The new CMD(h)
- a chance for reaching agreement in MRP and DCP?

Wissenschaftliche Prüfungsarbeit

zur Erlangung des Titels

„Master of Drug Regulatory Affairs“

der Mathematisch-Naturwissenschaftlichen Fakultät
der Rheinischen Friedrich-Wilhelms-Universität Bonn

vorgelegt von

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Bonn 2007

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List of Abbreviations

AR	Assessment Report
BE	Bioequivalence
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
CP	Centralised Procedure
CPMP	Committee for Proprietary Medicinal Products
CHMP	Committee for Medicinal Products for human use
CMD(h)	Coordination Group for Mutual Recognition and Decentralised Procedures (human)
CMD(v)	Coordination Group for Mutual Recognition and Decentralised Procedures (veterinary)
CMS	Concerned Member State(s)
DCP	Decentralised Procedure
EC	European Community
EEA	European Economic Area
EFTA	European Free Trade Association
EMEA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
FAQ	Frequently Asked Questions
HEVRA	Heads of Veterinary Regulatory Agencies
HMA	Heads of Medicines Agencies
HoA	Heads of Agencies
HMPC	Committee on Herbal Medicinal Products
HMPWG	Homeopathic Medicinal Products Working Group
MAH	Marketing authorisation holder
MS	Member State(s)
MRFG	Mutual Recognition Facilitation Group
MRP	Mutual Recognition Procedure
RMS	Reference Member State
PAR	Public Assessment Report
PI	Product Information
PrAR	Preliminary Assessment Report
PL	Package Leaflet
PSRPH	Potential Serious Risk to Public Health
PSUR	Periodic Safety Update Report
Q & A	Questions and Answers
SOP	Standard Operation Procedure
SPC	Summary of Product Characteristics
VMRFG	Veterinary Mutual Recognition Facilitation Group

1. Introduction

The so-called Review of pharmaceutical legislation was published on 30 April 2004 in the Official Journal. This new legislative package included among others the Regulation 726/2004/EC and Directive 2004/27/EC [1, 2]. The new Regulation replaced 2309/93/EC and describes the Centralised Procedure (CP), the supervision of medicinal products for human and veterinary use and establishes the European Medicines Agency (EMEA). The Directive 2004/27/EC amended Directive 2001/83/EC and contains many new provisions for getting a marketing authorisation via the Mutual Recognition Procedure (MRP) and the new Decentralised Procedure (DCP) in the European Union (EU).

Regulations and Directives are legally binding acts. The difference is that Regulations are directly applicable in all Member States (MS), whereas Directives have to be transposed into national laws [3]. The most parts of Regulation 726/2004/EC entered into force on 20 November 2005, whereas the MS had time to publish corresponding national acts to implement the Directive 2004/27/EC by 30 October 2005.

Germany implemented the Review on 6 September 2005 with the 14th amendment to the German Drug Law and was therefore one of the first MS. Most countries were not able to transpose the new provisions on time, e.g. Portugal published the new law on 30 August 2006 and some MS like France have not been able to implement the complete Review up to now [4].

Until the new legislation came into force it was possible to withdraw the application for a marketing authorisation without any consequences at any time during the MRP, even if that MS raised a potential serious risk to public health.

In practice the MS often did not recognise the marketing authorisation and the scientific evaluation carried out by another MS. Once objections of public health had been raised, it was difficult to reach agreement between the dissenting MS [5]. To avoid the time-consuming article 29 referrals the applications in the disagreeing countries were withdrawn so that the remaining CMS (Concerned Member States) and the RMS (Reference Member State) could reach agreement on day 90 of the MRP [5].

As all MS of the EU have implemented the Community pharmaceutical legislation which harmonised the standards for quality, safety and efficacy, this procedure was regarded as not being acceptable. If there is a potential serious risk to public health, the medicine should not be placed on any market in the EU as the primary purpose of the laws on medicinal products is to safeguard public health [6].

The European Commission report on the “evaluation of the operation of community procedures for the authorisation of medicinal products” also stated that the process of withdrawing the disagreeing member states “leads to delays in resolving issues that may raise legitimate health concerns” [7].

However the Directive also mentions that “this objective [the public health] must be achieved by means which do not hinder the development of the pharmaceutical industry” and therefore if no real risk to the patients exists, the free movement of medicinal products in Europe should not be avoided by MS which sometimes claim incomprehensible potential risks [6].

Based on Article 29(2) of Directive 2001/83/EC as amended the European Commission adopted a guideline that defines in which exceptional cases a member state can refuse to recognise a marketing authorisation (MRP) or a positive assessment (DCP) on the basis of a potential serious risk to public health [8].

The Review also established the Coordination Group for Mutual Recognition and Decentralised Procedures (human) (CMD(h)) which is responsible to settle the disagreements arising in the MRP or in the new DCP [3]. If a MS raises grounds for supposing that the authorisation of the medicinal product concerned may present a potential serious risk to public health, the procedure will now be referred to the CMD(h). The withdrawal of an application is still possible, but once a potential serious risk to public health has been raised during the 90 days in the MRP or the assessment phase II in the DCP, the issue will be referred to the CMD(h) [9]. If the MS fail to reach agreement in the group, an arbitration procedure will be initiated, leading to a single decision on the area of disagreement and binding on the MS concerned [6].

The next parts will focus on the tasks, composition and transparency measures of the CMD(h) and the difference to its predecessor MRFG (Mutual Recognition Facilitation Group). After a short description of the procedures that lead to referral to the coordination group and the 60-days CMD(h) procedure itself, a statistical evaluation of the number and reasons of new CMDs, outcome of the 60 days procedure and the cases that have to be referred to arbitration, will follow. Last but not least the advantages and disadvantages of the new group will be discussed and also proposals for improvement considered.

It should be mentioned that the MRP and DCP is mainly used by the generic industry and so the CMD(h) discusses in the majority of cases issues concerning abridged applications. Therefore this thesis will focus on generic medicinal products.

2. The old Mutual Recognition Facilitation Group

In 1995 the MRP was established. The MS recognised early that there needed to be a group that could coordinate and facilitate the operation of the procedure [10]. Although there was no legal basis in the European legislation, the so-called MRFG was established by the MS in March 1995 and held its first meeting three months later [10].

The group was made up of delegates from the EU, Iceland and Norway who met at the EMEA in London. Observers from the European Commission and from accession countries could participate in the monthly meetings.

The MRFG was chaired by the country which held the presidency of the EU and reported regularly to the Heads of Medicines Agencies [10].

The MRFG translated legal interpretations into practical recommendations, provided a forum to reach a common understanding of the procedures and coordinated the positions of MS on topics concerning the MRP. Furthermore they published best practice guides, for example the “best practice guide for mutual recognition procedure” and a series of procedural documents on the

website [10, 11]. The press release that was issued after each meeting, gave a summary of the new procedures and the issues that were considered [10].
Furthermore the European tracking database (Eudratrack), which allows the MS to follow the progress of all MR applications and variations, was initiated by the MRFG. The statistical information in the press releases is generated by that database.
It should also be mentioned that the unofficial group developed the Mutual Recognition Index (Product Index) which contains a list of products that were approved via MRP and also includes DCPs in the meantime.
The MRFG held regular meetings with the industry trade associations.
The veterinary section had a similar group called VMRFG (Veterinary Mutual Recognition Facilitation Group) and a close link had been established between MRFG and VMRFG [10].
For a report on the evaluation of the procedures carried out on behalf of the European Commission, the marketing authorisation holders (MAHs), regulatory authorities and trade associations were asked about the benefit of the MRFG [7]. According to this survey, 85% of the respondents considered that body to be useful, which shows that the MRFG had established itself as a major player in the European system.
However the lack of a legal basis and the fact, that the MRFG could not discuss scientific problems related to individual applications were recognised as a clear disadvantage for solving issues in MRPs.
The MRFG held its last meeting in October 2005 [12].

3. The new Coordination Group for Mutual Recognition and Decentralised Procedures

The evaluation of the operation of the MRPs revealed the need to improve the opportunities for cooperation between MS.
Therefore with the revision of Directive 2001/83/EC, the already existing group MRFG became an official status and was renamed to CMD(h).
The first CMD(h) meeting took place on 14 November 2005.
With the Review also the VMRFG was renamed in analogy as CMD(v) (Coordination Group for Mutual Recognition and Decentralised Procedures veterinary). In the following parts only the tasks and functions of the coordination group for human medicinal products will be described.

3.1 Composition and general rules

The coordination group is composed of one representative per EU MS, who is appointed for a period of three years, which may be renewed. The EFTA (European Free Trade Association) states Norway, Iceland and Liechtenstein could also nominate one representative for the CMD(h) for a period of three years [13].

The national competent authorities send regulatory and/or scientific experts, who should have sufficient authority to outline final positions and confirm their regulatory authority's intention to implement the final outcome.

According to article 27 of Directive 2001/83/EC as amended the CMD(h) made its own rules of procedure that were agreed in the group on 15 November 2005. Two days after the European Commission gave a favourable opinion the rules entered into force on 20 February 2006, and have been made public [13].

As already mentioned, the old MRFG was chaired by the country which held the presidency of the EU and therefore every six months a new person was appointed. For a better consistency of decisions this procedure has been changed with the new legislation. Therefore the chairperson of the CMD(h) has to be elected by and from amongst its members for a period of three years which could be renewed once. It should be mentioned that only the representatives of the EU and not of the EFTA states can be elected. An absolute majority of the members is necessary for the election of the chairperson by a secret ballot. At each round, the candidate with the lowest number of votes has to withdraw [13]. If only two candidates remain and an absolute majority for one CMD(h) member is not reached, then additional rounds of voting take place with the two remaining candidates, if it is likely that an absolute majority vote could be achieved. If this is not considered feasible a further voting is held with the candidate who has received the highest number of votes in the latest round only. This candidate is elected chairperson if he/she receives a majority of votes [13].

