

Report from the CMD(h) meeting held on 17th, 18th and 19th September 2007

CMD(h)/EMA Sub-Group on Paediatric Regulation

The CMD(h) and the EMA have agreed on a procedural guidance to facilitate the submission of information requested by the Paediatric Regulation.

Each Marketing Authorisation Holder is requested to fill in a template agreed by the CMD(h) and the EMA for all their authorised medicinal products and to submit it together with a standard declaration, which addresses paediatric studies already submitted to Competent Authorities.

The templates and the respective declarations should be sent to each Competent Authority(ies) where the medicinal products are authorised in electronic format only and copied to the EMA (paedstudies@ema.europa.eu). A list of the addresses to be used for each Competent Authority will be published on the website.

The CMD(h) and the EMA have agreed to invite Interested Parties for a meeting in the margins of the October 2007 CMD(h) meeting, to discuss the procedural guidance developed.

EU Work sharing Project – Assessment of paediatric data

The Paediatric Public Assessment Report for Ciproxin, ciprofloxacin will be made available on the CMD(h) website, under the heading 'Paediatric data assessment'

Referrals to CMD(h) in the first semester of 2007 – Statistical information

The CMD(h) has agreed to publish statistical information on the applications referred/concluded by the CMD(h) in the first semester of 2007, addressing referrals to CMD(h) per type of procedure (MRP vs DCP), per type of product, per legal basis, per grounds and per outcome.

Legal basis for generic applications where the reference medicinal product in the CMS(s) has fewer indications than in the RMS

The CMD(h) has agreed a Q&A to address the legal basis for generic applications where the reference medicinal product in the CMS(s) has fewer indications than in the RMS.

It has been agreed by the CMD(h) and confirmed by the EC that in the situations where the summary of product characteristics for the reference medicinal product is not harmonised between the RMS and the CMSs and the generic applicant is not applying for more indications than those authorised for the reference medicinal product in the RMS, the legal basis for the application should be Article 10(1) of Directive 2001/83/EC, as amended in all involved MSs (RMS and CMS(s)).

Meeting with EGA on Work-sharing for patient consultation

The CMD(h) has agreed to publish, for transparency reasons, the minutes from the meeting held on 19 June 2007, to discuss EGA proposal for a work-sharing initiative for patient consultation across Europe.

Manufacturing sites restricted to particular Member States in the Mutual Recognition Procedure (MRP) and Decentralised Procedure (DCP)

The CMD(h) has agreed a Q&A to clarify that manufacturing sites and batch release sites approved via the MRP/DCP are considered approved for all MSs included in the procedure and that it is not possible to delete manufacturing sites on a national basis, but a MRP variation procedure has to be followed.

Please note that it is not necessary to specify in the application form which site applies to which MS.

Guidance on submission dates for Applicants of the Mutual Recognition Procedure (MRP)

The CMD(h) has adopted an updated Guidance on submission dates for Applicants of the Mutual Recognition Procedure, in order to facilitate planning of submission dates for new applications in the MRP until November 2009.

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 adopted an updated guidance document with the timetables for MRP/DCP applications referred to the CMD(h) for the 60-days referral procedure for 2008.

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 27.07.2007, 09.08.2007 and 20.08.2007.

Name of the product in the RMS	Ceftazidim "Stragen"
Active substance	ceftazidime
Pharmaceutical form	Powder for solution for injection
Procedure number	DK/H/0925/001-006/DC
CMS	CZ, DE, FI, IE, NO, PL, SE, UK
Legal basis	Art 10.1 Dir 2001/83/EC - Generic
Grounds for referral to CMD(h)	Referral was raised by a CMS on grounds of the indication nosocomial pneumonia which was not approved for the brand leader in the CMS. Also missing response on some SPC concerns was referred.
Day 60	27.07.2007
Outcome	After having reviewed the supplementary documentation submitted by the company and after discussions with RMS the indication could be approved by CMS. Also the revisions to the SPC and PL were approved. At the CMD(h) meeting all MSs involved in the procedure could agree on the SPC and PL.

Name of the product in the RMS	Azyter 15mg/g
Active substance	azythromycin
Pharmaceutical form	Eye drops, solution
Procedure number	NL/H/0855/01/DC
CMS	AT, BE, DE, ES, FR, IT, LU, PL, PT
Legal basis	Art 8.3(i) Dir 2001/83/EC - Full dossier
Grounds for referral to CMD(h)	There is a concern with regard to indication 'purulent bacterial conjunctivitis' and the use in children <2 years of age in this indication.
Day 60	27.07.2007
Outcome	At the CMD(h) meeting the RMS presented its view and the applicant's written response were discussed. The applicant made use of an oral hearing. Following the discussion, the SPC was adjusted to limit the use of Azyter for the indication 'purulent bacterial conjunctivitis' to children >2 years of age. Agreement reached.

