The European Agency for the Evaluation of Medicinal Products
Human Medicines Evaluation Unit

29 June 1998
CPMP/1150/98

PRESS RELEASE

The Committee for Proprietary Medicinal Products (CPMP) held its 39th plenary meeting from 23-24 June 1998.
This meeting was followed by a joint EMEA/ISDB meeting (see attached statement - Annex V) on 26 June 1998.

Centralised Procedures

The Committee adopted the following Opinions:

- One positive Opinion on a Centralised Application by consensus relating to a Medicinal Product containing a new active substance (Part A), an immunosuppressive agent, indicated for the prophylaxis of acute organ rejection in *de novo* allogenic renal transplantation concomitantly with cyclosporin and corticosteroids.

- One positive Opinion by consensus relating to an application in accordance with Annex II of the Commission Regulation 542/95 (modified manufacturing process) for an already Centrally Authorised Medicinal Product containing a recombinant human insulin (Part A), indicated for the treatment of diabetes mellitus.

- Three positive Opinions by consensus for Centralised Type I Variations following the Type II procedure.

- Five positive Opinions by consensus relating to four active substances for Centralised Type II Variations.

Three Centralised Procedures have been started after validation (two for Part A relating to the same active substance and one for Part B).

A Rapporteur and a Co-rapporteur were assigned for one application (Part B) forthcoming in the Centralised Procedure within the next four months. A Rapporteur was assigned for an extension application for an already Centrally Authorised Medicinal Product (Part B).

An overview of Centralised Applications is given in Annex I.

Since the CPMP meeting in May 1998, the European Commission has granted a Marketing Authorisation for:

- Optison (Octafluoropropane), a diagnostic echocardiographic contrast agent for use in patients with suspected or established cardiovascular disease

- Pylori-Chek (^{13}C-urea), indicated for the *in vivo* diagnosis of gastroduodenal *Helicobacter pylori* infection

- Mabthera (Rituximab), indicated for the treatment of patients with relapsed or chemoresistant follicular non-Hodgkin's lymphoma.

See Annexes II & III for details.

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Scientific Advice

The Committee:

- Accepted six new requests for Scientific Advice as justified. Co-ordinators were appointed.
- Adopted two Scientific Advice by consensus on clinical issues and development plans concerning new products, one for Part A and one for Part B, intended for:
  - Treatment of steroid dependent patients suffering from Crohn's disease
  - Treatment and prophylaxis of influenza A & B infection
- Adopted a follow-up Scientific Advice on the manufacturing process for a Part B product intended as an anti-venom.

Referrals

Referral under Article 7.5 of Commission Regulation (EC) No. 541/95

The Committee noted the Referral for Arbitration to the CPMP of a Type II Variation relating to an extension for a new indication, concerning a Medicinal Product already authorised through the former Concertation Procedure. A Rapporteur and a Co-Rapporteur were assigned.

Referral under Article 10 of Council Directive 75/319/EEC, as amended

On 9 June 1998 the European Commission adopted a Decision for a Medicinal Product containing fluoxetin. This Decision endorses the Positive Opinion given by the CPMP in December 1997, following the Referral for Arbitration to the CPMP in May 1997 under the Mutual Recognition Procedure. The concerned Member States shall amend or issue the National Marketing Authorisations accordingly.

Working Parties and Organisational matters.

The CPMP heard reports from its Quality, Biotechnology, Safety, Efficacy and Pharmacovigilance Working Parties.

QUALITY WORKING PARTY

The following document was adopted for coming into operation in December 1998:

- Note for Guidance on dry powder inhalers (CPMP/QWP/158/96)

BIOTECHNOLOGY WORKING PARTY

A Concept paper addressing the comparability of biotechnology-derived products (CPMP/BWP/1113/98) was agreed and a CPMP Note for Guidance will now be drafted.

The Committee noted that Dr. P. Le Courtois has been appointed Head of Sector for New Chemical Substances within the Human Medicines Evaluation Unit of the EMEA, succeeding Prof. J. Torrent-Farnell.