At the inaugural CMD(h) meeting in November 2005, Mrs Truus Janse-de Hoog from the Medicines Evaluation Board of the Netherlands was elected as chairperson. As the chairperson loses the right to vote, another representative from the Netherlands was appointed to replace Mrs Janse-de Hoog as a member of the CMD(h) [13].

The vice-chairperson changes regularly, as he or she is appointed from among the members of the coordination group by that MS which has the presidency of the Council of the EU [9]. Therefore the CMD(h) meeting in December 2006 was the last one under the Finnish presidency. Dr. Peter Bachmann from the BfArM (Bundesinstiut für Arzneimittel und Medizinprodukte) has been appointed as vice-chairperson of the CMD(h) in January 2007, as Germany took over the presidency [14]. The vice-chairperson will replace the chairperson in his/her absence, but in this case he/she is not allowed to vote, i.e. the vote will be transferred to the member of his/her authority who attends the meeting[13].

The chairperson in collaboration with the vice-chairperson will be responsible for the efficient conduct of the business of the CMD(h), for example by ensuring constancy of agreement, management of the meeting with the conclusion on all items of the discussions and the regularly liaison with the EMEA secretariat to plan the work of the CMD(h). Furthermore the chair- and

vice-chairperson should monitor the compliance with the rules of procedure and should ensure that the best possible advice on regulatory issues is given [13, 15].

The CMD(h) meets normally once a month at the EMEA. The heads of the national competent authorities, the EMEA Executive Director, members of the EMEA secretariat and representatives of the Commission, could join all meetings of the CMD(h). Furthermore the Heads of Medicines Agencies (HMA) may propose that the coordination group invites representatives of international organisations as observers who are interested in the harmonisation of regulations applicable to medicinal products [13].

When a member of the coordination group is not able to attend a meeting, her or his place could be substituted by another representative of that country.

The members could be accompanied by further experts, who should be notified to the chairperson and the secretariat before the meeting. If further experts are needed in a particular field, the CMD(h) itself could request the contribution of further scientific specialists [13].

The members of the group and also all involved experts and observers have to disclose any information which is regarded as being confidential. This also applies after the cessation of their duties.

The CMD(h) shall only adopt agreements if at least two thirds of the members are present. The only exception is for applications for marketing authorisations or referrals in MRPs or DCPs where consensus is needed, as set out later. Each member has one vote [13].

It is recommended that agreements on the list of products for harmonisation, guidelines, SOPs (Standard Operation Procedures), recommendations, procedural or regulatory practices or position statements are reached by consensus. If no consensus could be found, they are deemed to be adopted if the absolute majority of the members of the CMD(h) support the issue. That means that statements could not be published in the absence of a majority position of the group [13].

According to article 11 of the rules of procedure of the CMD(h) urgent measures could be adopted by the written procedures between two meetings of the group, e.g. the adoption of draft agreements previously discussed by the CMD(h) or the implementation of measures adopted earlier. At the next meeting a report on the outcome should be given. Draft agreements are addressed to members of the CMD(h), who may demur within a given time period, to be established in agreement with the chairperson. If serious objections are raised, it is the decision of the chairperson whether the written procedure should be suspended and the adoption of the draft statement postponed to the next meeting of the coordination group [13].

Advice from the CMD(h) should be referred to the HMA if the issue is considered to be in the interest of the Community. The HMA should also be involved in cases that concern resources, policy or if a considerable national impact is possible [13].

The working language of the CMD(h) is English.

The secretariat is provided by the EMEA in London [17]. The CMD(h) secretariat proposes the agenda for each meeting to the chairperson, circulates all documents in due time and prepares the table of decisions and minutes of each meeting. Moreover the secretariat sets up and maintains a database that lists all regulatory and scientific agreements, and so it is possible to provide a list of positions taken on similar issues for each discussion in the CMD(h). That enables consistency of decisions. Another task is the assistance of the chairperson in the

preparation of the annual reports and of press releases that include monthly statistics about MRPs and DCPs [17]. The secretariat should also facilitate the liaison with EMEA Committees, working groups and interested parties and the contacts between the CMD(h) and the MAH. In case of referrals to the CMD(h), the secretariat proposes the timetable for the 60 days procedure to the chairperson and the RMS and also informs the CMD(h) members and the applicant in advance of the procedure. Moreover the applicant should be notified of the agreed list of questions and the information about the details concerning the organisation of an oral explanation. The secretariat assists the chairperson to monitor compliance with the official time periods in relation to referrals to the CMD(h). It should be mentioned that the secretariat is also involved in the contacts with representative organisations, as they send out invitation letters for meetings, together with the proposed agenda and a request to identify other potential points that should be discussed. Afterward the minutes will be produced and distributed to all participants[17].

3.2 Tasks

3.2.1 Tasks according to the legislation

The articles 27(1), 29(1), (3), (4) and 30(2) of Directive 2001/83/EC as amended specify the following tasks of the CMD(h):

Article 27 (1)
"A coordination group should be set up for the examination of any question relating to marketing authorisation of medicinal product in two or more member states." [6]

Article 29 (1), (3) and (4)
"If … a member state cannot approve the assessment report, the summary of product characteristics, the labelling and the package leaflet on the grounds of potential serious risk to public health, it shall give a detailed exposition of the reasons for its position to the reference member state, to the other member states concerned and to the applicant. The points of disagreement shall be forthwith referred to the coordination group.
Within the coordination group, all member states … shall use their best endeavours to reach agreement on the action to be taken.
If the member states fail to reach an agreement within the 60-day period… the Agency shall be immediately informed, with a view to the application of the procedure under Articles 32, 33 and 34. "[6]

Article 30 (2)
"In order to promote harmonisation of authorisations for medicinal products authorised in the Community, member states shall, each year, forward to the coordination group a list of medicinal products for which a harmonised summary of product characteristics should be drawn up.
The coordination group shall lay down a list taking into account the proposals from all MS and shall forward this list to the Commission." [6]

3.2.2 Description of the tasks

According to Article 27 of Directive 2001/83/EC as amended the coordination group is "set up for the examination of any question relating to marketing authorisation of a medicinal product in two or more member states" in the MRP and DCP and is, according to the Notice to Applicants, "responsible for the smooth functioning and good outcomes of the MRP and DCP with a mix of regulatory and scientific work" [6, 9]. This definition covers a variety of tasks, which will be described in the following part.

One of the main tasks of the coordination group is to address procedural scientific issues arising from the DCP and MRP. In the case of disagreement between MS during the procedure in relation to the assessment report, the SPC (Summary of Product Characteristics), labelling and PL (package leaflet) of a medicinal product on the grounds of a potential serious risk to public health, the matter will be considered by the CMD(h) [6]. The discussion in the coordination group was introduced as the evaluation of the operation of the MRP revealed the need to improve the opportunities for cooperation between the MS and the old MRFG had no mandate to consider issues with individual applications [3]. The involved countries should use their best endeavours to find a solution, but in the exceptional case that the CMD(h) is unable to reach agreement, the matter has to be referred to the EMEA for arbitration [6]. The goal is to solve the majority of issues and avoid article 29 referrals [16].

This procedure is applicable for new applications, extensions, repeat use and renewals [16].

Another task is the facilitation of dialogue between the MS through meetings and oral explanations in particular procedures and the provision of a forum to discuss any difficulties and seek for solutions [9].

Furthermore the group should facilitate the resolution of procedural and scientific issues arising from variation and renewal procedures, so that the harmonisation of marketing authorisations could be maintained after completion of a MRP and DCP or following referral [9].

According to article 10 of the rules of procedures the coordination group will provide advice for pharmaceutical companies or EEA (European Economic Area) MS, if the submitted question is not addressed in a guideline [13]. It should be considered that the CMD(h) will only deal with procedural and regulatory questions on MRPs and DCPs, as scientific matters should be referred to the EMEA. Moreover general scientific issues that relate more broadly to medicinal products could be answered by the national competent authorities, the CHMP (Committee for Medicinal Products for human use), its working parties or the HMPC (Committee on Herbal Medicinal Products) [16].

The CMD(h) released a question and answer document that describes the procedure and criteria for a request for advice [28]. Each issue should first be discussed with the national competent authority, which could bring the matter to the attention of the European group if a harmonised view in the EU is necessary. After the final discussion at the CMD(h) meeting, the answer will be provided by the secretariat or by the CMD(h) member who has forwarded the matter to the coordination group. If the discussed issue is also important for other applicants or MAHs, a "question and answer" document will be published on the CMD(h) website [28].

Furthermore the coordination group creates a list of medicinal products for which the SPC should be harmonised across the Community [9]. The list should take into account proposals from

MS and has to be forwarded to the Commission once a year [16]. The Commission or a MS, in agreement with the EMEA, could refer these medicinal products to arbitration [6].

The CMD(h) subgroup on harmonisation of SPCs has endorsed at the January 2006 CMD(h) meeting the criteria for the selection of products for SPC harmonisation [18, 19]. According to this published document differences in core parts of the SPC (sections 4.1 – 4.4), extent of the use of the product, number of EU countries where the product is authorised and the exclusivity and patent expiry dates should be taken into account for choosing the active substances. The last mentioned criterion is important for the authorisation of generic medicinal products. Harmonised texts should be available before the start of the MRP or DCP as agreement in the procedure is difficult if the originator SPC is different in the involved MS. The time for an article 30 referral should also be considered. The interest of originator companies to finish this forced procedure early is very low, as a harmonised product information could facilitate the approval of generic products.

The CMD(h) published a list with proposals for medicinal products for SPC harmonisation, which included for example the active substances losartan, ramipril and cetirizine [20]. The sub-group on harmonisation of SPCs discussed the received comments from interested parties [14]. According to the CMD(h) meeting report from January 2007 the CMD(h) concluded that no change was required and therefore the final list will be sent to the European Commission [14].

Prior to the start of the Article 30 procedures, the concerned MAHs will be invited for pre-referral meetings [14].

