

Report from the CMD(h) meeting held on 16th, 17th and 18th July 2007

Sub-group meeting on Harmonisation of SPCs

There was a meeting of the Sub-Group on harmonisation of SPCs, to discuss the proposals from Member States for products for which a harmonised SPC should be drawn up.

The Group agreed to prepare the rationale for selection of the products to be included in the list for SPC harmonisation, addressing the agreed criteria, for discussion at the October sub-group meeting. The Group agreed also to consider differences in information on pregnancy and lactation and to take into account patients' perspectives when considering differences in SPCs between MSs.

The CMD(h) Sub-Group on harmonisation of SPCs will continue its work with a view to laying down a 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.

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

There was a meeting of the Sub-Group on Paediatric Regulation, mainly to consider the action points identified at the meeting held on 21 May 2007 with representatives of Interested Parties and the comments received on the Q&A document addressing the submission of Paediatric studies according to Articles 45 and 46 of the Paediatric Regulation.

The revised Q&As, together with a procedure and template for Marketing Authorisation Holders to inform National Competent Authorities of the medicinal products with a Paediatric indication and of paediatric studies not yet submitted by the entry into force of the Paediatric Regulation will be published on the website.

Working Group on Validation issues/National requirements

Further to the work carried out by the Working Group set up to analyse validation issues and national requirements within the framework of the Decentralised and Mutual Recognition Procedures, the CMD(h) has agreed on the following documents that will be published on the website:

- Overview of the work undertaken so far by the Working Group on Validation issues/National requirements;
- Additional data requested for new applications in the Mutual recognition and Decentralised procedures;
- Common grounds for invalidation/delaying validation;
- Member States recommendation on the Cover Letter for new applications submitted through the MRP/DCP.

Possibility to refer to clinical studies performed by a Company different from the Company holding the initial marketing authorisation

The CMD(h) has agreed a Q&A to address the admissibility of an application for marketing authorisation based on an abridged dossier, which refers both to the complete dossier of a reference product and to clinical studies contained in a hybrid dossier, authorised according to Article 10(3) of Directive 2001/83/EC, as amended.

Assessment of the quality of medicinal products containing existing/known active substances

The CMD(h) would like to bring to the attention of Interested Parties the publication of the above mentioned document, 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, on the EMEA website for a 6 months public consultation period <http://www.emea.europa.eu/Inspections/docs/45065306en.pdf>.

CMD(h) Standard Operating Procedure for Article 61(3) changes to patient information

The CMD(h) has reviewed the draft procedure to maintain the harmonisation of labelling and package leaflet of medicinal products approved through the decentralised and mutual recognition procedure concerning changes not connected with the summary of product characteristics, in accordance with Article 61(3) of Directive 2001/83/EC, as amended.

The revised SOP, Flow chart and notification form will be published on the website.

Applicants should specify, in the notification form, the MR/DC product information amendment procedure number, which has its own series of sequential numbers, separate to other procedures, and should be started with the number 1.

Numbering of follow-up submissions and commitments

The CMD(h) has agreed a Q&A to address the numbering of follow-up submission and commitments for medicinal products authorised via the Mutual recognition and Decentralised procedures.

The CMD(h) has agreed the principle that irrespective of the type of submission (follow-up submission or commitment) there is a continuous numbering of the follow-up submissions and commitments and that only identical follow-up submissions/commitments are entitled to have the same chronological number.

EU Work sharing Project – Assessment of paediatric data

The Paediatric Public Assessment Report for Imigran, sumatriptan will be available on the CMD(h) website, under the heading ‘Paediatric data assessment’.

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 28.06.2007.

Name of the product in the RMS	Rhophylac 300
Active substance	human anti-D (Rh) immunoglobulin
Pharmaceutical form	Solution for injection
Procedure number	DE/H/0211/02/E003
CMS	NL, SE, UK (wave 1) BE, DK, EL, FI, FR, IE, IS, IT, LU, NO, PT (wave 2) AT, CZ, ES, HU, PL, SI, SK (wave 3)
Legal basis	Art 8.3(i) Dir 2001/83/EC - Full Dossier
Grounds for referral to CMD(h)	A potential serious risk to public health was raised by one Member state, based on a lack of appropriate demonstration of efficacy as not sufficient data on baseline characteristics of the population included in the main clinical trial were provided by the Applicant. In addition it was not considered possible by the CMS to develop anti-Rh IgG in the first pregnancy but only in subsequent pregnancies when these patients had previously delivered an Rh+ child. Therefore there was a lack of information on how many women were primiparae and how many were multiparae. Data of efficacy and safety of these subgroups, including baseline characteristics was felt to be necessary.
Day 60	28.06.07
Outcome	At the CMD(h) meeting the RMS and the Applicant presented their view on the product. The company adhered to the current Guideline (CPMP/BPWG/575/99) and the FDA Guidelines: An adequate number of Rh(D) negative non-immunised women gave birth to Rh(D) positive babies and were available for 11 months follow up assessment. None of them showed evidence of Rh(D) immunisation. It is common practise to treat all non-immunised rhesus negative women with anti-D, regardless of parity, thus, all women in the study could be regarded as “primiparae”, as sensitised women in previous pregnancies were excluded from the study. Therefore, a differentiation or subgroup analysis of primiparae and multiparae is not necessary. It was also confirmed by literature data that it is possible to develop anti-Rh IgG in the first pregnancy, thereby also explaining the success of the antenatal prophylaxis. The postmarketing data showed an excellent record for safety and efficacy. The sensitisation rate was incredibly

