

**CO-ORDINATION GROUP FOR MUTUAL RECOGNITION AND  
DECENTRALISED PROCEDURES – HUMAN (CMD(h))**

**SUMMARY OF ACTIVITIES IN 2007**

*January 2008*

**Web Sites:**

CMD(h)

<http://www.hma.eu/cmdh.html>

European product index

<http://www.hma.eu/mri.html>

**INTRODUCTION**

2007 was the second full year of operation of the Coordination Group for Mutual Recognition and Decentralised Procedures - Human, CMD(h), set up under the revised EU pharmaceutical legislation for the examination of any question relating to marketing authorisation of a medicinal product in two or more Member States, in accordance with the mutual recognition procedure (MRP) or the new decentralised procedure (DCP).

The CMD(h) is composed of one representative per Member State, including Norway, Iceland and Liechtenstein and an observer from the European Commission. The list of the CMD(h) Members, together with the respective professional qualifications, has been published on the Heads of Medicines Agencies website. The CMD(h) cooperates closely with the Heads of Medicines Agencies for human medicines.

A list of new and revised CMD(h) documents and questions & answers developed by the CMD(h) in 2007 is included as **Annex** to this document.

**GENERAL INFORMATION**

The CMD(h) met eleven times in 2007. The meetings were chaired by Mrs. Truus Janse-de Hoog, Chairperson of the CMD(h). The Vice-Chairpersons during the German and Portuguese presidencies of the Council of the European Union were, respectively, Mr. Peter Bachmann and Mrs. Marta Marcelino. Press releases with statistics, adopted documents and information on the applications referred to the CMD(h) were published monthly on the Heads of Medicines Agencies website. Two informal CMD(h) meetings were held in 2007, in Bonn, Germany and in Lisbon, Portugal.

The majority of the CMD(h) meetings held in 2007 (8/11) had a duration of 3 days, whilst the remaining meetings had a duration of 2 days, which reflects the extended scope of activities of the CMD(h).

The EMEA supported the chairperson, the CMD(h) and respective sub-groups in their activities. The CMD(h) secretariat was also in charge of answering the questions received at the EMEA in relation to the MRP and DCP, in liaison with the CMD(h) Chairperson.

The main activities carried out by the CMD(h) in the areas identified as priorities for 2007 in the CMD(h) work plan are summarised below:

### **Improvement and evaluation of existing procedures**

Further to the work carried out by the Working Group set up to evaluate the Decentralised Procedure and to consider the need for revision of the respective Standard Operating Procedure, the CMD(h) has agreed a revised Decentralised Procedure SOP, which has been subject to public consultation and presented to Interested Parties by the CMD(h).

The CMD(h) has also agreed a revised Best Practice Guide, to address both the mutual recognition and decentralised procedures and published the flow charts for the mutual recognition and decentralised procedures as separate documents on the website.

With a view to improving existing procedures, the CMD(h) has set up a Working group on Validation issues/National requirements, to analyse validation issues and national requirements within the framework of the MRP and DCP.

This Working group has reconsidered all national requirements, which resulted in a reduction of the additional data requested for new applications in the MRP and DCP. This information has been published on the CMD(h) website.

The CMD(h) has also endorsed a document prepared by the Working Group, aimed at providing guidance on common grounds for invalidation/delaying of validation and a recommendation and template for the cover letter for new applications in the MRP/DCP.

### **Referrals to CMD(h)**

The CMD(h) has continued to devote in 2007 considerable time and resources to trying to reach agreement for MRP and DCP applications, in the situations where a Member State cannot approve the assessment report, the summary of product characteristics (SPC), the labelling and the package leaflet (PL) on the grounds of potential serious risk to public health, in accordance with Article 29(1) of Directive 2001/83/EC, as amended.

The number of applications referred to the CMD(h) in 2007 (69) decreased by 34% compared to the number of applications referred to the CMD(h) in 2006 (105).

Of the Mutual Recognition Procedures finalised in 2007 (441), 10% (44) were referred to the CMD(h). This represents a decrease of 9% in the percentage of finalised MRP referred to CMD(h) in comparison with 2006.

Of the Decentralised Procedures finalised in 2007 with a positive outcome (386), 6.5% (25) were referred to the CMD(h) in this time period.

The lower percentage of DCP applications referred to the CMD(h) in comparison with MRP applications referred to the CMD(h) might be due to an early involvement of CMS(s) in the DCP applications and the possibility for the Applicant to address the issues raised by the RMS and CMS(s) in the clock-stop.

The number of oral explanations from Applicants with the CMD(h) in 2007 (21) has been maintained in comparison with 2006.