Another task of the group is the identification of issues which should be referred to the Commission, the Pharmaceutical Committee, the HMA and other appropriate bodies.

The CMD(h) works in close cooperation with the Pharmacovigilance Working Party (PhVWP) of the CHMP, to take forward recommendations for risk management for products approved through the MRP and DCP [9]. The coordination group also discussed the work sharing of PSURs (Periodic Safety Update Reports) across the MS and coordinated the synchronisation of birth dates [21].

Furthermore the CMD(h) should develop and regularly update guidelines, SOPs, and recommendations for member states, applicants and MAHs, respectively. If the group identifies the need for the development of a new guideline or the revision of an already existing one, the matter will be communicated to the EMEA [16].

The interpretation and implementation of Directives and Regulations often differs in the MS. Therefore the CMD(h) presents a harmonised view in order to facilitate the handling of procedures. The coordination group should for example control the practical application of the raised potential serious risks to public health taking into account the guideline that was adopted by the Commission which provides a definition and also the legal reasons for the refusal, suspension or revocation of an application or marketing authorisation according to the articles 26 and 116 of Directive 2001/83/EC as amended [16]. The agreed interpretation of the guideline on a potential serious risk to public health should be the basis for the referral of an application to the 60-days CMD(h) procedure and to arbitration [13].

The CMD(h) could create ad-hoc temporary working parties for the realisation of special projects, e.g. for the product information management or the harmonisation of SPCs. In this case the CMD(h) appoints the chairperson and members, that should preferably be from of the

coordination group but could also include representatives of any of the EMEA Committees or its working parties. Moreover national agencies can propose other experts. It is also possible that joint human-veterinary working parties take place, depending on the topic. Only one delegate per EEA MS should participate in the working parties, either a member of the CMD(h) or another specialist. However additional experts could also attend the meeting if is required by the agenda[13]. The coordination group adopts the mandate and goals of each working group, e.g. the "mandate for the CMD(h) sub group on harmonisation of SPCs" and also the duration of their activity [13, 18]. The tasks of new established working groups of the CMD(h) should not overlap with the work of already existing ones. The draft agenda of each meeting and also the written minutes of any working party should be distributed to all CMD(h) members as soon as possible. Companies or other interested parties could give oral presentations during the working party meetings in agreement with the CMD(h) [13].
Last but not least the CMD(h) will encourage and facilitate the approval of SPCs that reflect the current scientific knowledge and improve the quality of package leaflets by following the readability guideline of the European Commission [16, 25].

4. Differences between MRFG and CMD(h)

With the Review of pharmaceutical legislation the CMD(h) was established. The group also consists of representatives from MS like its predecessor MRFG and should improve the cooperation and discussion between the countries. Nevertheless there are a view important differences between MRFG and CMD(h) that will be compared in table 1.

	MRFG	CMD(h)
Legal basis	Informal group, no legal basis	Legal basis in Directive 2001/83/EC as amended
Scope	Coordination and facilitation of the operation of the MRP	Wider scope as the MRFG - to examine any question related to authorisation of medicinal products in more than one MS
Scientific discussion on particular applications	Only regulatory and procedural function; no scientific discussions	Mix of procedural, regulatory and scientific work; discussion of scientific problems related to individual applications; 60 days CMD(h) procedure
Composition	Delegates from the EU, Iceland and Norway	One representative from each MS, appointed for a renewable period of three years
Chairperson	Member of the country which holds the presidency of the EU	Elected by and from amongst the CMD(h) members for three years
Vice-chairperson	--	Appointed from among the members of the CMD(h) by that MS which holds the presidency of the Council of the EU
Transparency	Less transparency measures	Several transparency measures, e.g. publicly available “rules of procedure” and professional qualifications of each CMD(h) member

Table 1: Comparison MRFG – CMD(h)

5. Transparency

Transparency is a tool to improve the trust in the evaluation process of authorities and should also fulfil the expectations from patients, politicians and journalists to get objective information[22]. In the following parts the boundaries between confidentiality and transparency will be discussed. Furthermore the general measures for the MRP and DCP in comparison to the CP and the specific CMD(h) transparency policy will be described.

It should be mentioned that the CMD(h) decided to publish a position paper on its currents transparency measures that covers the press releases, guidance documents, questions and answers and the MRI-Product Index [14].

5.1 Comparison of transparency measures between CP and MRP/DCP

The EMEA has a long history of transparency measures and therefore many documents are publicly available on the website, e.g. the EPARs (European Public Assessment Reports) for medicinal products that have been authorised via the CP [23].

Also the Regulation 726/2004/EC includes more transparency measures than the Directive 2001/83/EC as amended. For example article 12.3 of the Regulation states that negative decisions and reasons in the CP should also be made publicly available, whereas no similar article could be found in the Directive for MR and DC procedures [1, 24]. Furthermore article 11 of Regulation 726/2004/EC concerns withdrawals: "if an applicant withdraws an application for a marketing authorisation submitted to the Agency before an opinion has been given on the application, the applicant shall communicate its reasons for doing so to the Agency. The Agency shall make this information publicly accessible and shall publish the assessment report, if available, after deletion of all information of a commercially confidential nature" [1]. This part is only applicable for the CP as the Directive 2001/83/EC as amended includes no similar article [26].

The strategy paper of the Strategy Implementation Group of the HMA states in section 3 (iii) "legal environment: transparency, commercially confidential information and conflict of interests" that it would be wishful to make such information also accessible for MRPs and DCPs if public health reasons are concerned [24].

The Review of pharmaceutical legislation includes many provisions to improve the transparency. Not only the EMEA, but also national regulatory authorities are required to provide information about the decision-making processes for the evaluation of medicinal products. According to article 21 of Directive 2001/83/EC as amended the national authorities have to make publicly available without delay the marketing authorisation and the SPC for each medicinal product [23]. Furthermore the assessment report for a new approved medicinal product and also the reasons for their opinion should be published after deletion commercially confidential information [6]. A justification has to be given for each applied indication.

The improved transparency measures are one of the challenging parts of the Review of pharmaceutical legislation as communication has to be directed to the pharmaceutical industry and also to health care professionals and the public.

The CMD(h) already took diverse measures to implement the legal obligations and increase the available information tools, e.g. CMD(h) and EMEA published their rules of procedure and information about their members, inform regularly about new developments and last but not least publish product specific information (e.g. the Public Assessment Report (PAR)) via the MRI Product Index [23].

The EMEA road map and also the HMA strategy paper address the transparency policy, which reflects the increased importance of that topic [24, 27].

5.2 Transparency versus confidentiality

Although there are obvious discrepancies between the Directive 2001/83/EC as amended and the Regulation 726/2004/EC concerning transparency, it is a general principle of the European Community law that information which could unfairly harm a competitor should not be publicly available [26]. For example the information that a particular generic company wants to launch a medicinal product that is not longer patent protected could lead to legal action by the innovator to avoid or delay the generic market entry, e.g. by purchasing of the API suppliers [26, 29].
Timing is often a major factor in order to determine whether information should be considered as commercially confidential or not. The disclosure of information before the decision could sometimes be critical, for example if a patent application is pending. Furthermore an independent scientific debate should not be avoided [26].
The determination whether certain information falls into the scope of commercially confidential is often difficult, as the European Union consists of different MS which have their own cultural and legal heritage. An EU specific guidance that addresses all issues that can or cannot be communicated to the stakeholders is not available. Therefore prior to the disclosure of information, the applicant should be consulted – if possible – which parts are considered to be commercially confidential, for example in the PAR, as the future MAH is the best person to judge[26].
Afterwards the authorities should decide if they follow the evaluation of the pharmaceutical industry concerning the confidential passages or make certain parts nevertheless publicly available, as it is the task of the national competent authorities to balance between the commercial interest of the company and the transparency for the public [26].

5.3 Transparency measures for the CMD(h) members

In comparison to the MRFG a few more transparency measures are foreseen for the CMD(h) [23]. So, the “rules of procedure” of the coordination group were published on the website. According to that document the membership and also the professional qualifications of each member shall be made publicly available [13].
According to the EU legal framework, the CMD(h) members and the European experts that participate in the work of the group shall not have any direct interests in the pharmaceutical industry which could affect their impartiality. The EMEA established a register listing all indirect interests which could relate to the pharmaceutical industry. The database could be accessed on request by the public at the EMEA office. The experts should also be independent and act in the public interest. They have to make declarations about their financial interests annually [13].
The EMEA policy on handling of conflicts of interest for Committee members and experts was adopted by the Management Board and is also applicable to the members of the CMD(h), working parties and further experts that support the work of the CMD(h) activities [13, 30].
The coordination group has agreed on a “guidance on contacts with representative organisation” which defines the scope and conditions of interactions with stakeholders which will be summarised later.