Name of the product in the RMS	Oracea
Active substance	doxycycline monohydrate
Pharmaceutical form	Capsule
Procedure number	UK/H/0892/001/DC
CMS	AT, DE, FI, IE, IT, LU, NL, SE
Legal basis	Art 8.3(i) Dir 2001/83/EC - Full dossier
Grounds for referral to CMD(h)	The procedure was referred to CMD(h) because potential serious risks to public health concerns were raised in relation to the overall risk:benefit for Oracea, the insufficient evidence of safety and efficacy in the proposed indication, including the lack of a comparison of Oracea with an active treatment, and the potential for bacterial resistance. Further evidence associated with the mechanism and

	expression of effect was considered necessary.
Day 60	27.07.2007
Outcome	<p>At the CMD(h) meeting the RMS and the applicant presented their view on the product. During CMD(h) meeting it was discussed whether the available data indicated that the overall risk:benefit for Oracea had been sufficiently demonstrated; there was also a discussion on the insufficient evidence of safety and efficacy in the proposed indication, including the lack of a comparison of Oracea with an active treatment and that the specific issue of the potential induction of bacterial resistance by Oracea in its intended use had not been adequately addressed.</p> <p>There was a different opinion between MSs on whether the submitted data were sufficient to conclude that the product was approvable. The RMS and other involved Member States shared the position that the application is not approvable. As consensus was not reached a referral to CHMP in accordance with Article 29(4) has been made.</p>

Name of the product in the RMS	Trandolapril
Active substance	trandolapril
Pharmaceutical form	Capsule
Procedure number	UK/H/0916/001-004/DC
CMS	CZ, DK, HU, IE, IT, MT, NL, PL, PT, SI, SK
Legal basis	Art 10.1 Dir 2001/83/EC - Generic
Grounds for referral to CMD(h)	Potential serious public health concerns were raised on whether bioequivalence was demonstrated between the applicant's products and the reference products approved in the EEA.
Day 60	27.07.2007
Outcome	<p>After the written responses by the Applicant and the final discussion in CMD(h), it was concluded that, in this particular case, bioequivalence between test and reference products can be concluded.</p> <p>Agreement was reached between all concerned Member States that the applications should be approved. CMD(h) noted that further clarification of the bioequivalence guidance in relation to parent and metabolite pharmacokinetic data would be helpful.</p>

Name of the product in the RMS	Kardilon 4mg
Active substance	doxazosin
Pharmaceutical form	Tablet
Procedure number	UK/H/0912/001/DC
CMS	IE
Legal basis	Art 10.1 Dir 2001/83/EC - Generic
Grounds for referral to CMD(h)	A potential serious public health concern was raised in relation to whether the in vivo performance of the applicant's product and that of the reference product were equivalent in the presence of food.
Day 60	09.08.2007
Outcome	<p>CMD(h) considered that the available data indicated that the in vivo performance of test and reference product might differ when taken in the fed state. CMD(h) considered that in the absence of a suitably designed study, amendment of the SPC of the applicant's product such that it differed from the reference product in respect of its administration instructions in relation to food, would not be acceptable. Consensus was reached between the involved Member States that the product should not be approved.</p>

Name of the product in the RMS	Oxycodolor	Oxycodon-ratiopharm
Active substance	oxycodone	
Pharmaceutical form	Prolonged release tablet	
Procedure number	DE/H/0789/001-003/DC	DE/H/0790/001-003/DC
CMS	CZ, DK, ES, FI, IE, NL, NO, SE, SI, SK, UK	CZ, DK, FI, NL, NO, SE, SK, UK
Legal basis	Art 10.1 Dir 2001/83/EC - Generic	
Grounds for referral to CMD(h)	<p>Oxycodone hydrochloride prolonged release tablets are a multi-particulate oxycodone-containing controlled release system with a break down of few minutes in the stomach and release of retarding pellets.</p> <p>A potential serious risk to public health was raised by one Member state, based on the fact that high percentage alcohol is influencing the prolonged release properties of the respective tablets.</p> <p>The CMS was asking for confirmation, based on a scientific rationale, that simultaneous intake of the respective oxycodone prolonged release tablets along with high percentage alcohol, although not in accordance with the instructions of the SPC, is without relevance regarding clinical safety of the product.</p>	
Day 60	20.08.2007	
Outcome	<p>The influence of ethanol on the dissolution profile of the controlled release formulation and potential dose dumping had been discussed extensively and evaluated.</p> <p>During the CMD(h) referral procedure the applicant provided further arguments to confirm clinical safety of the product.</p> <p>The presented <i>in-vitro</i> results, simulating inappropriate use of the product, by taking the tablets together with alcohol, demonstrated that an initial amount of oxycodone is rapidly released irrespective of the alcohol concentration.</p> <p>Exposed to an alcohol concentration of 40%, the formulation remained unchanged in its release behaviour.</p> <p>Further it was shown that contact with higher concentrations of ethanol for less than 1 hour, which was considered realistic for the <i>in vivo</i> situation in the stomach after consumption of alcohol under fasting conditions, did not result in relevant increases in oxycodone release. A 30-minute exposure to alcohol concentrations of up to 20% had no effect on oxycodone release and even in a 40% alcohol solution the amount of oxycodone released was higher than the value measured without the addition of alcohol but deemed to be of minor clinical relevance.</p> <p>It was clearly argued that the chosen <i>in vitro</i> test condition did not conform to the <i>in-vivo</i> situation, where larger quantities of high percentage alcohol (40%) are diluted by the gastric juices in the stomach immediately after ingestion, i.e. before it can accelerate oxycodone release. The latter one is furthermore supported by the effect of fast absorption of the alcohol or its subsequent dilution in the duodenum.</p> <p>The revised text of the SPC and PL contained already information that alcohol intake was contraindicated with oxycodone. The information was further strengthened with the outcome of those results by declaring, that the simultaneous intake of oxycodone and alcoholic beverages needs to be avoided.</p> <p>Clinically relevant safety concerns can be eliminated, if the product is taken according to the informations given in the SPC and PL.</p> <p>The objecting CMS and all other (including non concerned) member states agreed to recognise the MA without further comments. The procedure was positively concluded by consensus.</p>	