Of the 85 referral procedures finalised by the CMD(h) in 2007 (which includes 35 applications referred to CMD(h) in 2006), the CMD(h) was able to reach agreement for 74% of the procedures (63) and referred to the CHMP 26% of the procedures (22).

6 applications were withdrawn in the RMS and all CMSs within the CMD(h) referral procedure in 2007.

Even though the number of applications referred to CHMP in 2007 has not changed in comparison to 2006, its percentage has decreased slightly from 29% to 26%.

The 22 applications referred to the CHMP for arbitration include 7 multiple applications and thus correspond to 15 different applications for 14 different active substances referred to the CHMP in 2007.

7 of the applications referred to the CHMP were for full dossiers, 7 for generic medicinal products and 1 for a well-established use medicinal product.

Of the 15 different applications referred to the CHMP in 2007, the CHMP concluded 7 referrals in 2007, 4 of which with a positive opinion and 3 with a negative opinion.

The CMD(h) has agreed a revised SOP to clarify certain aspects of the procedure, e.g. referral to CMD(h) if the RMS is negative but one or more CMSs are positive, possibility to close the procedure earlier than day 60, etc and two new Q&As.

The CMD(h) has also 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 and has published statistical information on the applications referred /concluded by the CMD(h) in the first semester of 2007, for transparency.

### **Readability tests – Better guidance for industry and harmonisation in assessment of user tests**

The CMD(h) has agreed a document to support extending use of test results to related products, aimed at providing guidance on when bridging will be accepted by Competent Authorities and the type of evidence which will need to be provided, in the situations where a user test or evidence of compliance with Article 59(3) is required.

The CMD(h) has also reviewed the Q&As on product information and agreed two new Q&As to address the need for user consultation for medicinal products to be renewed according to the new legislation and to refer to the results of user tests on other package leaflets.

The CMD(h) endorsed, in principle, a proposal from EGA for a work-sharing initiative for patient consultation across Europe and set up a Working Group to take this initiative forward and to have contacts with Interested Parties. This Working Group held a meeting with EGA in the margins of the June CMD(h) meeting.

The CMD(h) encouraged Industry to participate in this industry led work-sharing initiative.

The EMEA and CMD(h) organised the 2<sup>nd</sup> workshop on user consultation in the context of readability testing of package leaflet for medicines. The workshop “User testing and how to review the data” was a follow up from the one held in 2006 and was aimed at reviewing and bringing together experience and expertise of European regulators with readability testing of the package leaflet by target patient groups.

### **Strengthening cooperation with PhVWP**

The CMD(h) and PhVWP have agreed a document on interaction between PhVWP and CMD(h), to ensure timely and effective exchange of information between the CMD(h) and the PhVWP regarding the outcome of product related scientific and regulatory issues, as outlined in both groups’ mandates.

The CMD(h) and the PhVWP have agreed a guidance document aimed at providing specific guidance on the submission of data related to the pharmacovigilance system and risk management plans and how these are assessed during MRP and DCP.

The CMD(h) and the PhVWP held a meeting with representatives of Interested Parties to discuss co-ordinated Europe wide implementation of core safety information for antidepressants.

### **Transparency – Update of information and better structure of information on the CMD(h) website**

A new CMD(h) website was launched on 1<sup>st</sup> March 2007 <http://www.hma.eu/cmdh.html>. The CMD(h) will continue to work on the improvement of the new website, to ensure a better structure and easy access to the information published.

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

### **Implementation of the Paediatric Regulation**

The CMD(h) and the EMEA have agreed on a procedural guidance, to facilitate the submission of information requested by the Paediatric Regulation and on a Q&A document to address the submission of paediatric studies according to Articles 45 & 46 of the Regulation No 1901/2006, as amended.

A list of addresses to be used for the submission of paediatric information for each Competent Authority has been published on the CMD(h) website.

The CMD(h) and the EMEA held two meetings with Interested Parties in 2007, to discuss, respectively, a proposal for a question and answers document to address the submission of Paediatric studies according to Articles 45 and 46 of the Paediatric Regulation and the procedural guidance developed to facilitate the submission of information pursuant to the Paediatric Regulation.

With regard to the on-going Work-sharing procedure in the assessment of paediatric data, the CMD(h) published the list of active substances in the Work sharing procedure and published also paediatric public assessment reports, for the work-sharing procedures finalised.

The CMD(h) has also revised the Best Practice Guide EU Work Sharing procedure in the assessment of paediatric data, with information on the finalisation of the work sharing procedure and to address the implementation of the outcome of the EU work sharing procedure to generics.