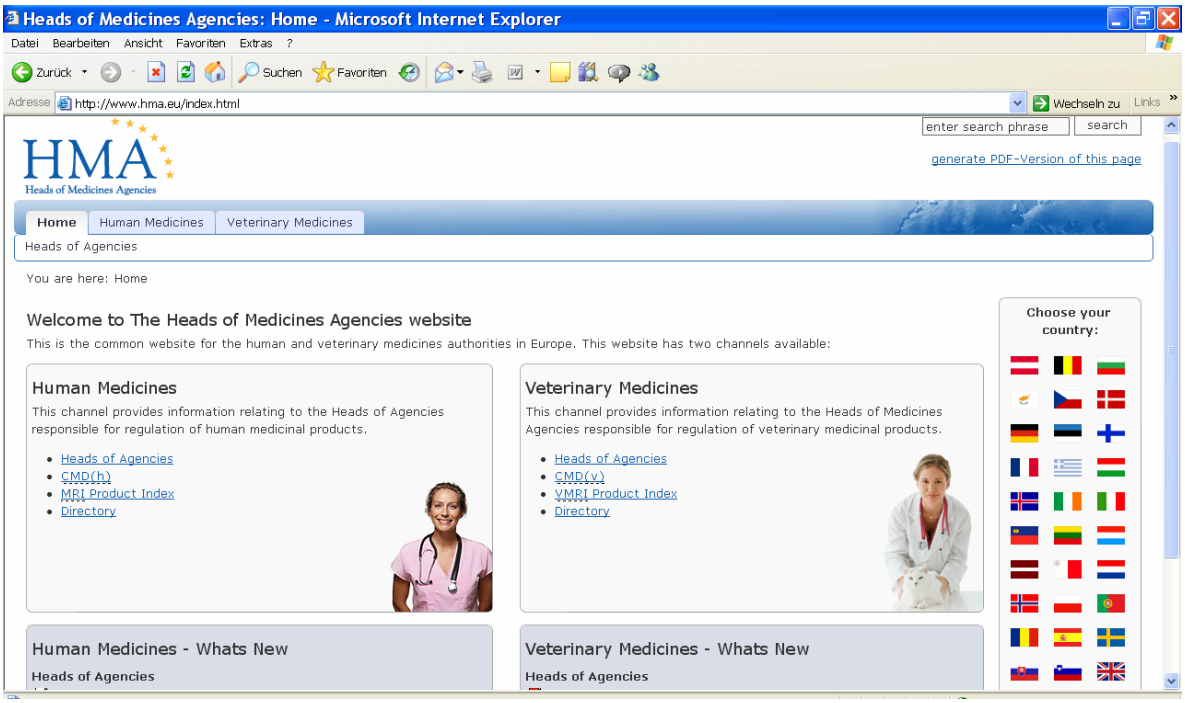
The discussion within the coordination group could lead to a potential conflict of interests for a participant. According to the "rules of procedure" of the CMD(h), it is the role of the chairperson and vice-chairperson to ensure that any potential conflict of interests is declared before any particular item is discussed by the CMD(h) [13]. Furthermore the person should remind in the meeting of his/her interests before the start of the discussion. To guarantee the independence of the group, he/she may be asked by the chairperson to leave the meeting for that discussion or only answer direct questions from the chairperson [13].

5.4 Websites of the HMA, CMD(h) and the MRI Product Index

5.4.1 The HMA website

The HMA is a European working forum of heads of human and veterinary regulatory authorities of the EU and the EEA states Norway, Iceland and Liechtenstein [31]. The group is a combination of the formerly called "Heads of Agencies" (HoA) and the "Heads of European Veterinary Regulatory Authorities for medicinal products" (HEVRA) [31]. The network discusses issues which are of Community interest and exchange views on the coordination and application of the pharmaceutical law [31, 32]. The HMA normally meets twice in each presidency [32].
In 2007 a new website (www.hma.eu) for the Heads of Medicines Agencies was established that is hosted by the BfArM. The screenshot 1 shows the start page.
The website consists of the human and the veterinary channel and of general information about the HMA that is applicable for all medicines.
On the start page a section for new documents for human and veterinary products is available and also general information about the HMA in all languages, together with a link to the national homepages of the competent authorities.
Further services for applicants and MAHs have been established. So, the new website consists of a search function, the possibility to subscribe to the newsletter, to generate pdf-versions of pages and to view the site map. Moreover links to the European/International bodies and institutions (e.g. EMEA, ICH), to interested parties (e.g. EGA, AESGP), to regulatory bodies worldwide (e.g. USA) and sites of scientific interest institutions (e.g. National Library of Medicine) are available.

From the first page links lead to the Heads of Agencies, the CMD(h)/(v), the MRI/VMRI Product Index and to the directory.
The directory includes the name, address, email and websites of all EU and EEA member states. The MRI Product Index and the CMD(h) webpage will be described later.



Screenshot 1: The start page of the HMA

Screenshot 2 shows the common internet page of the HMA that contains information for both, human and veterinary products.

The first page outlines the mission statement and the tasks of the group.

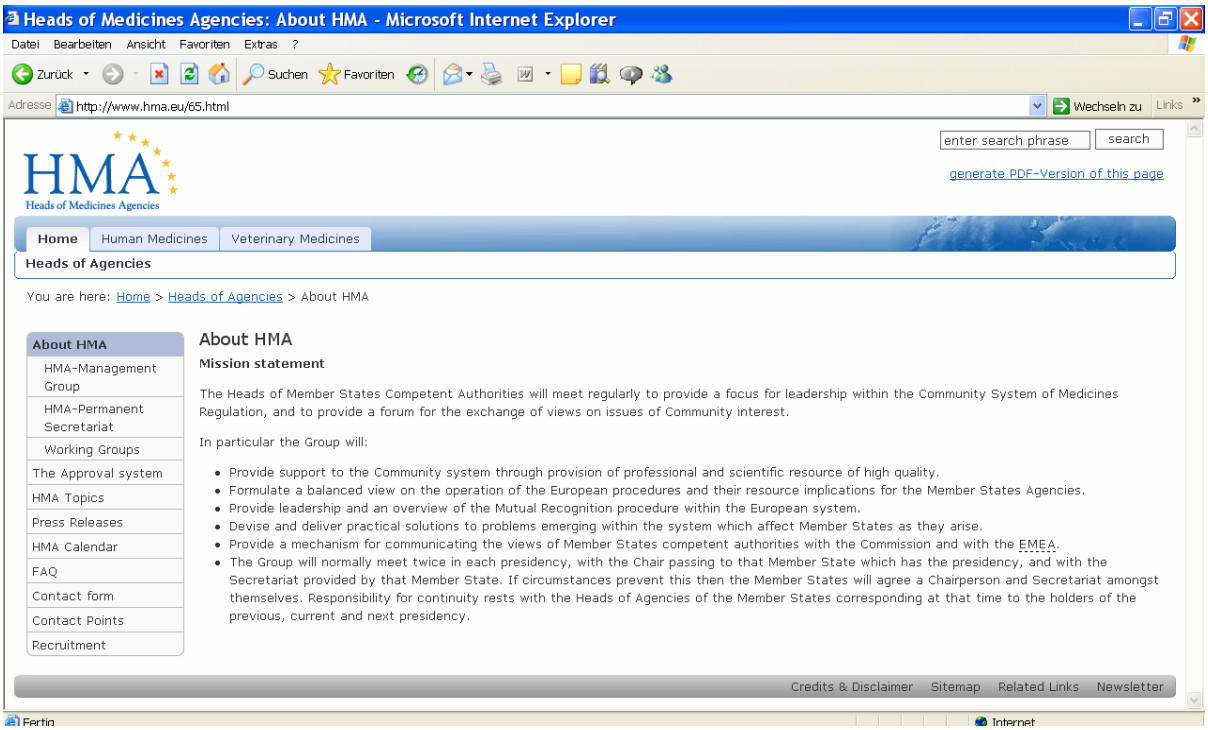
Furthermore information about the HMA Management Group and the HMA permanent secretariat is available. The topic “working groups” contains the report of the ad hoc working Group set up by HoA/HEVRA which considered the role of new coordination group that was foreseen in the new legislation [34].

The description of the approval system covers the CP, the MRP and national procedures. It is obvious that this page has not been updated, as for example the DCP is not mentioned and also the CHMP is called CPMP (Committee for Proprietary Medicinal Products) and the EMEA is mentioned as the “European Agency for the Evaluation of Medicinal Products”, although the renaming in “European Medicines Agency” took place in 2004.

The HMA released a strategy paper on how the network of national authorities should prepare for the challenges in the next few years [24]. The document complements the EMEA road map, as the focus is on the MRP, DCP and national procedures, which are under the responsibility of the HMA [24]. The outcome of the consultation process and the summary of the meeting with partners and stakeholders is available under the section “HMA topics” [26, 78]. This part also includes information about the benchmarking of European Medicines Agencies and Telematics in pharmaceuticals.

Furthermore the internet page contains the press releases that give a short summary of the last HMA meetings and the topic “HMA calendar” lists the date of the meetings of the group.

The FAQ (Frequently Asked Questions) part contained no information in February 2007, but it is likely that this will be changed in the future, as the internet page is still in construction. Last but not least a contact form and contact points are publicly available.



Screenshot 2: The common HMA internet site for human and veterinary medicinal products

The specific HMA part for human medicines (see screenshot 3) contains a few documents and sections that are also available on the general HMA internet page and will therefore not be described again.

The “best practice guide for the permanent secretariat support to the HMA Management Group” includes profiles about the committees and working groups [33]. Under the topic “about HMA”, information about the Clinical Trials Facilitation Group, the Homeopathic Medicinal Products Working Group and the Working Group on PSUR synchronisation is available.

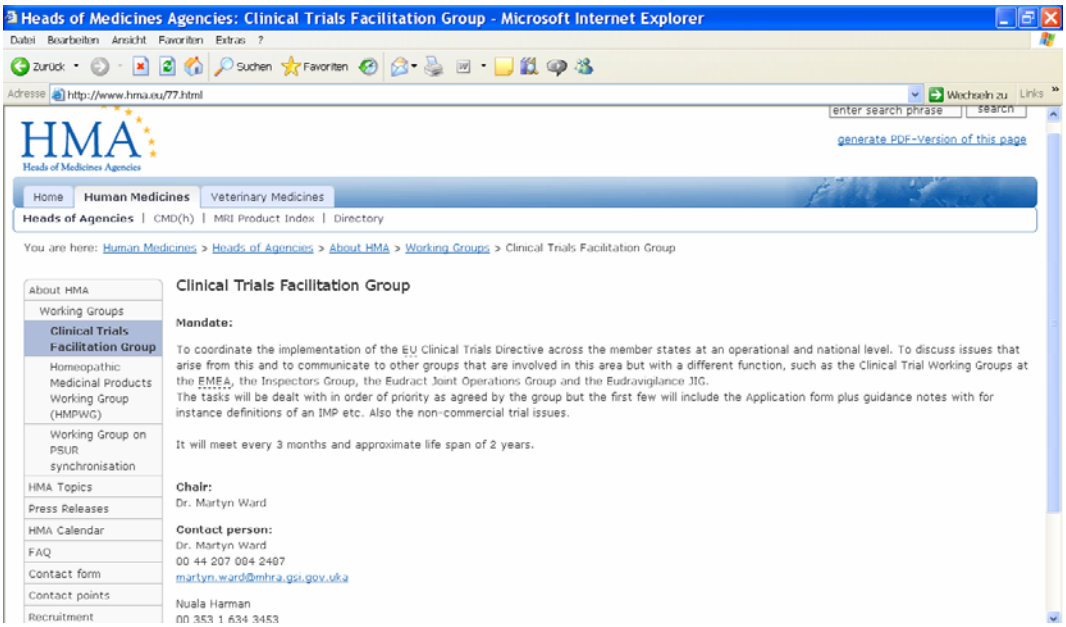
The Clinical Trials Facilitation Group coordinates the implementation of the Clinical Trials Directive 2001/20/EC and discusses clinical issues. The Homeopathic Medicinal Products Working Group published documents concerning the non-clinical safety of homeopathic medicinal products, guidance for Module 3 and points to consider on the safety of products from biological material [31]. The Working Group on PSUR Synchronisation released useful documents, e.g. about the EU harmonised birth dates and questions and answers on that issue. The goal of the group is to ensure that medicinal products with the same active substance follow the same PSUR submission scheme in all EU MS [38].

