

Report from the CMD(h) meeting held on 21st, 22nd and 23rd May 2007

Best Practice Guide for Decentralised and Mutual Recognition Procedures

The CMD(h) has agreed a revised Best Practice Guide, to address both the Mutual Recognition and Decentralised Procedures and to structure the document into the following sections: Introduction, Pre-procedural phase, During the procedure, Break-out sessions, teleconferences and discussion at CMD(h), Finalisation of the procedure, CMD(h) referral and National implementation, which is aimed at facilitating the readability of the Best Practice Guide.

The CMD(h) has also agreed to publish the Flow chart for the Mutual Recognition Procedure and the template for CMS comments on the Mutual Recognition Procedure as separate documents to the Best Practice Guide.

Requests for advice from the CMD(h)

The CMD(h) has considered the comments received from Interested Parties on the questions and answers document which addresses the procedure and criteria for acceptance of requests for advice submitted by Companies or EEA Member States and agreed to clarify in Q&A 3 that a first discussion of the question raised will take place at the following CMD(h) meeting, which is normally within 30 days after the question has been received by the CMD(h) secretariat.

The revised Q&A document on requests for advice from the CMD(h) will be published on the website.

CMD(h) Standard Operating Procedure – Disagreement in Procedures – Referral to CMD(h)

The CMD(h) has agreed a revised SOP to clarify that it is the duty of the RMS to refer a DCP application to the CMD(h) in the situation where the RMS is negative but one or more of the CMS are prepared to grant a marketing authorisation.

The revised SOP will be published on the website.

Questions and Answers on submission of Pharmacovigilance System and Risk Management Plans

The CMD(h) has agreed a Q&A document to address the submission of Pharmacovigilance System and Risk Management Plans for generic or hybrid applications.

The Q&A document will be published on the website.

The CMD(h) has also reviewed the DCP RMS Day 70 Preliminary Assessment report Template, the DCP RMS Day 120 Draft Assessment Report Template and the Assessment Report MRP Overview Template, to address under Scientific Overview and Discussion, Clinical aspects, the assessment of Pharmacovigilance system and Risk Management Plan.

The revised templates will be published on the website.

Submission of Paediatric studies according to Articles 45 and 46 of the Regulation of the European Parliament and of the Council (EC) No 1901/2006, as amended

The CMD(h) and the European Medicines Agency (EMA) held a meeting on 21 May 2007 with representatives of AESGP¹, EFPIA² and EGA³, to discuss a proposal for a questions and answers (Q&As) document to address the submission of Paediatric studies according to Articles 45 and 46 of the Paediatric Regulation, including the data and format to be used.

The CMD(h) and the EMA agreed to publish the draft Q&As for a 2 week period of public consultation and finalisation in June 2007.

Any comments on the draft Q&As should be sent to the attention of the CMD(h) secretariat (sonia.ribeiro@emea.europa.eu) by 14 June 2007.

¹ Association of the European Self-Medication Industry

² European Federation of Pharmaceutical Industries and Associations

³ European Generic Medicines Association

EU Work sharing Project – Assessment of paediatric data

The Paediatric Public Assessment Report for Cosopt, eye drops solution (dorzolamide/timolol) and Pulmicort Nebuliser Suspension (budesonide) 0.125/0.25/0.5 mg/ml will be available on the CMD(h) website, under the heading 'Paediatric data assessment'.

Submission of premature dossiers in the Decentralised Procedure

The CMD(h) has agreed to refuse applications for marketing authorisation in the decentralised procedure on the basis that the studies requested should be provided before the granting of the marketing authorisations.

The CMD(h) has agreed, as a general rule, that applications for marketing authorisation in the decentralised procedure based on incomplete dossiers should be refused and studies missing should not be accepted as post-approval commitments.

Applicants are, therefore, advised to avoid the submission of premature dossiers in the decentralised procedure.

Informal CMD(h) meeting, 7-8 May 2007, Bonn, Germany

The CMD(h) convened for an Informal meeting on 7th and 8th May 2007 in Bonn, Germany, held as part of a programme of events organised under the German Presidency of the EU, in parallel to the informal CHMP and COMP meetings.