NEW APPLICATIONS

Mutual Recognition Procedure

The CMD(h) noted that **78** Mutual Recognition Procedures were finalised during the months of July and August 2007. **11** Mutual Recognition Procedures were referred to CMD(h) in this period. **No** Mutual Recognition Procedure was referred to CHMP in this period.

The status as of 31st August 2007 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 during CMD(h) referral	Applications referred to CHMP	
				For procedures referred in 2006	2007		For procedures referred to CMD(h) in 2006	2007
2007	329	160	33	25	14	1	9	4

79 Mutual Recognition Procedures (regarding **174** products) started in July and August 2007. The categories of these procedures are as follows:

13 known active substance (already authorised in at least one member state) applications, including **6** repeat use applications.

59 abridged applications, including **24** multiple and **2** repeat use applications.

7 line extension applications.

The new procedures started in July and August related to **10** full dossiers, **59** generics, **1** hybrid, **6** fixed combination and **3** bibliographic applications.

76 of these procedures consisted of chemical substances, **2** biological blood products and **1** biological other.

78 of these procedures related to prescription-only medicinal products and **1** procedure related to a non prescription medicinal product in the reference Member State¹.

Number of countries involved in the new applications in Mutual Recognition procedure started in July and August 2007.

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
AT (3)	2
AT (3)	20
AT (1)	18
CZ (2)	6
CZ (3)	13
DE (1)	2
DE (3)	2
DE (7)	7
DE (2)	18
DE (1)	17
DE (5)	1
DK (3)	6
DK (2)	12
DK (2)	3

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.

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
DK (2)	8
DK (2)	2
DK (2)	1
DK (2)	3
DK (2)	6
DK (2)	4
ES (3)	23
FR (4)	13
FR (1)	3
FR (1)	7
FR (1)	11
FR (4)	4
FR (1)	12
HU (1)	7
HU (2)	10
IE (3)	5
IE (3)	1
IE (3)	1
IE (3)	1
IE (3)	1
IE (3)	1
IE (3)	1
IE (3)	1
IE (3)	1
IE (3)	4
IE (3)	1
IE (3)	1
IE (2)	1
NL (1)	4
NL (1)	6
NL (1)	1
NL (1)	4
NL (3)	13
NL (3)	1
NL (3)	1
NL (1)	10
NL (1)	6
NL (1)	2
NL (1)	5
NL (2)	1
NL (2)	1
NL (2)	1
NL (2)	4
NL (2)	1
PT (2)	2
PT (1)	7
SE (1)	8
SE (2)	13
SE (2)	12
SE (2)	6
SE (1)	1
SE (4)	2
SE (3)	1
SE (3)	1
SE (3)	11
SE (3)	1
SE (3)	4
SE (3)	13
SE (1)	18
UK (2)	4
UK (1)	11
UK (1)	11
UK (1)	11
UK (1)	13
UK (3)	19

Decentralised Procedure

The CMD(h) noted that there were **59** new Decentralised Procedures finalised during the months of July and August 2007.. There were **4** Decentralised Procedures withdrawn at day 120 and **4** at day 210 during the months of July and August 2007. In addition, there was **1** Decentralised Procedure with negative outcome during this period. **7** Decentralised Procedures were referred to the CMD(h) in this period. **1** Decentralised Procedure was referred to the CHMP.