The “HMA topics” include information about the risk management and medicines for children (status: February 2007). The task of the European Risk Management Strategy Facilitation Group is the development of a European strategy for risk management based on the resources and expert knowledge of the national competent authorities, which incorporates also the responsibilities of the EMEA [33]. The group released for example an “overview of the pharmacovigilance resources in Europe – survey of national competent authorities” and action plans to further progress the European risk management strategy [35, 36, 37]. The section “medicines for children” describes the EU work sharing in the assessment of paediatric data. For medicines that are already on the market, the national authorities required the submission of all

data on the use of the product in children. The MS are working together in the assessment of the data with the intention to agree on the same information and to share the workload. This initiative is called the “EU Work sharing procedure in the assessment of paediatric data”. The conclusions from the assessment will be published and should be included in the product information.

The HMA website for human medicines also includes a FAQ part that contains questions and answers on the EU synchronisation of PSUR submission schemes of medicinal products authorised through national, mutual recognition and decentralised procedures.

The categories “press releases”, “HMA calendar”, “contact form” and “contacts points” have already been described in the first general HMA part.



Screenshot 3: The specific HMA human section

One positive aspect of the listed documents is that the publication date or the last update is mentioned.

Furthermore a few improvements have been made in comparison to the old website (http://heads.medagencies.org). For example on the old page the documents were listed without a clear structure. The new site lists the documents under particular topics and therefore it is easier for applicants or MAHs to find specific information. Furthermore new services, for example the search function and the subscription to the newsletter are available.

Nevertheless, improvement of the internet page is still possible, e.g. the description of the approval system has to be updated. In comparison to the CMD(h) not all scheduled meetings of the HMA are listed for 2007. It would also be an advantage to outline the key topics of the upcoming HMA sessions.

Moreover the press releases give only a very short summary about the discussed issues. For example the report after the meeting in February 2005 mentioned in one sentence that the end of 2009 was adopted as the target date for the eCTD [39]. The question occurred if 2009 is the date when all applicants have to submit their documents in eCTD or when all MS should be

ready to accept eCTD. For the clarification of such important issues it would be an advantage to summarise the HMA decisions and the discussed matters in more details.
Last but not least it should be mentioned that the reports are sometimes published several months after the meeting took place. A more timely publication could assist the applicants and MAHs to identify the issues that are currently under discussion at the European level.

5.4.2 The CMD(h) website

The new website of the coordination group (see screenshot 4) could be accessed over the HMA internet page. Many general documents about the group and its responsibilities are available.
Under the topic “general information” documents about functions, tasks of the CMD(h) and the CMD(h) secretariat and a summary of the MRFG/CMD(h) activities in 2005 and 2006 could be found. For transparency reasons also the guidance on contacts with representative organisations, the role of the vice-chairperson and the “rules of procedure” are published.
The part “CMD(h) composition” lists all members of the coordination group together with their professional qualification. Furthermore information about sub-groups, e.g. on harmonisation of SPCs is available.
The section “statistics” contains useful information that will be discussed in detail later.
Furthermore a description of the activities of the old MRFG is still available.
The topic “procedural guidance” contains many useful documents that are grouped in the following categories:

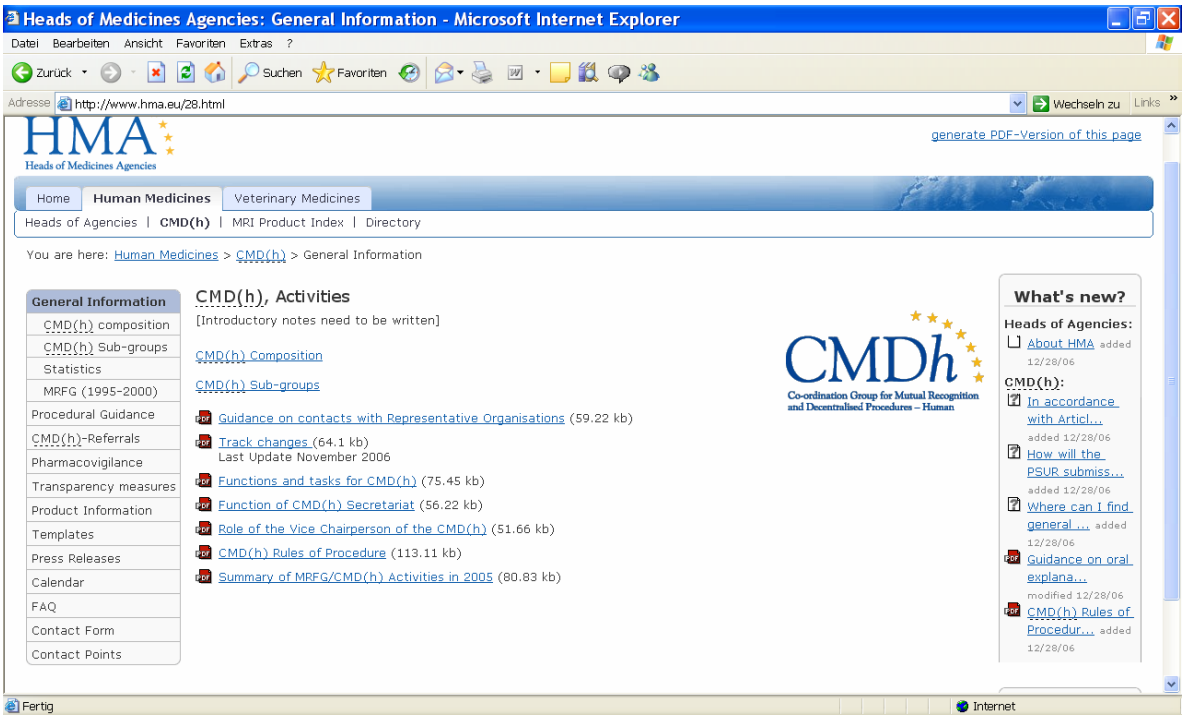
- General Info
- Application
- DCP
- MRP
- Repeat-use
- Renewal
- Variation
- Break-out session
- Applicant’s responses
- Paediatric data
- Post referral phase
- Art 61.3 procedure

The part “CMD(h) – Referrals” contains documents that describe the 60 days procedure.
It should be mentioned that information about CMDs together with the raised potential serious risk to public health could be found in the CMD(h) reports, whereas the CHMP monthly reports list the new article 29 referrals together with the issue that has to be solved. These last mentioned documents also include a short summary about CHMP opinions in arbitration procedures. After the European Commission Decision background information on the referral, as well as the adopted SPC, PL and labelling are publicly available on the homepages of the

EMEA and the European Commission (section “the Community register of medicinal products”) but not on the internet page of the CMD(h).
The topic “pharmacovigilance” includes information about urgent safety restrictions. The part “transparency measures” contained in February 07 only the “best practice guide for the public assessment report in the DCP and MRP” [51].
The assessment reports from the EU project on work sharing in the evaluation of paediatric data are available under “paediatric data assessment”. At the end of February 2007 reports for the active substances carboplatin, tolterodine, fluticasone proprionate and zolmitriptan were published.
The section “product information” lists core SPCs and the QRD templates, whereas all other templates could be found in the corresponding category.
The CMD(h) internet page also includes press releases from the CMD(h) plenary meetings, that will be described later.
The scheduled meetings of the coordination group are available under the topic “calendar” and according to the “rules of procedure” the dates of the meeting should be published on an annual basis[13].
Whereas the question and answers documents could be found on several places on the old internet page, the new structured website established a new category named “FAQ” that contains all of these documents.
The section “contact points” includes the email addresses for the submission of translations in MRP and DCP, of electronic versions of the responses to the list of questions for applications referred to the CMD(h) and addresses for advice on MRP and DCP. Furthermore the new web site contains a list of categories for specific contact points in the MS:

- All
- Submission of translations
- MRP and DCP
- Variations
- Renewals
- Validation of applications
- Referrals
- CMD(h) member

All documents on the website of the CMD(h) are listed with their publication date or the time point of the last changes. That is useful, as you could identify older documents which have not been updated yet and therefore may contain outdated information. For example the “position paper on repeat use of mutual recognition procedure” has not been changed since the Review came into force, and therefore the document does not mention the repeat use of DC procedures[40].
Taking everything into consideration, the website of the CMD(h) contains useful information. In comparison to the HMA, the CMD(h) lists all meetings for 2007 and in most cases the press releases are published timely.



Screenshot 4: The CMD(h) section of the HMA website

5.4.3 The MRI Product Index

The MRI Product Index (see screenshot 5) was launched in 1999 and includes information about medicinal products that have been approved in the EU, Iceland, Norway and Liechtenstein via MRP and DCP [9].