The main topics discussed at the meeting included MSs experience with work sharing initiatives, a proposal for work sharing for patient consultation, evaluation of referrals to the CMD(h), MSs follow up to Article 30 and 31 referral procedures, the revision of the Variation Regulation, the experience with national implementation following MRP/DCP and the impact of the Paediatric Regulation on National Competent Authorities business processes.

Most of the issues discussed at the informal meeting will be taken forward at regular CMD(h) meetings, such as the update of guidance for Applicants on the transfer of medicinal products to MRP, following an Article 30 or 31 referral procedure, the development of a paper on work sharing initiatives, the agreement to set up a sub-group to develop guidance on the work sharing initiative for patient consultation, the agreement to further discuss the timeframe and quality of translations submitted in the MRP and DCP, etc.

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 03.05.2007.

Name of the product in the RMS	TESTOPATCH
Active substance	testosterone
Pharmaceutical form	Transdermal patch
Procedure number	FR/H/297/01-03/MR
CMS	BE, CZ, DE, EL, ES, IT, PL, PT
Legal basis	Art 10.3 Dir 2001/83/EC - Hybrid
Grounds for referral to CMD(h)	The procedure was referred to the CMD(h) on the following grounds: <ul style="list-style-type: none">- the use of DEET as solvent under occlusive conditions in a transdermal patch, in particular with respect to intended long term treatment, may cause local skin irritation;- the use of this transdermal patch would result in a considerable long-term daily exposure to DEET, which is expected to be absorbed through the skin with unknown consequences.
Day 60	03.05.2007
Outcome	On the basis of all the data submitted by the company including toxicological and safety studies, data on the transdermal delivery system, an agreement was reached before the CMD(h) meeting. The applicant committed: <ul style="list-style-type: none">- to monitor neurological adverse drug reactions and to present an updated Risk Management Plan addressing the potential (increased) risk for central nervous system effects, the potential risk of interaction with drugs known for their pro-convulsive effects.- to perform single and repeat dose skin irritation studies.

Name of the product in the RMS	Tramadol HCl Duiven retard 100, 150 & 200 mg
Active substance	tramadol
Pharmaceutical form	Modified release tablet
Procedure number	NL/H/539/01-03/MR
CMS	ES, IT, PT
Legal basis	Art 10.1 Dir 2001/83/EC - Generic
Grounds for referral to CMD(h)	There is a concern with regard to the demonstration of bioequivalence of the test product and the reference product.
Day 60	03.05.2007
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 all involved Member States could agree on a commitment from the applicant to submit in vitro – in vivo correlation data in addition to the available studies to demonstrate bioequivalence. It was noted that this should not be taken as a precedent, but that only in this particular case (the product is marketed for several years in a number of member states) the lack of studies was accepted. Agreement reached.

Name of the product in the RMS	Azithromycin Sandoz 100 mg/5 ml	Azithromycin Sandoz 200 mg/5ml
Active substance	azithromycin	
Pharmaceutical form	Powder for oral suspension	
Procedure number	NL/H/886/01-02/MR	
CMS	BE, EL, PL, SI, SK	AT, BE, DE, EL, FI, IT, PL, SE, SI, SK, UK
Legal basis	Art 10.3 Dir 2001/83/EC - Hybrid	Art 10.1 Dir 2001/83/EC - Generic
Grounds for referral to CMD(h)	There is a concern with regard to the increased prevalence of azithromycin resistance. Therefore, the applicant was requested to provide all necessary information on efficacy and safety of azithromycin in acute otitis media (AOM), sinusitis, acute bronchitis and mild to moderate severe community acquired pneumonia (CAP) in the light of increased prevalence of azithromycin resistant <i>Streptococcus pneumoniae</i> in Belgium and other European countries.	
Day 60	03.05.2007	
Outcome	At the CMD(h) meeting the RMS presented its view and the applicant's written response were discussed. Following the discussion all involved Member States could agree on a proposal to adapt the SPC. The following is added to section 4.1: "Azithromycin is not the first choice for the empiric treatment of infections in areas where the prevalence of resistant isolates is 10% or more (see section 5.1)." In section 4.4, all warnings related to limitations of the indications are listed under a separate heading. Agreement reached.	