MUTUAL RECOGNITION

The CPMP noted the report from the Mutual Recognition Facilitation Group (MRFG) meeting held on 22 June 1998, which is circulated together with this press release (Annex VI)

Prof. R. Bass
Head of Human Medicines Evaluation Unit

This press release and other documents are available on the Internet at the following address: http://www.eudra.org/emea.html

CENTRALISED APPLICATIONS TO THE EMEA

	Part A	Part B	Total
Scientific Advice	27	34	61

	Part A	Part B	Total
Applications submitted since 1 January 1995	56	100	156
Withdrawn	4	13	17
Opinions given by the CPMP	28	54	82**
Marketing Authorisations granted by the Commission	26	36	62***

	Part A	Part B	Total
Variations type I	86	117	203
Variations type II	26	50	76
Extensions	11	3	14

* These figures include the 18 ex-concertation procedures submitted before January 1995 of which 14 have been authorised and 4 withdrawn before end 1996

** 82 Opinions corresponding to 64 substances

*** 62 Marketing Authorisations corresponding to 52 substances

Medicinal Products granted a Community Marketing Authorisation under the Centralised Procedure since the May 1998 Press Release

PRODUCT	**Brandname**	OPTISON
	INN	Octafluoropropane
	Part A/B	B
COMPANY ORIGIN	**Country**	United States of America
MARKETING AUTHORISATION HOLDER	**Name**	Mallinckrodt Medical GmbH (Germany)
THERAPEUTIC AREA	**ATC Code**	V08D
	Indication	A diagnostic echocardiographic contrast agent for use in patients with suspected or established cardiovascular disease
PRESENTATION	**Pharmaceutical form**	Solution for injection
	Strength	Equivalent to 0.22 mg/ml octafluoropropane gas
	Number of presentations	2
EMEA/CPMP	**Validation**	21/03/97
	Date of Opinion	28/01/98
	Active time	192 days
	Clock stop	122 days
COMMISSION DECISION	**Opinion receipt date**	04/03/98
	Date of Commission Decision	18/05/98

PRODUCT	**Brandname**	PYLORI-CHEK
	INN	^{13}C-urea
	Part A/B	B
COMPANY ORIGIN	**Country**	The Netherlands
MARKETING AUTH-ORISATION HOLDER	**Name**	Alimenterics B.V. (The Netherlands)
THERAPEUTIC AREA	**ATC Code**	V04CX
	Indication	The *in vivo* diagnosis of gastroduodenal *Helicobacter pylori* infection
PRESENTATION	**Pharmaceutical form**	Powder and solvent for oral solution
	Strength	100 mg
	Number of presentations	1
EMEA/CPMP	**Validation**	20/06/97
	Date of Opinion	25/02/98
	Active time	194 days
	Clock stop	56 days
COMMISSION DECISION	**Opinion receipt date**	01/04/98
	Date of Commission Decision	15/06/98

PRODUCT	**Brandname**	MABTHERA
	INN	Rituximab
	Part A/B	A
COMPANY ORIGIN	**Country**	Switzerland
MARKETING AUTHORISATION HOLDER	**Name**	Hoffman la Roche (United Kingdom)
THERAPEUTIC AREA	**ATC Code**	L01XX
	Indication	For the treatment of patients with relapsed or chemoresistant follicular non-Hodgkin's lymphoma.
PRESENTATION	**Pharmaceutical form**	Solution for infusion
	Strength	100 mg, 500 mg
	Number of presentations	2
EMEA/CPMP	**Validation**	21/03/97
	Date of Opinion	28/01/98
	Active time	179 days
	Clock stop	132 days
COMMISSION DECISION	**Opinion receipt date**	09/03/98
	Date of Commission Decision	02/06/98

OPTISON

International Non-proprietary Name (INN): **Octafluoropropane**

Abstract*

On 18 May 1998, the European Commission issued a Marketing Authorisation valid throughout the European Union for the medicinal product Optison, which contains octafluoropropane. This Decision was based on the assessment report and on the favourable opinion adopted by the Committee for Proprietary Medicinal Products (CPMP) on 28 January 1998. The Marketing Authorisation Holder responsible for this medicinal product is Mallinckrodt Medical GmbH.

The approved indication is for use as a diagnostic echocardiographic contrast agent for the enhancement of left ventricular endocardial border delineation in patients with suspected or established cardiovascular disease. Detailed conditions for the use of this product are described in the Summary of Product Characteristics (SPC) which can be found in the EPAR and is available in all European Union official languages.