The data (e.g. product name, name of marketing authorisation holder, etc.) are transferred from the Communication and Tracking System, whereas the maintenance of the index is a decentralised responsibility, i.e. the competent authority acting as RMS or CMS is responsible for keeping the Product Index up to date [9].

According to the frequently asked questions on the website the “database is updated on a regular basis and the aim is to update the MRL weekly” [41].

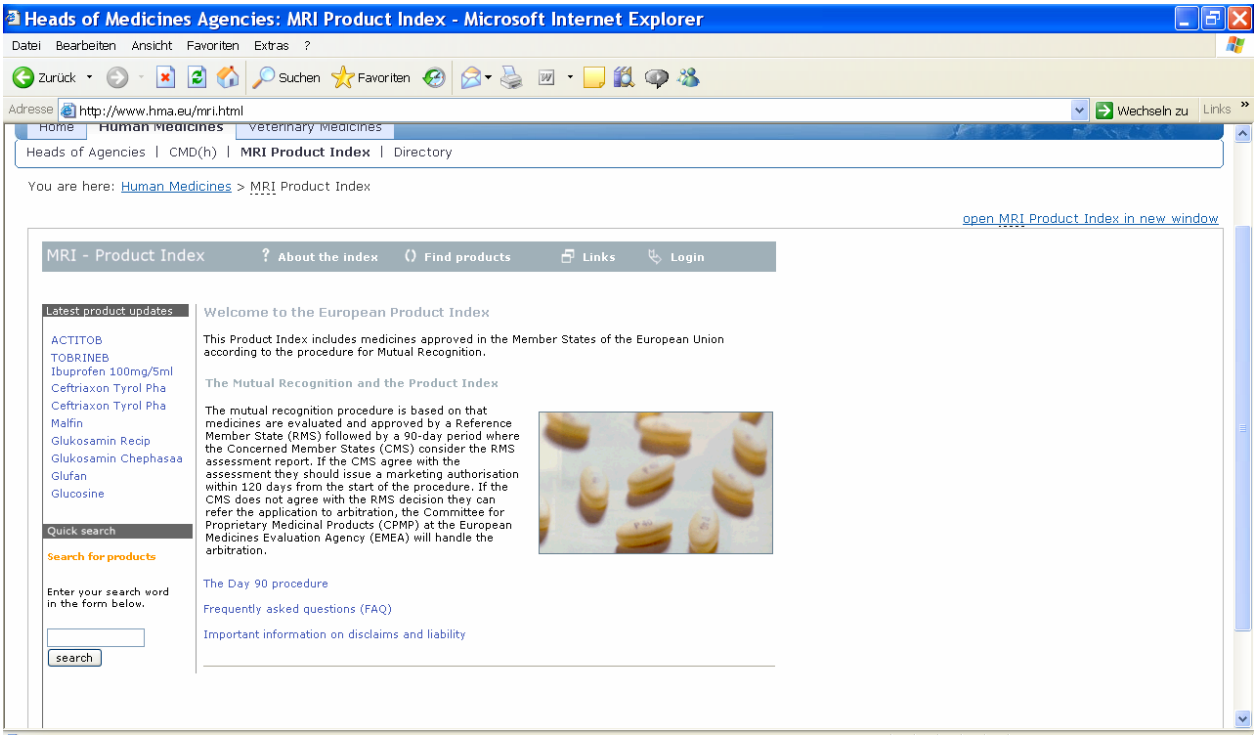
The following information is available for each medicinal product:

- Type of application (e.g. full dossier/generic/fixed combination, line extension/repeat use, new active substance/known active substance, prescription only/OTC, herbal/chemical/biological, etc.)
- Active substance
- Form
- Strength
- Marketing authorisation holder
- RMS country
- CMS country and domestic product name
- MR number
- Date of day 90
- SPC, PL, PAR (not always available)

The PAR was one new provision that was included in the new legislation in order to increase the transparency and avoid individual requests. The PAR reflects the scientific conclusion reached at the end of the evaluation process and provides a summary of the reasons for approval of the marketing authorisation for a specific medicinal product [51].
The PAR should be published in the MRI Product Index within 60 calendar days after finalisation of the MRP or DCP [51].
It is the duty of the RMS to draft the English PAR on the basis of the overview part of the final assessment report. The report consists of six modules. The first module includes information about the initial procedure, e.g. the type of application, the active substance and the involved MS. The modules 2 to 4 contain the SPC, PL and the labelling and part 5 outlines the scientific discussion during the initial procedure.
The last module lists the steps taken after the initial procedure with an influence on the public assessment report (Type II variations, PSURs, commitments) [51].
Before the publication, the applicant will be requested to identify issues that are considered as commercially confidential. Generally the non-clinical and clinical parts of the assessment report could be published, whereas the part that evaluates the quality/chemical-pharmaceutical data should normally be considered as confidential. The only exceptions are for example the qualitative and quantitative composition of the active substance, the pharmaceutical form and the shelf life or storage conditions. Discussions in the CMD(h) will briefly be described, and therefore also withdrawals of MS during the MRP and after day 120 in the DCP will be included in the PAR, as these issues are also discussed in the coordination group.
Withdrawals of applications for a new indication should only to be published if there is an overriding public health issue to inform prescribers or patients.
The PAR has to be updated in line with major updates of the dossier [51].
The CMD(h) published the “best practice guide for the public assessment report in the decentralised and mutual recognition procedures” and also corresponding templates to clarify the structure and content of the PAR [51, 52].

The MRI Product Index offers a few search possibilities for medicinal products, e.g. you could view products by RMS or CMS countries, by day 90, by application type level or a combination or criteria.
On the one hand the MR-Index is at the moment the only source of information about all new MRPs and DCPs, as not all MS of the EU have publicly available national databases. Furthermore these databases only list the regional available medicinal products and the information is normally not available in English.
On the other hand the index is not always reliable, e.g. CMS are mentioned although they have been withdrawn during the procedure and sometimes the data is not complete, e.g. the active substance is missing and the PAR is not available for all new products. Furthermore the information about finalised procedures occurs in some cases months after day 90 in the database.
Also the search functions could be improved as it is not possible to list all the medicinal products for a specific active substance or for example all finished DCPs.

It should be mentioned that the EMEA has launched a new public database called “EudraPharm”. At the moment the database gives access to information about medicines that have been authorised via the CP, but in the future all products that are available in the EU will be included, independent of the approval procedure [42].The database gives access to the SPC, PL and the labelling of the medicinal products. Currently the information is only available in English, but the other official EU languages will follow at a later phase, together with improved search functions [42].



Screenshot 5: The MRI Product Index

5.5 Guidance documents

The definitive legal requirements are those that are outlined in the Community legislation, e.g. in Directives and Regulations. Although guidance documents do not have legal force, they are nevertheless very useful, as they describe many procedures in detail. Furthermore the CMD(h) documents reflect the position of the MS and should therefore be followed by applicants, MAHs and also national competent authorities to facilitate assessment and approval of medicinal products in the EU.

The CMD(h) publishes different kind of guidance documents, e.g. SOPs, guidelines, best practice guides, position papers, recommendations and questions and answers.

The CMD(h) recommends that the best practice guides, for example the “best practice guide for mutual recognition procedure” are followed by the national authorities, the applicant and MAHs to facilitate and harmonise the procedures [11].

SOPs, e.g. the “decentralised procedure member states' standard operating procedure” or the „CMD(h) standard operating procedure: disagreement in procedures – referral to CMD(h)” are indented to provide written instructions for a specific procedure or of a process [43]. These documents should facilitate the cooperation of the MS and achieve uniformity of the performance of a specific process, e.g. in the DCP.

The CMD(h) also publishes recommendations, for instance the “CMD(h) recommendation on implementation of article 30 decisions for generic products” [44].

Position papers, e.g. the “MRFG position on changing the reference member state” reflect the opinion of the CMD(h) [45].

Furthermore the CMD(h) releases agreements, e.g. the “CMD(h) agreement on the sunset clause and its application to marketing authorisations granted in more than one member state”[46]. It should be considered that there is no obligation for the MS to apply the sunset clause provisions of the legislation as outlined in this paper. The document only reflects the CMD(h) interpretations.

Moreover several questions and answers (Q & A or frequently asked questions) documents provide additional public information on particular topics of interest, e.g. the “questions and answers on the implementation of the new legislation” and the “questions and answers on requests for advice from CMD(h)” [28, 47]. The intention is to outline briefly in easily comprehensible language, requirements, practices or interpretations to the most frequent questions in a specific area.

According to the “rules of procedure” of the CMD(h), the group should adopt guidelines, SOPs, recommendations, procedural or regulatory practices and position statements whenever possible by consensus [13]. In the absence of consensus they are deemed to be adopted if an absolute majority of the members of the CMD(h) support it [13].

For transparency reasons the CMD(h) released a list of guidance documents in the MRP under revision to reflect the new pharmaceutical legislation [48].

In comparison to the Notice to Applicants and guidelines that are available on the EMEA homepage, the CMD(h) publishes new versions of documents with a track change function. That is very useful for applicants and MAHs as the changes could be identified easily.

5.6 Dialogue with stakeholders

As already mentioned the coordination group published a “guidance on contacts with representative organisations” which defines the scope and conditions of interactions with stakeholders. The document describes the rules of meeting with patients, consumers and users of medicines, healthcare professionals, academia, learned societies and also with the pharmaceutical industry [49]. The communication of the coordination group shall include general issues like guidance documents, experience with the system or procedures and also transparency issues. Individual procedures should not be discussed [49].

A meeting of the CMD(h) with patients/consumers´ organisations or healthcare professionals can be initiated by the CMD(h) or the stakeholders. CMD(h) observers could be nominated in the plenary sessions for the participation of activities of the EMEA Human Scientific Committees

Working Party with Patients and Consumers Organisations (PCWP) and the EMEA/CHMP Working Group with Health Care Professionals, respectively [49].