Name of the product in the RMS	Azithromycin TEVA 200 mg /5 ml
Active substance	azithromycin
Pharmaceutical form	Powder for oral suspension
Procedure number	NL/H/945/01/MR
CMS	AT, BE, CZ, DE, DK, EE, EL, ES, FI, IE, IT, LU, MT, NO, PL, PT, SK, UK
Legal basis	Art 10.1 Dir 2001/83/EC - Generic
Grounds for referral to CMD(h)	There is a concern with regard to the increased prevalence of azithromycin resistance. Therefore, the applicant was requested to provide all necessary information on efficacy and safety of azithromycin in acute otitis media (AOM), sinusitis, acute bronchitis and mild to moderate severe community acquired pneumonia (CAP) in the light of increased prevalence of azithromycin resistant <i>Streptococcus</i>

	<p><i>pneumoniae</i> in Belgium and other European countries.</p> <p>There was an additional concern regarding the duration of treatment (3 days versus 5 days).</p>
Day 60	03.05.2007
Outcome	<p>At the CMD(h) meeting the RMS presented its view and the applicant's written response were discussed. Following the discussion all involved Member States could agree on a proposal to adapt the SPC.</p> <p>The following is added to section 4.1: "Azithromycin is not the first choice for the empiric treatment of infections in areas where the prevalence of resistant isolates is 10% or more (see section 5.1).".</p> <p>In section 4.4, all warnings related to limitations of the indications are listed under a separate heading.</p> <p>It was agreed that the available data in the innovator dossier for Zithromax and in the public domain justify mentioning a 5-day treatment regimen in addition to the 3-day regimen.</p> <p>Agreement reached.</p>

Name of the product in the RMS	Alnok
Active substance	cetirizine
Pharmaceutical form	Effervescent tablet
Procedure number	SE/H/595/01/DC
CMS	PL, UK
Legal basis	Art 10.1 Dir 2001/83/EC - Generic
Grounds for referral to CMD(h)	Potential serious risk to public health was raised by one concerned member state with regard to the proposed posology in children. In the objecting member state, the posology in children for the originator is based on age, while the posology in children in the RMS is based on body weight.
Day 60	03.05.2007
Outcome	<p>The following issues were discussed during the CMD referral:</p> <p>i) the patient factor used to dose according to (body weight or age) and</p> <p>ii) the cut-off value (30 kg child or 6 years old).</p> <p>Following the review of the data and the applicant's response, there does not appear to be great differences between the RMS's and objecting CMS's proposed dosing recommendations. Further, in the perspective of the upcoming harmonisation of SPCs for cetirizine in the CHMP (Article 30 referral for the cetirizine originator), and that the applicant commits to submit a variation to harmonise with the outcome of the Article 30 referral for the originator within 90 days after the publication of the Commission Decision, the RMS accepted to change the SPC in line with the objecting CMS SPC, <i>i.e.</i> the dose adjustment in children will be made on the basis of age instead of body weight.</p> <p>Agreement reached.</p>

NEW APPLICATIONS

Mutual Recognition Procedure

The CMD(h) noted that **27** new Mutual Recognition Procedures were finalised during the month of April 2007. **5** Mutual Recognition Procedures for new applications were referred to CMD(h) in this period. **No** Mutual Recognition Procedures for new applications were referred to CHMP in this period.

The status as of 30th April 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 in the CMD(h)	Arbitrations referred to CHMP
2007	165	194	17 N.A.	29	1	11

40 Mutual Recognition Procedures (regarding **73** products) started in April 2007. The categories of these procedures are as follows:

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

25 abridged applications, including **9** multiple applications.

1 new active Substance, which was a repeat use application.

1 line extension application, which was a repeat use application.

The new procedures started in April related to **10** full dossiers, **23** generics, **2** hybrid applications, and **5** bibliographic applications.

These procedures consisted of **38** chemical, **1** biological other and **1** biological vaccine substances.