	low even by literature standards. The objecting CMS agreed to recognise this MA and did not have any further comments.
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Name of the product in the RMS	Pulairmax
Active substance	budesonide
Pharmaceutical form	Inhalation powder
Procedure number	DK/H/1018/01-03/MR
CMS	AT, BE, CY, CZ, DE, EE, EL, ES, FI, IE, IT, LT, LU, LV, MT, NL, NO, PL, PT, SE, SK
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 basis that therapeutic equivalence to the RMP could not be shown due to an inappropriate design of the clinical studies, which were insensitive to detect differences between the test and the RMP. The procedure was also referred to the CMD(h) on quality grounds, as the requirement to investigate a range of flow rates and compare the devices should be fulfilled and the delivered dose compared.
Day 60	28.06.07
Outcome	At the meeting the RMS presented its view and the applicant's written response was discussed. The applicant made use of an oral hearing. It was discussed which clinical studies should be required to prove efficacy and safety for inhalation products and no consensus was reached. Referred to CHMP for arbitration.

Name of the product in the RMS	Bisoprolol-TEVA comp
Active substance	bisoprolol HCTZ
Pharmaceutical form	Film-coated tablet
Procedure number	DE/H/0686/01-02/DC
CMS	<u>DE/H/686/01/DC</u> : AT, BE, CZ, FI, HU, NL, SK <u>DE/H/686/02/DC</u> : AT, BE, CZ, ES, FI, HU, NL, SK
Legal basis	Art 10.1 Dir 2001/83/EC - Generic
Grounds for referral to CMD(h)	The use of HCTZ should not be contraindicated during the second and third trimesters of pregnancy.
Day 60	28.06.07
Outcome	Agreement was reached to retain a contraindication for HCTZ during the second and third trimesters of pregnancy for the specific indication 'essential hypertension'. This agreement is based on the availability of other medicinal products with proven safety for the treatment of essential hypertension during pregnancy. The question if a contraindication in the second and third trimester of pregnancy for HCTZ is justified in the indication 'essential hypertension' and other approved indications will be forwarded to the relevant scientific working party.

Name of the product in the RMS	Omeprazol 10, 20 & 40 mg	Itomed 10, 20 & 40 mg
Active substance	omeprazole	
Pharmaceutical form	Gastro-resistant capsule, hard	
Procedure number	NL/H/973/01-03/MR	NL/H/974/01-03/MR
CMS	<u>NL/H/973/01-02/MR</u> : AT, DE, DK, FI, HU, IT, PL, SI, SK <u>NL/H/973/03/MR</u> : AT, DE, DK, FI, HU, PL, SI, SK	<u>NL/H/974/01-02/MR</u> : CZ, DE, DK, EL, ES, FI, HU, IT, LT, NO, PL, PT, SE, SI, SK <u>NL/H/974/03/MR</u> : DE, DK, EL, ES, FI, HU, LT, NO, PL, PT, SE, SI, SK
Legal basis	Art 10.3 Dir 2001/83/EC - Hybrid	
Grounds for referral to CMD(h)	The procedure was referred to the CMD(h) because a potential serious risk to public health was raised with regard to the demonstration of	

	bioequivalence with the formulation that is on the national market. Bioequivalence is demonstrated against the reference product (Losec gastro-resistant capsules) and not against Losec MUPS enterotablets. Losec gastro-resistant capsules is no longer registered in the Member State referring these applications.
Day 60	28.06.07
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 that a bioequivalence study comparing the test product vs Losec MUPS enterotablets is not required, since bioequivalence only has to be demonstrated against the reference product. However, the applicant committed to submit additional dissolution profiles (i.e. including all strengths) of the test product and Losec MUPS enterotablets. Agreement reached.