The active substance of Optison is octafluoroproane stabilised in the form of gaseous microbubbles by heat-treated human albumin. It is the number and size of these microbubbles which, taken together constitute an echogenic contrast-improving system.

Two open-label, randomised, comparative phase III trials were conducted in the USA at fourteen centres recruiting 203 patients, which included a subgroup of 79 patients with chronic pulmonary disease and/or moderately severe cardiac disease. These studies demonstrated that Optison provided improved image enhancement of the left ventricle and allowed for a more complete examination when compared to another echogenic contrast agent.

In addition to the above studies, six studies contributed to the assessment of safety, including studies in special patient populations, e.g. the elderly, patients with hepatic, renal or pulmonary impairment, patients with concomitant acute (cerebro) vascular disease etc. One result of these safety studies was a contraindication in patients with severe pulmonary hypertension. The human albumin component was considered to present no significant safety risk, however the possibility of transmission of infectious agents during administration of products prepared from human blood or plasma cannot be totally excluded and a warning to this effect is included in the SPC. The most frequently reported adverse effects associated with the administration of Optison were transient altered taste (2.5%), headache (2.0%) and warm sensation/flushing (2.0%).

The CPMP, on the basis of efficacy and safety data submitted, considered that Optison showed adequate evidence of diagnostic efficacy and a satisfactory safety profile and therefore recommended that the Marketing Authorisation should be granted.

* This text is the Abstract of the complete EPAR

PYLORI-CHEK

International Non-proprietary Name (INN): **^{13}C-urea**

Abstract*

On 15 June 1998 the European Commission issued a Marketing Authorisation valid throughout the European Union for the medicinal product Pylori-Chek, which contains ^{13}C-urea. This Decision was based on the assessment report and on the favourable opinion adopted by the Committee for Proprietary Medicinal Products (CPMP) on 25 February 1998. The Marketing Authorisation Holder responsible for this medicinal product is Alimenterics B.V.

The approved indication is for the *in vivo* diagnosis of gastroduodenal *Helicobacter pylori* infection. Detailed conditions for the use of this product are described in the Summary of Product Characteristics (SPC) which can be found in the EPAR and is available in all European Union official languages.

The active substance in this product is 100mg ^{13}C-urea, i.e. urea labelled with the non-radioactive stable isotope ^{13}C. It is presented in the form of a powder to be dissolved in water prior to oral administration. The diagnostic principle is based upon the urease activity of *Helicobacter pylori*. In the case of gastroduodenal *Helicobacter pylori* infection, the ^{13}C-urea is metabolised by urease and $^{13}CO_2$ is liberated in the exhaled air. Breath samples are collected and the $^{13}CO_2/^{12}CO_2$ ratio is estimated; it is this ratio that provides a quantitative indicator of *Helicobacter pylori* infection. Since other urease-producing bacteria are seldom found in the gastric flora, the detection of $^{13}CO_2$ in the breath above a certain limit is indicative of the presence of duodenal *Helicobacter pylori* infection.

Clinical data supporting the safety and efficacy of this product consists of one trial in 600 patients using equipment that is different from that proposed for marketing, a supplementary study in 200 patients with the equipment that is intended for marketing and an extensive review of the literature. The specificity is approximately 90% in comparison to culture and histology. The clinical studies reported in the dossier used the LARA (Laser Assisted Isotope Ratio Analyser) system of analysis to analyse breath samples, although any other objectively qualified method may be applied, provided it is suitably validated for use with this product by a competent laboratory. None of the clinical studies performed with the product reported side effects due to ^{13}C-urea. In view of the fact that urea is intrinsically present in the body and only a small additional amount is to be administered in the form of this product, it is considered to be safe.

Although Pylori-Chek is a diagnostic test to detect Helicobacter pylori infection with acceptable specificity and sensitivity (approximately 90%), differential diagnosis with invasive endoscopic methods might be indicated in order to examine the presence of any other complicating conditions, e.g. ulcer, autoimmune gastritis and malignancies. It should also be kept in mind that the performance of the test will be affected by treatments which may interfere with Helicobacter pylori status or urease activity, e.g. antibiotics or proton pump inhibitors, and these restrictions are set out in the SPC.