### **INTERACTION WITH EMEA SCIENTIFIC COMMITTEES AND WORKING PARTIES**

The CMD(h) has liaised regularly with EMEA Scientific Committees and Working Parties and sent requests for scientific opinions and/or for interpretation of scientific guidelines or guidance documents, mainly arising from discussions for applications referred to the CMD(h) in case of disagreement between the involved MSs in a MRP or DCP application.

The CMD(h) welcomed on this regard the publication of the draft Guideline on the requirements for clinical documentation for orally inhaled products (OIP) including the requirements for demonstration of therapeutic equivalence between two inhaled products for use in the treatment of asthma and chronic obstructive pulmonary disease (COPD), CPMP/EWP/4151/00 rev.1 on the EMEA website for a 6 months public consultation.

The CMD(h) was also involved in agreeing on the Reflection paper on advice to Applicants/Sponsors/CROs of Bioequivalence studies, adopted by the GCP Inspectors Working Group and released for a 6 months public consultation.

The CMD(h) welcomed also the publication on the EMEA website for a 6 months public consultation of the document ‘Assessment of the quality of medicinal products containing existing/known active

substances' aimed at clarifying the assessment strategy that should be followed by Competent Authorities when assessing quality of products containing existing/known active substances (e.g. generics), including guidance for Applicants.

CMD(h) Observers have continued to participate in the EMEA/Human Scientific Committees WP with Patients' and Consumers' Organisations and in the EMEA/CHMP Working Group with Health Care Professionals' Organisations.

## **INTERACTION WITH INTERESTED PARTIES**

The CMD(h) has liaised regularly with representatives of Interested Parties, through public consultation of CMD(h) documents and discussion of questions raised by Interested Parties.

The CMD(h) held a meeting with representatives of Interested Parties in 2007, mainly to discuss the revised Decentralised Procedure SOP, a report from the activities of the Working Group on Validation issues/National requirements, experience with consultation with target patient groups and recommendations for bridging, experience with national implementation following MRP/DCP and Member States' resources in the Mutual recognition and Decentralised procedures.

The CMD(h) has also held meetings with representatives of Interested Parties through its Sub-groups/Working-groups, e.g. Sub-group on Paediatric Regulation.

The CMD(h) has collaborated with EGA in the organisation of the 1<sup>st</sup> Workshop on Bioequivalence – Study design, Working to GCP and Interpreting the Guidelines, held in Lisbon, 23<sup>rd</sup> – 24<sup>th</sup> October 2007.

The CMD(h) has also finalised the Q&A document which addresses the procedure and criteria for acceptance of requests for advice submitted by Companies or EEA Member States.

## **CMD(h) SUB-GROUPS/WORKING GROUPS**

A number of CMD(h) subgroups meetings were held during 2007.

The Communication tracking system (CTS) Working Group (Hum + Vet), which is in charge of the MRP and DCP tracking system, met 6 times in 2007.

The CTS WG was also involved in the drafting of the specifications for updating CTS in line with new procedures following implementation of the Paediatric Regulation.

The CMD(h) Sub-group on harmonisation of SPCs, set up in view of the role of the Co-ordination group to lay down a list of products for which a harmonised SPC should be drawn up, met 5 times in 2007.

The Sub-group has agreed a new list of products for SPC harmonisation, in accordance with Article 30(2) of Directive 2001/83/EC, as amended, which was published on the CMD(h) website for an eight week period for public consultation.

The Joint CMD(h)/Pharmacovigilance Working Party Working Group, set up to discuss issues of common interest to the CMD(h) and PhVWP, e.g. PSUR work sharing project, evaluation of EU Risk management plans and Pharmacovigilance systems, met 3 times in 2007.

The ad hoc WG on PSUR synchronisation and work sharing met 8 times in 2007, one of which with participation from Industry.

A Guidance document for marketing authorisation holders on submission under the PSUR synchronisation scheme and revised document and Q&A on EU synchronisation of PSUR submission schemes of medicinal products authorised through national, mutual recognition and decentralised procedure were published on the Heads of Medicines Agencies website.

An updated list of EU Harmonised Birth Dates and related Data Lock Points, including allocated P-RMSs has also been published on the Heads of Medicines Agencies website.

### **MRP/DCP STATISTICS**

The number of new applications submitted in 2007 via the MRP and DCP (1429) has increased by approximately 37% compared to 2006.