Name of the product in the RMS	Tibolone 2.5mg
Active substance	tibolone
Pharmaceutical form	Tablet
Procedure number	UK/H/0919/01/MR
CMS	AT, BE, DE, ES, FR, LU, NL, PL
Legal basis	Art 10.1 Dir 2001/83/EC - Generic
Grounds for referral to CMD(h)	The application was referred to CMD(h) as there were unresolved quality issues on the drug substance intermediate, validity of the bioanalytical method, and the effect of the solubility and dissolution difference of polymorphs on bioavailability raised by one Member State.
Day 60	28.06.07
Outcome	The applicant provided additional data to resolve the outstanding issues, along with a revised drug substance specification. Agreement was reached before the CMD(h) meeting

NEW APPLICATIONS

Mutual Recognition Procedure

The CMD(h) noted that **27** new Mutual Recognition Procedures were finalised during the month of June 2007. **4** Mutual Recognition Procedures for new applications were referred to CMD(h) in this period. **1** Mutual Recognition Procedure for new applications was referred to CHMP in this period.

The status as of 30th June 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	251	154	22 N.A.	25	14	1	9	4

19 Mutual Recognition Procedures (regarding **39** products) started in June 2007. The categories of these procedures are as follows:

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

16 abridged applications, including **2** multiple and **2** repeat use applications.

1 line extension application.

The new procedures started in June related to **1** full dossier, **16** generics and **2** bibliographic applications.

All of these procedures consisted of chemical substances.

All of these procedures related to prescription-only medicinal products in the reference Member State¹.

Number of countries involved in the new applications in Mutual Recognition procedure started in June 2007.

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
DE (2)	2
DE (2)	4
DE (1)	4
DE (4)	9
DE (4)	1
DK (1)	5
DK (1)	1
FI (2)	11
IT (1)	1
NL (2)	7
NL (2)	2
NL (1)	1
NL (1)	6
NL (2)	7
NL (2)	1
NL (6)	4
NL (1)	3
SE (2)	1
UK (2)	15

Decentralised Procedure

The CMD(h) noted that there were **44** new Decentralised Procedures finalised during the month of June 2007. There were **2** Decentralised Procedures referred to the CMD(h) in this period. There was **1** Decentralised Procedure withdrawn and **1** with negative outcome at day 210 during the month of June 2007.

The status as of 30th June 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	132	2	9	740	13	1	6	3	--	--

92 Decentralised Procedures (regarding **201** products) started in June 2007. The categories of these procedures are as follows:

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

5 known active substance applications, including **2** multiple applications.

3 Line extension applications.

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.

¹ After day 120 of the procedure.

Report from the CMD(h) meeting held in July 2007

The new Decentralised procedures started in June related to **82** generic, **6** full dossier, **3** hybrid and **1** fixed combination applications.

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

89 of these procedures related to prescription-only medicinal products and **3** 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 June 2007.

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
AT (3)	4
AT (3)	1
BE (1)	13
CZ (1)	5
CZ (1)	6
CZ (1)	2
CZ (1)	3
CZ (1)	3
CZ (1)	6
CZ (1)	10
DE (2)	1
DE (1)	5
DE (1)	5
DE (2)	16
DE (5)	8
DE (5)	3
DE (5)	3
DE (3)	2
DE (5)	1
DE (2)	1
DE (1)	7
DE (1)	7
DE (1)	7
DE (1)	6
DE (1)	1
DE (1)	1
DE (1)	1
DE (1)	1
DE (1)	1
DE (1)	1
DE (1)	1
DE (1)	1
DE (1)	1
DE (1)	1
DE (1)	1
DE (1)	1
DE (2)	1
DE (2)	2
DE (2)	1
DE (4)	12
DE (4)	8
DE (2)	3
DE (2)	1
DE (2)	1
DE (2)	1
DE (2)	4
DE (1)	1
DE (1)	6
DE (1)	2
DE (1)	1
DE (1)	1
DE (1)	1
DE (4)	1
DE (4)	1
DK (1)	27
DK (1)	8

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.

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
DK (4)	14
DK (4)	3
DK (4)	1
DK (4)	1
DK (4)	1
DK (4)	1
DK (4)	1
DK (4)	1
DK (4)	1
DK (4)	1
DK (1)	3
DK (1)	1
FI (3)	2
FI (3)	4
FI (3)	1
FI (3)	1
FI (3)	1
FI (3)	1
FI (3)	1
NL (1)	5
NL (1)	14
NL (1)	15
NL (1)	16
NL (3)	10
NL (3)	19
NL (1)	11
NO (2)	14
NO (3)	8
NO (2)	9
PL (5)	2
UK (2)	1
UK (2)	1
UK (2)	1
UK (1)	25
UK (4)	6
UK (1)	3
UK (1)	8
UK (3)	11
UK (13)	6
UK (1)	4
UK (1)	3
UK (1)	1
UK (2)	12

VARIATIONS AND RENEWALS

Mutual Recognition and Decentralised Procedures

The CMD(h) noted that **495** type IA variations, **234** type IB variations and **196** type II variations were finalised during the month of June 2007. **25** renewals were finalised in this period.

The status as of 30th June 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	2793	1069	1044	194	2

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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