The status as of 31st August 2007 of procedures under Decentralised Procedure is as follows:

Year	New applications finalised		New applications withdrawn ¹	New applications in process	Referred to CMD(h)	Agreement reached in the CMD(h) For procedures referred in		Withdrawn during CMD(h) referral	Referred to CHMP For procedures referred to CMD(h) in	
	Positive outcome	Negative outcome				2006	2007		2006	2007
2007	191	3	17	877	20	1	9	3	--	1

201 Decentralised Procedures (regarding **433** products) started in July and August 2007. The categories of these procedures are as follows:

188 abridged applications, including **67** multiple applications.

8 known active substance applications.

5 Line extension applications.

The new Decentralised procedures started in July and August related to **172** generic, **4** full dossier, **17** hybrid, **4** informed consent, **3** bibliographic and **1** fixed combination applications.

200 of these procedures consisted of chemical substance applications and **1** procedure related to a biological blood product.

194 of these procedures related to prescription-only medicinal products and **7** procedures related to non-prescription medicinal products in the reference Member State².

Number of countries involved in the new applications in Decentralised procedures started in July and August 2007.

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
AT (3)	1
AT (3)	1
AT (3)	1
AT (3)	1
AT (3)	1
AT (3)	10
AT (3)	12
AT (3)	1
AT (3)	1
AT (3)	1
AT (3)	2
AT (1)	12
AT (2)	20
BE (1)	3
CZ (3)	4

¹ After day 120 of the procedure.

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.

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Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
CZ (1)	4
DE (1)	16
DE (1)	13
DE (3)	3
DE (3)	3
DE (2)	8
DE (2)	1
DE (2)	1
DE (2)	1
DE (1)	1
DE (1)	1
DE (2)	3
DE (2)	1
DE (4)	11
DE (2)	3
DE (2)	13
DE (2)	2
DE (4)	23
DE (5)	1
DE (1)	11
DE (1)	4
DE (1)	3
DE (1)	1
DE (2)	1
DE (2)	1
DE (2)	5
DE (1)	5
DE (6)	6
DE (6)	19
DE (6)	3
DE (1)	1
DE (1)	4
DE (4)	9
DE (3)	11
DE (3)	3
DE (3)	1
DE (3)	1
DE (4)	1
DE (4)	1
DE (4)	1
DE (4)	2
DE (4)	1
DE (4)	9
DE (4)	2
DE (4)	2
DE (1)	5
DE (1)	1
DE (2)	14
DE (1)	1
DE (1)	1
DE (2)	2
DE (2)	7
DE (3)	4
DE (2)	1
DE (2)	1
DE (2)	2
DE (2)	1
DK (1)	15
DK (2)	4
DK (2)	5
DK (4)	7
DK (4)	5
DK (2)	4
DK (1)	14
DK (1)	1

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
SE (3)	2
SE (3)	11
SE (3)	1
SE (3)	3
SE (3)	2
UK (2)	25
UK (1)	5
UK (1)	2
UK (3)	11
UK (5)	5
UK (1)	6
UK (1)	6
UK (1)	1
UK (3)	23
UK (3)	4
UK (3)	23
UK (5)	8
UK (2)	14
UK (2)	5
UK (2)	14
UK (2)	17
UK (2)	8
UK (2)	4
UK (4)	8
UK (1)	9
UK (1)	13
UK (1)	12
UK (1)	5
UK (1)	16
UK (2)	2
UK (3)	4
UK (5)	12
UK (2)	1
UK (1)	1
UK (4)	11
UK (2)	1
UK (2)	1
UK (2)	6
UK (1)	1
UK (2)	1
UK (2)	3
UK (2)	7
UK (2)	4
UK (1)	1
UK (6)	3
UK (3)	15
UK (2)	13
UK (2)	1
UK (2)	1
UK (2)	4
UK (2)	7
UK (2)	5
UK (2)	1
UK (2)	1
UK (6)	4
UK (2)	1

VARIATIONS AND RENEWALS

Mutual Recognition and Decentralised Procedures

The CMD(h) noted that **1037** type IA variations, **448** type IB variations and **426** type II variations were finalised during the months of July and August 2007. **75** renewals were finalised in this period. **1** Mutual Recognition Procedure for a Type II variation application was referred to CHMP in this period

The status as of 31st August 2007 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	Applications referred to CHMP
2007	3830	1517	1470	269	3

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

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

Mrs. Truus Janse-de Hoog

Phone: + 31 70 356 74 08

College ter Beoordeling van Geneesmiddelen

Fax: + 31 70 356 75 15

Kalvermarkt 53

E-mail: gm.janse@cbg-meb.nl

NL – 2500 Den Haag , The Netherlands

*Or you could visit the **CMD(h) web site** at:*

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