The CPMP, on the basis of efficacy and safety data submitted, considered that Pylori-Chek showed adequate evidence of diagnostic efficacy and a satisfactory safety profile and therefore recommended that the Marketing Authorisation should be granted.

* This text is the Abstract of the complete EPAR

MABTHERA

International Non-proprietary Name (INN): **Rituximab**

Abstract*

On 2 June 1998, the European Commission issued a Marketing Authorisation valid throughout the European Union for the medicinal product Mabthera, which contains rituximab. This Decision was based on the assessment report and on the favourable opinion adopted by the Committee for Proprietary Medicinal Products (CPMP) on 28 January 1998. The Marketing Authorisation Holder responsible for this medicinal product is Hoffman-La Roche.

The approved indication is for the treatment of patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy. Detailed conditions for the use of this product are described in the Summary of Product Characteristics (SPC) which can be found in the EPAR and is available in all European Union official languages.

The active substance of Mabthera, rituximab is a chimeric mouse/human monoclonal antibody, which binds to a target protein- the antigen CD20 -located on the surface of specific white blood cells, the B-lymphocytes, thereby stopping the pathological growth of these cells.

Clinical trials were designed to investigate tumour response rate, duration of response, follow-up of response duration and time to progression. These studies showed that Mabthera had a good tolerability profile with a good response rate and a sufficiently prolonged duration of response. Additional follow-up data confirm that rituximab is beneficial in terms of efficacy and safety in the treatment of patients having stage III-IV follicular lymphoma and normally considered to be almost unresponsive to conventional chemotherapy.

The most frequent adverse reactions observed during treatment were a cytokine release syndrome with fever and chills, as well as mild hypotension and bronchospasm. Only mild common bacterial and viral infections were observed. Grade 4 haematological toxicity is infrequent as compared to conventional chemotherapy.

The CPMP, on the basis of the overall benefit/risk ratio considered that Mabthera showed a satisfactory safety profile and adequate evidence of efficacy and therefore recommended that the Marketing Authorisation should be granted.

* This text is the Abstract of the complete EPAR

EMEA vs Pharmaceutical Industry Football Match, Score 3:3
23 June 1998 at 20h00

EMEA Players: Eric Abadie, Paul Brown, Christoph Buchhierl, David Drakeford, Gerard O'Malley, Jose Felix Olla Maranon, Lamin Njie, Jean Louis Robert, Pasqualino Rossi, Per Sjöberg, Ziggy Springer, Jan Stevens, Achilleas Voutsas

EFPIA Players: Ernesto Bertarelli, Brian Deane, Anthony Faupel, Richard Horne, Hakan Mandahl, Bob O'Donnell, Anthony Pac-Soo, Mike Page, Stratos Pegidis, Jim Ritchie, Edwin Ruighaver, Stefan Schwoch, Craig Whitehead

Drawing on last year's success (5:1 in 1997) the EFPIA football team last night again attempted to dominate the game. The younger and increasingly versatile EMEA team however, resisted well to their fierce attacks and fought back successfully. EFPIA needed all CEO power available from a dynamic European Biotech company to secure the draw 3:3.

More (QMS) scorecards and performances are now awaited from EMEA within strict regulatory time frames, says EFPIA.

All monies contributed – albeit budgetary problems - reported from both teams - will go to a localDocklands charity (Woodlands Centre Trust).

Reporting from Mile End pitch

Fernand Sauer **Brian Ager**

ISDB/EMEA meeting on 26 June 1998 in London

On 26 June, 1998 a meeting took place at the European Agency for the Evaluation of Medicinal Products (EMEA), co-organised by the ISDB (International Society of Drug Bulletins) and the EMEA. This meeting was held to review the quality and usefulness of information routinely provided publicly by the EMEA since its inauguration in 1995, in particular through the European Public Assessment Reports (EPARs).

The meeting was attended by more than fifty persons, including CPMP members and CPMP experts, representatives of National Competent Authorities, ISDB members, consumer organisations and networks, representatives of professional journals, WHO, as well as by EMEA staff members. It was chaired by J. Collier (ISDB) and R. Bass (EMEA).