The number of new applications submitted in 2007 via the MRP has decreased by 34% compared to 2006. However, the number of new applications submitted in 2007 via the DCP has increased by 130%

The number of applications finalised via the MRP and DCP (827) in 2007 has increased by 40% compared to 2006 (592). This might be explained by the fact that most of the decentralised procedure applications submitted in 2006 were finalised in 2007, due to a timetable of 210 days as opposed to the 90 days of the MRP. The number of applications finalised via the MRP in 2007 has decreased slightly (approx. 16%), which might be due to the increase use of the Decentralised procedure.

The number of variations submitted and finalised in 2007 has increased by 15% and 17%, respectively, compared to 2006.

Statistical information on applications under the MRP and the DCP was provided by the EMEA and presented in the monthly CMD(h) press releases.

	<b>Total started in 2007*</b>	<b>Under evaluation in 2007*</b>	<b>Ended positively in 2007*</b>	<b>Referrals to CMD(h) in 2007</b>	<b>Referrals to CHMP in 2007</b>
New applications MRP	396	159	441	44	15
New applications DCP	1033	1038	386	25	7
Type-IA variations	5864	134	5640	N/A	N/A
Type-IB variations	2355	236	2298	N/A	2
Type-II variations	2461	1130	2167	N/A	6

*\*The numbers include multiple procedures as stated at 31 December 2007.*

## ANNEX

### NEW DOCUMENTS

#### **Document**

#### **Adoption**

#### **About CMD(h)**

##### **CMD(h) Work plan**

CMD(h) Work plan for 2007

February, 2007

##### **Transparency Measures**

Position paper on transparency policy of the CMD(h)

February, 2007

#### **CMD(h) Subgroups**

##### **CMD(h) Subgroup on Harmonisation of SPCs**

Draft 2007 List of Products for SPC Harmonisation (*For consultation until 2<sup>nd</sup> January 2008*)

November, 2007

#### **Procedural Guidance**

##### **General Information**

CMD(h) guidance for MAHs on the pharmacovigilance system and risk management plan in the MPR & DCP

November, 2007

##### **Application for Marketing Authorisation**

Introduction to published papers on validation

July, 2007

Additional data requested for new applications in the MRP/DCP

July, 2007

Common grounds for invalidation/delaying validation

July, 2007

Document	Adoption
MS recommendation on the Cover Letter for new applications submitted through MRP/DCP	July, 2007
[MRP] Flow chart of the Mutual Recognition Procedure	May, 2007
<b>Art. 61(3) Procedure</b>	
Flow-chart for the Article 61(3) procedure	July, 2007
<b>Consultation with target patient groups</b>	
Consultation with target patient groups – Meeting the requirements of Article 59(3) without the need for a full test recommendations for bridging	October, 2007
<b><u>CMD(h) Referrals</u></b>	
Overview of timetables 2007 – CMD(h) 60 day procedures for MPR/DCP Applications	January, 2007 <i>(Updated in September 2007)</i>
Overview of timetables 2008 – CMD(h) 60 day procedures for MPR/DCP Applications	September, 2007
<b><u>Paediatric Data Assessment</u></b>	
<b>Responsibilities from Paediatric Regulation</b>	
Procedural guidance concerning submission of information about medicinal products as requested by the Paediatric	September, 2007
Template for submission of information on paediatric studies from MAH to NCAs – line listing	September, 2007
Annex I: MAH Declaration	September, 2007 <i>(Updated in October 2007)</i>
Annex II: Listing of products already authorised for Paediatric Use	September, 2007
Sample for line listing of paediatric studies	September, 2007

**Document****Adoption****Worksharing project**

List of active substances in the EU Worksharing procedure in the assessment of paediatric data

April, 2007

**Templates****AR**

[MRP] Template CMS Comments in MRP

May, 2007

**Application for MA**

Cover letter for Submission of Application Dossier(s)

November, 2007

## NEW QUESTIONS & ANSWERS

### Document

### Adoption

### Paediatric Data Assessment

#### Responsibilities from Paediatric Regulation

**Q&A** – Submission of Paediatric studies according to Art. 45 &46 of the Regulation of the European Parliament and of the Council (EC) No 1901/2006, as amended (Paediatric Regulation) and other Paediatric information

October, 2007  
*(Updated in December 2007)*

### FAQs

#### [General FAQs]

#### New Application

Is it possible to use as reference medicinal product for the purpose of the data exclusivity period a medicinal product authorised in a Member State prior to its accession to the EU, and thus not in accordance with the Community acquis, knowing that upon accession to the EU the medicinal product has been brought in accordance with the Community acquis?

March, 2007

#### [General FAQs]

#### Miscellaneous

Which MRP-number should be assigned to follow-up submissions and commitments?

July, 2007

#### [General FAQs]

#### Miscellaneous

Is it possible in a MRP/DCP to register a manufacturing site or batch release site for a limited number of Member States (i.e. not all MSs included in the procedure)?

