to public health:</p> <ul style="list-style-type: none"> <li>- Indication needs to be restricted in view of the available data;</li> <li>- a starting dose of 12 µg/h needs to be supported;</li> <li>- Information on the use in a pediatric population is to be added as post approval procedure only;</li> <li>- With regard to the patient population proposed the conversion table morphin to fentanyl is not sufficiently justified;</li> <li>- The Bioequivalence studies submitted in support of the application are not deemed appropriate in design and choice of strength being compared;</li> <li>- For safe use, the SPC and PL need to be amended in relevant sections; e.g. contraindications as concerns concomitant drug treatment, use while breast feeding.</li> </ul>	
<b>Day 60</b>	18.12.06	
<b>Outcome</b>	<p>At CMD(h) and during the final phase of the referral a number of issues could be resolved by proposing amended text in the Product information, respectively agreement by the applicant to extend the application to include use in a paediatric population at a later stage only. Though, no consensus could be achieved with regard to the indication, proper conversion table, bioequivalence, concomitant treatment with other opioids and use during breast-feeding. The matters were referred to CHMP for arbitration.</p>	

<b>Name of the product in the RMS</b>	Opratifi 50mg
<b>Active substance</b>	opipramol
<b>Pharmaceutical form</b>	Coated tablet
<b>Procedure number</b>	DE/H/659/01/MR
<b>CMS</b>	CZ, HU, PL
<b>Legal basis</b>	Art 10 a Dir 2001/83/EC - Bibliographic
<b>Grounds for referral to CMD(h)</b>	<p>CMS questioned that the bibliographic data submitted sufficiently supported the claim of 'well-established use' for this medicinal product leaving certain aspects on the dose finding, efficacy and safety open, thus not allowing to draw a final conclusion on the risk-benefit ratio.</p>
<b>Day 60</b>	21.12.06
<b>Outcome</b>	<p>During the CMD(h) meeting the RMS clarified that opipramol has been extensively used since 1962 resulting in a substantial number of publications in support of the efficacy and safety of the drug substance. However, it was noted that the use, which is based on the history of the active substance, has been limited to some MSs predominantly in Germany and that most of the literature is older one in German language. As no agreement could be reached at the CMD(h) discussion, the applicant decided to withdraw the marketing authorisation and applications in the RMS and CMS.</p>

<b>Name of the product in the RMS</b>	Cabergonicht	Kabergolin IVAX
<b>Active substance</b>	cabergoline	
<b>Pharmaceutical form</b>	Tablet	
<b>Procedure number</b>	SE/H/651/02-04/MR	SE/H/570/02-04/MR
<b>CMS</b>	AT, CZ, DE, DK, IT, NL, PL	AT, BE, CZ, DE, EL, FI, HU, IE, IT, LU, NL, NO, SK
<b>Legal basis</b>	Art 10.1, Directive 2001/83/EC - Generic	
<b>Grounds for referral to CMD(h)</b>	Potential serious risks to public health were raised by two member states who considered that efficacy of cabergoline for the indication Parkinson's disease had not been sufficiently demonstrated, and that cardiac valvulopathy and subsequent cardiac pathology as a class effect of ergot derived dopamine agonists is a serious safety issue which has consequences for the benefit risk of the product.	
<b>Day 60</b>	21.12.06	
<b>Outcome</b>	At the CMD(h) meeting the RMS presented its view and the applicants written explanation was discussed. The objection concerning the efficacy of cabergoline for treatment of Parkinson's disease was resolved during the referral procedure. The issue of cardiac valvulopathy was discussed by the PhVWP at their meeting in December 2006 before the CMD(h) meeting. In a PhVWP report to the CMD(h), the PhVWP concluded that the increased risk of cardiac valvulopathy associated with cabergoline was at least equivalent to pergolide. The SmPC for cabergoline products should therefore be updated in line with the SmPC for pergolide products i.e. restricted second line indication, contraindications and warnings for use and monitoring requirements. The SmPC for Kabergolin IVAX/Cabergonicht was subsequently revised in line with the SmPC for pergolide products, and circulated to CMS. The proposal for a revised SmPC was accepted by all CMS. Agreement was therefore reached.	

## NEW APPLICATIONS

### Mutual Recognition Procedure

The CMD(h) noted that **53** new Mutual Recognition Procedures were finalised during the month of December 2006. **20** Mutual Recognition Procedures for new applications were referred to CMD(h) in this period. **2** Mutual Recognition Procedures for a new application were referred to CHMP in this period.

The status as of 31<sup>st</sup> December 2006 of procedures under Mutual Recognition is as follows:

Year	New applications finalised	New applications in process	Referred to CMD(h)	Agreement reached in the CMD(h)	Withdrawn in the CMD(h)	Arbitrations referred to CHMP
2006	535	219	104 N.A.	53	5	22

**34** Mutual Recognition Procedures (regarding **87** products) started in December 2006. The categories of these procedures are as follows:

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

**1** new active substance for a repeat use application.

**22** abridged applications, including **6** multiple and **3** repeat use applications.

**3** line extension applications.

The new procedures started in December related to **7** full dossiers, **24** generics, **2** hybrid applications and **1** bibliographic application.