39 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 April 2007.

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
AT (1)	1
CZ (1)	8
DE (2)	2
DE (1)	1
DE (1)	5
DE (4)	2
DK (1)	2
DK (1)	2
DK (2)	2
DK (2)	1
DK (2)	16
DK (2)	4
DK (2)	7
DK (2)	4
DK (2)	4
FI (2)	14
FI (1)	16
FI(1)	8
FR (1)	3
FR (5)	21
NL (2)	1
NL (2)	1
NL (2)	6
NL (2)	1
NL (2)	1
NL (2)	2
NL (2)	4
NL (2)	3
NL (2)	4

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
NO (2)	1
SE (1)	2
SE (6)	12
SE (1)	1
SE (1)	1
SE (2)	1
UK (2)	10
UK (1)	9
UK (1)	6
UK (1)	6
UK (1)	10

Decentralised Procedure

The CMD(h) noted that there were **19** new Decentralised Procedures finalised during the month of April 2007. There was **1** Decentralised Procedure referred to the CMD(h) in this period.

The status as of 30th April 2007 of procedures under Decentralised Procedure is as follows:

Year	New applications finalised with positive outcome	New applications withdrawn ⁴	New applications finalised with negative outcome	New applications in process	Referred to CMD(h)	Agreement reached in the CMD(h)	Arbitrations referred to CHMP
2007	46	2	1	702	6	1	--

79 Decentralised Procedures (regarding **234** products) started in April 2007. The categories of these procedures are as follows:

71 abridged applications, including **26** multiple applications.

6 known active substance applications.

2 new active substances.

The new Decentralised procedures started in April related to **65** generic, **3** full dossier, **6** hybrid, **3** fixed combinations (1 initial and 2 multiple applications) and **2** bibliographic applications.

78 of these procedures consisted of chemical substance applications and **1** herbal substance.

76 of these procedures related to prescription-only medicinal products and **3** procedures related to non-prescription medicinal products in the reference Member State⁵.

Number of countries involved in the new applications in Decentralised procedures started in April 2007.

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
AT (1)	1
BE (1)	4
CZ (2)	7
DE (1)	2
DE (1)	8
DE (1)	4
DE (2)	12
DE (1)	5
DE (1)	5

⁴ After day 120 of the procedure.

⁵ 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.

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
DE (1)	4
DE (1)	12
DE (2)	2
DE (4)	3
DE (4)	1
DE (4)	4
DE (6)	1
DE (6)	1
DE (6)	1
DE (6)	1
DE (2)	2
DE (2)	1
DE (2)	8
DE (7)	17
DE (1)	3
DE (5)	4
DE (2)	1
DE (2)	1
DE (2)	1
DE (2)	1
DE (2)	1
DE (4)	1
DK (1)	10
DK (1)	7
DK (1)	7
DK (1)	1
DK (1)	4
DK (1)	1
DK (1)	3
DK (5)	1
DK (7)	1
DK (7)	1
DK (7)	2
DK (7)	1
DK (7)	1
DK (7)	1
DK (7)	1
DK (7)	3
DK (7)	2
DK (7)	8
DK (7)	11
FI (2)	1
NL (6)	1
NL (1)	12
NL (1)	1
NL (4)	13
NL (4)	13
NL (2)	27
NL (2)	15
NL (1)	1
NL (4)	1
NL (1)	4
NO (1)	1
NO (1)	2
SE (4)	4
SE (4)	3
SE (4)	3
SE (1)	1
UK (1)	2
UK (1)	13
UK (1)	6
UK (1)	1
UK (1)	13
UK (1)	5
UK (1)	21

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
UK (1)	1
UK (1)	1
UK (2)	4
UK (1)	3
UK (6)	1

VARIATIONS AND RENEWALS

Mutual Recognition and Decentralised Procedures

The CMD(h) noted that **405** type IA variations, **154** type IB variations and **198** type II variations were finalised during the month of April 2007. **26** renewals were finalised in this period.

The status as of 30th April 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	Arbitrations referred to CHMP
2007	1801	640	687	150	--

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):

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