September, 2007

#### [General FAQs]

#### Miscellaneous

How should a change in the name of a medicinal product between finalisation of a MRP or DCP and prior to granting a national marketing authorisation, be handled?

November, 2007

#### [New legislation]

#### Q&A 16

Is it possible to submit text proposals for the SPC, PL and labelling for applications for variations and renewals to marketing authorisation granted via the mutual recognition or the decentralised procedure in English only?

October, 2007

Document		Adoption
[New legislation]	<u>Q&amp;A 18</u> Will consultation with target patient groups be required for medicinal products for which the marketing authorisation has to be renewed according to the new legislation?	January, 2007
[New legislation]	<u>Q&amp;A 22a</u> What should be the procedure for the harmonisation of the labelling and package leaflet?	January, 2007
[New legislation]	<u>Q&amp;A 19</u> Is it possible to justify that a package leaflet complies with the requirement of Article 59 by referring to results of consultation with target patient groups on other package leaflets?	January 2007
[Advice from CMD(h)]	Q&As on Requests for advice from CMD(h)	May, 2007
[Referrals to CMD(h)]	<u>Q&amp;A 2a</u> If the RMS is negative but one or more CMSs are positive will the application be referred to CMD(h)?	June, 2007
[Referrals to CMD(h)]	<u>Q&amp;A 2b</u> If there is consensus among Member States concerned by the end of a CMD(h) referral procedure that the DCP application is not approvable, should the application be referred to CHMP?	October, 2007
[Renewals]	Application for the renewal of a marketing authorisation granted via the MRP or DCP prior to the granting of the marketing authorisation in all involved MS(s)	October, 2007
[Generics]	Q&As on the submission of a description of pharmacovigilance system and EU risk management plans for generic and hybrid applications	May, 2007
[Generics]	Possibility to refer to clinical studies performed by a company different from the company holding the initial marketing authorisation	July, 2007
[Generics]	Legal basis for generic applications where the reference medicinal product in the CMS(s) has fewer indication(s) than in the RMS	September, 2007
[Biologicals]	Guidance for applicant on biologicals	June, 2007 <i>(Updated in October 2007)</i>
[Homeopathics]	Homeopathic medicinal products disagreement in procedures referral to CMD(h)	June, 2007

## REVISED DOCUMENTS

<b>Document</b>	<b>Adoption</b>	<b>Last Update</b>
<b><u>Procedural Guidance</u></b>		
<b>General Information</b>		
Best practice guide for the exchange of regulatory and administrative information regarding orphan medicinal products between the EMEA and the national competent authorities	October, 2003	February, 2007
<b>Application for Marketing Authorisation</b>		
Best Practice Guide for Decentralised and Mutual Recognition Procedures	October, 1996	May, 2007
Recommendations on Multiple applications in Mutual Recognition Procedures	May, 1999	June, 2007
[DCP] Decentralised procedure - Member States' SOP	October, 2005	November, 2007
[DCP] Guidance on submission dates for Applicants of the Decentralised Procedure	October, 2005	October, 2007
[MRP] Guidance on submission dates for Applicants of the Mutual Recognition Procedure	October, 2002	September, 2007
<b>Art. 61(3) Procedure</b>		
CMD(h) Standard Operating Procedure - Procedure for Article 61(3) changes to patient information and the notification for product information amendment under Article 61(3) (not accompanying a variation change)	October, 2005	July, 2007
<b><u>CMD(h) Referrals</u></b>		
CMD(h) Standard Operating Procedure Disagreement in procedures – Referral to CMD(h) (incl. <i>annex</i> Guidance on OE to CMD(h))	October, 2005	December, 2007

<b>Document</b>	<b>Adoption</b>	<b>Last Update</b>
<b><u>Paediatric Data Assessment</u></b>		
<b>Worksharing project</b>		
Best Practice Guide for the preparation of the Public Assessment Report in the EU Work sharing project for the assessment of paediatric data	June, 2006	March, 2007
Best Practice Guide EU work sharing project in the assessment of paediatric data	July, 2005	March, 2007
<b><u>Templates</u></b>		
<b>AR</b>		
[DCP] Templates AR/Comments	February, 2006	May, 2007
[MRP] Template on Assessment Report MRP CTD format	January, 2003	May, 2007
[Variations] Type II PVAR/FVAR		December, 2007
<b>MRP/DCP Referral to CMD(h)</b>		
RMS Notification of referral to CMD(h)	February, 2006	June, 2007
D90/D210 CMS Request for referral to CMD(h)	February, 2006	May, 2007