The EMEA presented and clarified the principles on which its transparency is developed, based on legal requirements and internal initiatives: organisation of various workshops, adoption of *rules on access to documents of the EMEA*, EMEA internet web site to facilitate circulation of documents, etc.

ISDB presented basic requirements when informing patients and health professionals on medicinal products, addressing in particular key points to consider when assessing critically the benefit/risk value of these products. Both ISDB and EMEA recognised that patient's information must lead the efforts of transparency.

ISDB provided an in-depth analysis of nine EPARs, regarding their formats and their scientific contents. The results of this work will be circulated and used at CPMP/EMEA level in order to improve the process leading from the assessment reports to the EPARs. This evaluation will be utilised in an existing project to develop a new EPAR template later this year.

Information on the Mutual Recognition Facilitation Group, established in March 1995, was provided by its current Chairman, Dr. Jefferys, on the efforts to achieve more visibility and, where possible, more transparency. The fundamental role of the National Competent Authorities regarding communication on mutually recognised medicinal products will be discussed during an ad hoc workshop in the fall.

The EMEA presented an overview of the different provisions regarding the information related to pharmacovigilance, including in crisis situations. A particular consideration was made on the difficult balance between the objective of early access to safety information and the risk of unnecessary alarm and possible bias in the review process.

In conclusion, the attendees agreed on the need for EMEA information to be trustworthy, clear, updated, complete and coherent, the main objectives being adequate information on medicinal products to patients and health professionals. EMEA will achieve these objectives in collaboration with all interested parties, including ISDB.

MRFG
Mutual Recognition Facilitation Group

Report from the meeting held on 22nd June 1998

The MRFG noted that 11 new mutual recognition procedures have been finalised during the month of May 1998 as well as 22 type I and 17 type II variations.
The status as of 31st May 1998 of procedures under mutual recognition is as follows:

Year	Procedures from New applications finalised	Procedures from New applications in process	Procedures from Type I variations finalised	Procedures from Type I variations pending	Procedures from Type II variations finalised	Procedures from Type II variations pending	Arbitrations referred to CPMP
1998	65	58	100	46	78	112	1 var.

18 new procedures (regarding 29 products) have been started in May 1998. The categories of these procedures are as follows:

New active substance[1]	Line extensions[2]	Fixed combinations	Generics	Herbal products[3]	OTC[4]	Others[5]
3	1	3	5	0	1	5

1. When in one of the involved Member States it concerns a new active substance according to the definition in the Notice to Applicants Part IIA;
2. Line extensions are those applications which extend a range of products, e.g. an additional strength, or a new pharmaceutical form from the same Marketing Authorisation Holder;
3. In this category products are classified as herbals when the RMS has considered them as herbal product;
4. In this category products are classified as OTC products when the RMS has approved it for OTC use, although the legal status is not part of the Mutual Recognition Procedure;
5. When the product is not classified in the previous six categories.

Each application can be classified in only one category.

Number of countries involved in the started new applications procedures in May 1998:

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
DE (3)	2
DK (2)	5
DK (1)	5
FI (1)	4
FR (1)	14
FR (2)	10
IR (1)	5
NL (1)	6
NL (1)	3
SE (2)	1
SE (1)	13

SE (1)	12
SE (1)	12
SE (1)	2
UK (1)	2
UK (1)	7
UK (2)	10
UK (2)	10

General issues

- The MRFG agreed on improved version of the Breakout Protocol Document which should further help to reduce withdrawals and enhance the operation of the procedure. The revised document is attached to this Press Release and is published on the MRFG web site. The new time lines will be used for new procedures commencing from the 1st July 1998.

- Following the adoption of the revised variations regulations the MRFG agreed a procedure for the automatic validation of Type I variations. A copy of this revised protocol which will be used from the 1st July is attached to the Press Release and is also available on the web site.

- The group received a further report from its EudraTrack subgroup and noted the encouraging further use of the system. A list of possible future enhancement was noted.

- The group held a productive wide ranging discussion with the three trade associations EFPIA, AESGP and EGA. A further liaison meeting will be held in October.

- The June meeting was the last under the UK Presidency. Austria will take over the Chairmanship from the 1st July and Dr. Christa Wirthumer Hoche will become the chairperson. She should be contacted in future for details of the MRFG procedure and for information about press releases.