According to the guideline at least one meeting with representative organisations of the pharmaceutical industry should be organised per year. Date and topics of the meeting will be decided in the CMD(h) plenary session approximately two months before the meeting. Ad hoc groups could be established for the preparation of the content, which will be supported by the secretariat. All CMD(h) members could attend the meetings [49].

For the transparency and balance, all representative organisations of the European pharmaceutical industry should generally be invited at the same time, and after the meeting the key points and all agreements have to be included in a CMD(h) press release [49].

5.7 Reports from the CMD(h) meetings

After each CMD(h) plenary meeting at the EMEA, a report is published on the website. These documents summarise the discussed issues, list the new or updated CMD(h) documents and also include information on MR and DC procedures for new active substances that have been finalised.

Furthermore the reports contain information about finalised CMD(h) procedures, e.g. the involved active substances, as well as the grounds and outcome of the CMD(h) referrals. Knowledge about the discussed issues could be useful for the pharmaceutical industry in order to avoid further referrals, evaluate the chance for reaching agreement in own procedures and get ideas about how similar problems could be solved during the MR or DC procedure.

Moreover the press releases include statistical information, e.g. the number of finalised MRPs and DCPs in comparison to the amount of procedures referred to CMD(h) and CHMP per period. Also the application types (e.g. hybrid, full, generic, bibliographical), number of multiple or repeat use applications, the new procedures per RMS and the number of involved CMS are listed. This information has an influence on the choice of the RMS for future applications. First it reveals that several MS are obviously not willing to act as RMS, whereas others start many new MRPs or DCPs per year. On the one hand these last mentioned countries have a lot of experience, but on the other hand it should be considered if they have the capacity to start further procedures on time.

Last but not least the statistics list the number of finalised type IA, IB and type II variations per month.

5.8 Statistical information about MR and DC procedures

As already mentioned in the last part the monthly reports from the CMD(h) meetings also include statistical information.
Further annual statistics about the MRP, DCP and the referral to the CMD(h) have been made publicly available by the old MRFG and the CMD(h), respectively. The charts that are available on the website of the CMD(h) illustrate for example the number of finalised MR and DC procedures for new active substances and generics and the type of active substances, i.e. chemical, biological and herbal substances per year.
Further presentation slides show the number of line extensions and the finalised procedures per RMS [50]. The newest statistic also includes information about the referrals to the CMD(h) in 2006, e.g. the types of the procedures (MRP versus DCP), types of products, the legal bases, the reasons and the outcome [50].

6. Which types of applications are eligible for the CMD(h) referral?

MRP and DCP have been established to facilitate the access to the European market by relying upon the principle of mutual recognition [9]. In both cases, the authorisation or the assessment of the RMS, should normally be recognised by the national authorities of the CMS. According to Directive 2001/83/EC as amended, the MS that are involved in the procedure have to approve the assessment report, the SPC, package leaflet and the labelling, unless a MS raise grounds that the authorisation of the medicinal product could present a potential serious risk to public health [9]. The point of disagreement will be discussed in the CMD(h) according to article 29 of the above mentioned Directive.
The scope of this 60 days CMD(h) procedure is not only limited to new MRP and DCP applications for medicinal products but by analogy will also be followed for repeat use submissions, extensions and renewals [16]. Theses procedures will shortly be described in the following part. It will also be outlined why variations are excluded.

6.1 MRP

If the medicinal product has already received a marketing authorisation in a MS the MRP has to be used in order to get approvals in further countries as described in article 28 of Directive 2001/83/EC as amended [6].
The MS which has already granted a national marketing authorisation has to act as RMS and has to prepare or update the assessment report together with the approved SPC, labelling and PL within 90 days after receipt of a valid MR application. The assessment report includes all variations and any additional information concerning quality, safety and efficacy since the initial marketing authorisation has been granted. The MAH has to submit an identical application to the

national authorities of each of the MS where a marketing authorisation should be obtained. Afterwards the assessment report of the RMS and the approved SPC, PL and labelling is sent to the CMS and to the applicant [9].

In the following validation phase the CMS checks that all necessary documents are available and that the fees have been paid according to the CMD(h) document "procedure for automatic validation of MR procedures for new applications" [54] .

In case of minor issues, the MAH has the opportunity to amend the application within two weeks after notification of the missing information [9].

50 days after the start of the procedure the CMS should give their comments, distinguishing between points for consideration and potential serious risks to public health, which should be stated in detail [11]. The response from the applicant that is submitted prior to day 60, should address the objections or questions and include a new proposed SPC, PL and labelling. It is recommended that the document follows the CMD(h) guidance "applicant's response document in mutual recognition (CTD-format)" [55].

The RMS evaluates the response from the applicant and circulates a report to all CMS. A break-out session may be organised for discussing the application or finding a solution to outstanding issues [9]. The organisation for that meeting is described in the CMD(h) document "best practice guide on break-out sessions" [56]. At the latest on day 85 the CMS should send their final comments. If consensus is reached at day 90 with all CMS, the RMS closes the procedure and distributes the final agreed SPC, PL and labelling [11].

The applicant provides the national required documentation, e.g. translations of the agreed product information within five days after the end of the procedure. Afterwards the national authorities should grand a corresponding national marketing authorisation theoretically within 30 days after finalisation of the MRP [9]. Practically the MS need approximately two to six months and some authorities even more than one year.

However, if a CMS raises grounds for supposing that the authorisation of the medicinal product concerned may present a potential serious risk to public health, the procedure will be referred to the coordination group according to Article 29(3) of Directive 2001/83/EC as amended. The reasons for the negative opinion have to be explained in detail by the CMS [11]. The applicant could withdraw the application for a marketing authorisation at any time during the procedure, but once a potential serious risk to public health has been raised, the issue will be discussed in the coordination group. If the MS fail to reach agreement in the CMD(h), arbitration will be initiated. This procedure could only be avoided, if all applications and existing marketing authorisations for the medicinal product are withdrawn.

From November 2005 to December 20006 114 MRPs have been referred to the CMD(h)

6.2 DCP

In comparison to the MRP, the DCP could be used to get approvals in several MS where the medicinal product has not yet obtained a marketing authorisation in the Community at the time of application [9].

It is recommended that the applicant informs the chosen RMS about the intention to submit a DCP as soon as possible, as many MS require a few months to offer a possible start date for the procedure [43].

The applicant submits an application to the authorities of the RMS and each CMS, which is based on an identical dossier.

The Decentralised Procedure is divided in four steps, namely the pre-procedural step, that includes the validation phase, the assessment step I, assessment step II with discussion at the CMD(h), if needed and last but not least the national step [43].

Although it is not mentioned in the guidance document, a pre-submission meeting is recommended by some MS to discuss regulatory issues, for example concerning the legal basis and indications, with the applicant [79].

In the first phase, the RMS and the CMS validate the application. In comparison to the MRP the validation phase of the DCP is more difficult, as the dossier has not been approved yet and therefore the MS have in most cases more comments [79].

After the successful validation the RMS starts the assessment step I. At day 70 of the procedure the RMS distributes the preliminary assessment report (PrAR) on the dossier, including the SPC, PL and labelling to the CMS and the applicant [9].

By day 100 the CMS should comment on the report of the RMS and the dossier, differentiating between issues for clarification and potential serious risks to public health [43].

The RMS could stop the clock at day 105, in order to allow the applicant to respond to the questions and update the proposed SPC, PL and labelling. The so-called applicant's response document has to be submitted to the RMS and all CMS within the agreed timeframe, which will usually not exceed three months, unless there are justified reasons [55]. After receipt of the requested data the RMS restarts the clock at day 106 [43].

By day 120 the RMS distributes the SPC, PL and labelling and the draft assessment report (DAR), which includes an evaluation of the documentation upon quality, safety and efficacy. Day 120 corresponds to day 0 of assessment step II [43].

By day 145 (i.e. day 25 of the 90 days period) the CMS should send their comments differentiating between potential serious risks to public health and remaining points for clarification [43].

If no agreement could be reached by day 150, the RMS sends a list with outstanding issues to the applicant. The applicant submits the response document by day 160.

The RMS evaluates the response and prepares a report for the CMS and the applicant at the latest at day 180 [43].

A break-out session could be organised at the EMEA to discuss the unresolved issues [9]. The CMD(h) "best practice guide on break-out sessions" outlines the procedure [56].

Moreover the RMS could use the meeting of the CMD(h) as an opportunity to discuss major issues that are raised during the procedure and seek assistance in solving the problems [43].

If consensus is reached the RMS closes the procedure at the latest on day 210 (i.e. day 90 of the 90 days period) and distributes the final agreed SPC, labelling, PL and the final AR.
Afterwards the MS should grant a national marketing authorisation theoretically within 30 days, as already described in the MRP.
It should be mentioned, that there are several earlier time points (day 105, day 120 or day 150) to end the DCP if agreement is reached.
If no consensus is achieved at day 210 due to a potential serious risk to public health, the procedure will be referred to the coordination group. This also applies if the applicant has withdrawn the application in a MS that raised a potential serious risk after day 120 [43].
However if there is consensus that the product is not approvable, no national step will follow [43].
In 2006 only one DCP was referred to the CMD(h).

6.3 Repeat use

A MAH can use the MRP more than once to obtain marketing authorisations in countries that have not been involved or were withdrawn in the first procedure [40]. The MRP could also be used after a DCP to get marketing authorisations in further MS.
The new CMS in a repeated MRP should normally recognise the authorisation granted in the previous procedure, including the SPC, PL and the labelling. In exceptional circumstances, where a CMS considers that the product will cause a potential serious risk to public health, the matter will be referred to the coordination group. As already mentioned in the description of the MRP and DCP, the applicant cannot avoid this procedure by withdrawing the application in the referring MS [9]. If the CMD(h) has not achieved a common position, the matter is referred for arbitration to the EMEA.
If the issue was already discussed by the group in a previous MRP or DCP, the question should not be raised again in any subsequent procedure except there are justified reasons. This also applies if the matter was already referred to arbitration in a previous procedure [9].
Nevertheless the new CMS could propose some changes to SPC, PL and labelling. The applicant has to submit a variation immediately after the finalisation of the procedure, so that the requested product information changes could be evaluated and discussed by all CMS, i.e. old and new ones.
CMS involved in the previous MRP or DCP cannot raise new issues during repeat use procedures unless they claim that a serious risk to public health may be caused because of any new data submitted in the updated dossier [40].