These procedures consisted of **33** chemical and **1** biological other substances.

**31** of these procedures related prescription-only medicinal products and **3** procedures related to non-prescription medicinal products in the reference Member State<sup>1</sup>.

Number of countries involved in the new applications in Mutual Recognition procedure started in December 2006.

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
CZ (3)	7
CZ (1)	6
DE (1)	2
DE (3)	5
DE (3)	1
DE (1)	2
ES (1)	16
ES (1)	3
FR (1)	1
HU (5)	5
HU (3)	9
NL (3)	11
NL (3)	6
NL (2)	4
NL (1)	26
NL (3)	4
NL (3)	1
NL (2)	1
NL (3)	1
NL (2)	1
NL (2)	1
NL (2)	1
PT (2)	6
PT (1)	13
SE (2)	12
SE (1)	8
SE (2)	5
SE (7)	7
SE (6)	5
SE (7)	2
SE (7)	1
SE (1)	13
UK (1)	8

### **Decentralised Procedure**

The CMD(h) noted that there were **38** new Decentralised Procedure finalised during the month of December 2006. There were **no** Decentralised Procedures referred to the CMD(h) in this period.

The status as of 31<sup>st</sup> December 2006 of procedures under Decentralised Procedure is as follows:

Year	New applications finalised	New applications withdrawn	New applications in process	Referred to CMD(h)	Agreement reached in the CMD(h)	Arbitrations referred to CHMP
2006	57	4	402	1	--	--

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<sup>1</sup> 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.

**38** Decentralised Procedures (regarding **96** products) started in December 2006. The categories of these procedures are as follows:

**33** abridged applications, including **14** multiple applications.

**3** known active substance applications.

**2** Line Extension applications.

The new Decentralised procedures started related to **23** generic, **11** hybrid, **2** full dossier, and **2** bibliographic applications.

**All** of these procedures consisted of chemical substance applications.

**36** of these procedures related to prescription-only medicinal products and **2** procedures related to non-prescription medicinal products in the reference Member State<sup>2</sup>.

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

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
DE (4)	19
DE (4)	3
DE (2)	1
DE (4)	2
DE (4)	1
DE (4)	2
DE (3)	1
DE (1)	9
DE (1)	12
DE (3)	18
DE (1)	1
DE (1)	4
DE (1)	2
DE (4)	4
DE (3)	4
DE (3)	1
DE (1)	1
DE (2)	8
DK (2)	13
DK (2)	5
DK (2)	3
DK (1)	14
DK (1)	9
DK (1)	4
DK (3)	10
DK (6)	8
DK (6)	1
DK (3)	1
DK (6)	1
NL (1)	24
NL (4)	12
SE (1)	8
SE (2)	2
SE (1)	2
UK (1)	1
UK (2)	1
UK (4)	13
UK (1)	1

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<sup>2</sup> 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.

## VARIATIONS AND RENEWALS

### Mutual Recognition and Decentralised Procedures

The CMD(h) noted that **406** type IA variations, **176** type IB variations and **207** type II variations were finalised during the month of December 2006. **29** renewals were finalised in this period.

The status as of 31<sup>st</sup> December 2006 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	4524	2209	1916	354	--

The global status since 1<sup>st</sup> January 1995 is as follows (further detailed statistics can be found at the CMD(h) website):

YEARS	MRP NEW APPLICATIONS FINALISED	DCP NEW APPLICATIONS FINALISED	TYPE I VARIATIONS FINALISED	TYPE IA VARIATIONS FINALISED	TYPE IB VARIATIONS FINALISED	TYPE II VARIATIONS FINALISED	MRP/DCP REFERRED TO CMD(H)	ARBITRATIONS REFERRED TO CHMP
1995	10		16			17		1 N.A.
1996	84		49			73		1 N.A. and 1 variation
1997	146		101			163		1 N.A. and 1 variation
1998	182		339			222		1 N.A. and 4 variations
1999	228		671			301		2 N.A. and 2 variations
2000	306		1007			320		3 N.A. and 2 variations
2001	443		1487			474		1 N.A. and 3 variations
2002	420		2104			527		2 N.A. and 7 variations
2003	529		2473	230	94	754		5 N.A. and 3 variations
2004	760		43	3240	1998	1083		9 N.A.
2005	954		N/A	4044	1944	1509	10 N.A.	2 N.A. and 7 variations
2006	535	57	N/A	4524	2209	1916	105 N.A.	22 N.A.
1995-2006	4597	57	8290	12038	6245	7359	115 N.A.	50 N.A. and 30 variations

**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/>