Information on the above mentioned issues can be obtained by the presiding chair of the MRFG:

Dr David Jefferys
Medicines Control Agency
Market Towers
1 Nine Elms Lane
UK - London SW8 5NQ
Phone: +44.171.273.0454 or
+44.171.273.0451

From the 1st July 1998:

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*or you could visit the **MRFG web site** at the EUROPEAN NATIONAL MEDICINES AUTHORITIES WINDOW:*

http://heads.medagencies.org/

Annex to the MRFG Press Release

REVISION 1

MUTUAL RECOGNITION FACILITATION GROUP BREAK-OUT SESSION PROTOCOL

MRFG agreed at it's June meeting that from the beginning of July this protocol will be in operation and reviewed after 6 months

1. INTRODUCTION

In order to facilitate discussion of serious public health concerns by Member States, meetings, referred to as break out sessions, can be arranged. These meetings are to be considered as exceptional within the MRP, are not routinely required for every procedure and will take place when considered necessary and useful by the member states involved. When appropriate, applicants may be requested to attend.

2. OBJECTIVE OF BREAK-OUT SESSION

The objective of the Break-out session is :

- to provide a structured forum for interaction between representatives from the RMS and all of the CMS with a view to enabling them through negotiation to find agreement on the points of public health concern and the SmPC.

The break-out session may also provide an opportunity for the applicant company, if requested, to further explain outstanding issues to concerned member states.

3. PARTICIPANTS

The participants should include the Reference Member State (RMS) who should chair the discussions and representatives from all CMS and as necessary, from the applicant company. The RMS and CMS where possible should be represented by the relevant assessors/experts of the application. Full use should be made of video or tele-conferencing facilities, if available, in order to facilitate the participation of the different member states.

When a CMS cannot send a representative, or in the case of full agreement when a CMS does not need to attend, the RMS should be informed prior to the meeting. In these cases, the RMS has to be informed by fax at least one working day before the meeting, and a contact name and telephone number for the CMS should be provided.

The applicant company should be represented by not more than five persons in total; a list of the names of proposed attendees representing the applicant should be sent to the RMS and the EMEA-Human Unit - the week before the meeting.

Other Member States with an interest or concern in the particular product, the active substance or the therapeutic area in question should be permitted to attend the meeting.

4. TIMING

4.1 New Applications

Break-out sessions, when required, will normally be arranged around Day 75 of the procedure.

- At Day 55 CMS will inform the RMS of their concerns and will indicate if any of the public health concerns are negotiable (e.g by SmPC changes).

- By Day 68 the RMS will confirm the need for a break-out session circulating an agenda, and its expected length of time. Where appropriate, extended break-out sessions will be held to permit full discussion of the issues.

- Where a CMS has raised public health concerns and would find it helpful, it may hold a bilateral meeting with the applicant for discussion and/or explanation of the serious public health issues which have been raised. The RMS and CMS will be informed of the outcome of meeting prior to or at the break-out session or by Day 75. Bilateral meetings may also be held after Day 75, keeping the RMS and other CMS fully informed.

4.2 Variations

Break-out sessions for Type II variations are not required routinely, but may be necessary in some cases, for example when adding a new indication or agreeing new safety information.

The exact timing of a break-out session will be dependent upon the individual situation for an application, but the following possibilities exist :

- At Day 30, in rare cases for difficult emerging situations identified by the RMS ahead of circulation of preliminary VAR (at Day 40).

- During clock-off period, after receipt of supplementary information from the company and before circulation of finalised VAR (at Day 60).

- At Day 75, ahead of CMS notifying acceptance/non-acceptance of VAR decision (at Day 85). The RMS will restart the clock (Day 60) by circulating the VAR at an appropriate time point in relation to the next MRFG meeting.

The RMS will choose the most relevant situation appropriate for the nature of the variation.

5. REQUIREMENTS FOR APPLICANTS

Applicants will receive the CMS points when available or by day 56.

Applicants will provide their responses to CMS and RMS, on day 65.

Applicants should arrive at the EMEA premises no earlier than half an hour before the break-out session, checking in at the reception on the 4th floor. Applicants should then leave the EMEA as soon as the break-out session is ended, checking out at the EMEA reception.

Although applicants attending EMEA for the break-out session should be aware that they may not be required to participate in the session, they may be asked to agree amendments to SmPC or to answer questions from the Member States. It is, therefore, beneficial if applicants attend EMEA. Applicants should ensure that their representatives are able to take decisions on amendments to SmPC's being proposed by member states.

6. MEETING OUTLINE

The meeting should be conducted in three parts as follows,

- a discussion, aimed at resolving differences, between member states,
- as necessary the applicant will be asked to join the meeting to respond to outstanding issues. The company should not give general presentations,
- a wrap-up discussion between member states.

The RMS and CMS should have a discussion aimed atresolving, if possible, some or all of the outstanding issues and then prioritising any remaining issues. An agreed approach to the questioning of the applicant should be informally defined by the member states before inviting the applicant to participate.

The RMS should start by introducing the representatives of the member states present to the applicant company and invite the company to do likewise.

The RMS should then identify the outstanding issues of concern to the applicant. When the applicant has been informed that he should be prepared to give a presentation, a time limit for this will have been set. Upon completion of the questions and discussion the applicant should be informed that they will be notified by the RMS about any residual issues.

Following the departure of the applicant from the room the member states should then continue their discussions on the outstanding issues, with a view to trying to reach agreement where possible.

7. MEETING SUMMARY REPORT

A brief summary report of the break-out meeting should be prepared by the RMS as soon as possible after the meeting has finished . The report should be copied to the chairman of the Mutual Recognition Facilitation Group (MRFG), the Mutual Recognition liaison person at the European Medicines Evaluation Agency (EMEA) and all CMS whether present at the meeting or not.

Outcomes of all break-out sessions will be monitored by MRFG.

22nd JUNE 1998

REVISION 1

PROCEDURE FOR VALIDATION OF MUTUAL RECOGNITION PROCEDURES FOR VARIATIONS

An automatic validation procedure for new applications was agreed at MRFG with effect from 1 May 1998, for a 6 month trial period. Whilst experience is gained from this procedure, the following arrangements apply for variations.

Completion of Eudratrack records by all member states is essential for the operation of the procedure (see Behaviour Code for RMS and CMS).

- **Type I Variations**

  Note: The new Variation Regulation amendments (EC no 1146/98) do not require the CMS to notify the RMS of the receipt of the application. RMS will notify the start of procedure.

Procedure to follow (effective from 1 July 1998):

Submission of Variation application simultaneously to RMS and CMS by **applicant**.

The **applicant** should fax in a single document to the RMS and CMS all the despatch dates of the variation application when despatch is complete, and state that the relevant national fees have been paid.

RMS completes Eudratrack record.

RMS notifies applicant and CMS of procedure start date. This is Day 0.

- **Type II Variations - Majority of applications where change request is initiated by the applicant**

Existing arrangements for validation apply. See Notice to Applicants.

CMS should notify receipt of a valid/invalid application within 10 working days. Complete Eudratrack record.

Note: Experience from the automatic new application procedure will be gained before implementing for Type II variations.

- **Type II Variations - Where RMS identifies a safety need (including safety changes at the initiation of the applicant)**

  Note: Examples of such Type II safety variations are

  - Type II variations submitted following the introduction of an Urgent Safety Restriction.
  - Changes to the SPC involving safety information eg contraindications, warnings, undesirable effects.

Procedure to follow (effective from 1 June 1998):

Submission of Variation application simultaneously to RMS and CMS by **applicant**.

The **applicant** should fax in a single document to the RMS and CMS all the despatch dates of the variation application when despatch is complete.

RMS completes Eudratrack record.

CMS to confirm receipt by updating the Eudratrack record.

If after 5 working days of notification of application despatch, some or all confirmations of receipt are still lacking, the **RMS** will notify (initially by fax) the CMS who have not sent their confirmation of receipt (completed the Eudratrack record) that the clock will start at the end of the next 5 working day period unless notification of an invalid application is received.

RMS notifies applicant and CMS of procedure start date. This is Day 0.

If a CMS has previously informed the RMS that the application is not valid, the clock will be started when that **CMS** informs the RMS when the application is valid.

The **CMS** must inform the RMS that the application has become valid within 5 working days of the missing information being supplied.

June 1998