6.4 Extension

A change of a medicinal product according to Annex II of the Regulation 1084/2003/EC is regarded as an extension to this authorisation [3, 60].
The MAH of the extension application has to be the MAH of the originator product. Furthermore the name of the medicinal product for the 'extension' will be identical with that of the existing marketing authorisation [3, 61].
As extensions are fundamental changes, they fall outside the definition of a variation and therefore require a new application [3]. The European Commission published a "guideline on the categorisation of extension applications (EA) versus variations applications" [57].
An example for a extension is the addition of a new strength or pharmaceutical form.
If a MS that is involved in the procedure considers that the product will cause a potential serious risk to public health, the matter will also be referred to the coordination group.

6.5 Renewal

According to article 24 of Directive 2001/83/EC as amended, a marketing authorisation is valid for five years [6]. MAHs who wish that their products could be marketed for a longer period have to renew the marketing authorisation on the basis of a re-evaluation of the risk-benefit balance [3].
The MAH has to submit a consolidated version of the file in respect of the quality, safety and efficacy including all variations introduced since the marketing authorisation has been granted, at least six months before the marketing authorisation expires [3].
Once renewed, the marketing authorisation is valid for an unlimited period unless the authority decides that another five-year renewal is necessary due to pharmacovigilance reasons [3]. The MS have agreed on a 90 day procedure for renewals of MRP and DCP marketing authorisations which include the possibility of a clock stop for a maximum of 30 days that could in exceptional circumstances be extended [58]. The RMS leads the procedure and is responsible for the distribution of the timetable.
In the case that the MS are unable to achieve agreement during the 90 days due to a raised potential serious risk to public health, the procedure will be referred to the coordination group. If the CMD(h) is not able to solve the outstanding issue, the matter will be referred to the CHMP for arbitration according to article 30 or 31 of the Directive 2001/83/EC as amended [58].
A consideration of the procedure in the CMD(h) is also recommended, if the draft decision of the RMS is unfavourable and also the CMS agree that the marketing authorisation should not be renewed [58].

The most critical issues occur normally during the MRP and DCP, for example concerning different originator SPCs in the MS or the demonstration of bioequivalence with the reference medicinal product. So, these problems are already resolved before the renewal procedure takes place. This may be the reason, why no renewal has been referred to the 60 days CMD(h) procedure up to now.

6.6 Variations

The Commission Regulation 1084/2003/EC came into force on 1 October 2003 and is applicable for subsequent changes to the marketing authorisation for a medicinal product that has been authorised via MRP or DCP [85].

According to the Regulation there are three types of changes, namely type IA and IB notifications and type II variations [87].

In all cases the variation application has to be send simultaneously to the RMS and all CMS.

Type IA or so-called „tell and do“ variations are considered as minor changes, e.g. of the administrative data or changes without an impact on the quality of the medicinal product. These types of variations are only possible if all conditions of annex I of Regulation 1084/2003/EC are met [60]. For example the change in the name and/or address of the MAH is regarded as a type IA variation. The RMS is responsible for making the decision on the validity of the whole notification on behalf of all CMS within 14 days following the receipt of the notification [86]. Afterwards the RMS informs the CMS and the MAH.

Type IB or so-called “tell, wait and do variations” are also considered as minor changes, but in comparison to type IA, the amendment to the documentation has to be evaluated [85].

Also in this case the conditions that have to be fulfilled are set out in the annex of Regulation 1084/2003/EC. It is the responsibility of the RMS to evaluate the change applied for within 30 days. If necessary the clock could be stopped within the procedure. The RMS informs the CMS and the MAH of the outcome. For instance a minor change in the manufacture of the finished product is regarded as a type IB variation. Within 10 calendar days of the completion of the procedure (either in the case of approval or in case of disagreement with the outcome) the MAH and the CMS have the right to refer the matter to the CHMP for arbitration [85].

Type II variations are all major changes to the marketing authorisation, which can not be deemed to be a IA or IB notification and which are not regarded as an extension to the marketing authorisation [87]. These variations are normally processed according to a 60-days time scale for completion of the assessment report. However the time may be reduced for amendments concerning safety issues or extended to 90 days for changes or additions of therapeutic indications [86]. The timeline for a clock stop is set by the RMS. After the end of the procedure the RMS informs the MAH and the CMS. Also in this case the procedure can be referred to the CHMP by the CMS or the MAH [87]. According to Volume 9 of the NTA, updates to the information provided in the detailed description of the pharmacovigilance system are considered as type II variations [88].

As variations are not covered by Directive 2001/83 as amended, they can not be referred to the 60 days CMD(h) procedure. But, as already mentioned above it is possible that type IB and II variations are referred to arbitration.
Nevertheless variations could be discussed in the regular work of the coordination group [53].

7. Definition of a potential serious risk to public health

As already mentioned a marketing authorisation or the assessment in the RMS should in principle be recognised by the national authorities of the other MS, unless there are grounds for supposing that the approval of the medicinal product concerned may present a potential serious risk to public health [9].
According to the report on the "evaluation of the operation of Community procedures for the authorisation of medicinal products" carried out on behalf of the European Commission by Cameron McKenna and Anderson Consulting in 2000, MAHs believed that there was widespread abuse of this provision, with some MS using it to cloak national preferences and requirements [7]. For example for generic applications, some MS were unwilling to accept a SPC which differed from the product information for the local originator product, even if additional data was provided to cover the differences [7].
As foreseen in article 29 (2) of the Directive 2001/83/EC as amended the Commission adopted a guideline on the definition of serious risks to public health to set out in more detail in which exceptional cases a MS can refuse to recognise a marketing authorisation (MRP) or a positive assessment (DCP) on the basis of a potential serious risk to public health. The goal is to limit the variety and number of objections raised by MS [8].
According to the guideline a risk is "the probability that an event will occur" and a potential serious risk to public health is defined "as a situation where there is a significant probability that a serious hazard resulting from a human medicinal product in the context of its proposed use will affect public health" [8]. The term "serious" means a "hazard that could result in death, could be life-threatening, could result in patient hospitalisation or prolongation of existing hospitalisation, could result in persistent or significant disability or incapacity, or could be a congenital anomaly/birth defect or permanent or prolonged signs in exposed humans" [8].
For the evaluation if a potential serious risk to public health exists, also the positive therapeutic effects of the concerned medicinal product has to be taken into account. Therefore the term potential serious risk to public health should be interpreted as relating to the overall risk-benefit assessment of the medicinal product, taking into account the positive therapeutic effects in relation to the risks [8].
The guideline lists specific cases concerning the efficacy, safety, quality, overall risk-benefit and the product information when a potential serious risk to public health could exist. For example if the "proposed production and quality control methods cannot guarantee that a major deficiency in the quality of the product will not occur" or if the "risk-benefit-balance for the product is not considered to be favourable, taking into account the nature of the identified risk(s) and the potential benefit in the proposed indication(s) and target patient population(s)" [8]. Furthermore a

product Information that is “misleading or incorrect for either the prescribers or the patients to ensure the safe use of the medicinal product” could lead to a referral to the CMD(h) [8].
DG Enterprise and Industry published a list of examples which should not be considered as a risk, e.g. if the “claimed indication cannot be granted because this would trigger the need to harmonise Summary of Products Characteristics of other products approved at a national level” [59]. This list will be updated based on the experience gained in the CMD(h) [59].

8. The 60 days CMD(h) procedure

MS that cannot approve the assessment report, SPC, labelling or PL due to serious risks to public health, have to send a notification to the RMS, the CMS, the CMD(h) secretariat at the EMEA and the applicant at day 90 (MRP, repeat use, renewal) or 210 (DCP) at the latest [62].
The reasons for the negative opinion have to be explained in detail by the disagreeing MS. Afterwards it is the duty of the RMS to formally initiate the referral procedure. The chairperson of the CMD(h) and the RMS decide on the starting date, which should not be later than 30 days after day 90 and 210, respectively [62].
The CMD(h) released a guidance document that gives an overview of the possible timetables in 2007 for MRP/DCP applications referred to the CMD(h) for the 60 days referral procedure [63]. According to this document it is not in every case possible to comply with the 30 days rule in all situations, due to the calendar of the CMD(h) meetings [63].
Withdrawal of the application in the MRP or DCP from one or more MS is always possible in the complete procedure, e.g. for marketing reasons [62]. However if the withdrawal has been made in a MS after that country raised a potential serious risk to public health, the 60 days procedure could not be avoided [53]. In case of a MRP the point of disagreement based on a serious risk to public health is always referred to the CMD(h), whereas in the DCP, this will only be applicable after day 120 [62].
In the CMD(h) procedure, the RMS provides all MS that were not involved in the procedure with the latest assessment report, the proposed SPC, labelling and PL and the explanation of the grounds of referral to the CMD(h) [62].
Whereas all members of the coordination group could participate in the discussion in the CMD(h), agreement has only be reached by the MS concerned by the application. The latter mentioned also includes CMS where the application was withdrawn as mentioned before.
The negotiation in the group is led by the RMS.
It is the responsibility of the CMD(h) secretariat to coordinate the procedure, e.g. sending timetables, keep the minutes and establish contact with all involved parties [62].
RMS and CMD(h) do not check before the initiation of the referral if the CMS has a valid potential serious risk to public health in compliance with the definition of the guideline, as this discussion takes place in the meetings [53]. During the 60 days, that are described in the “CMD(h) SOP on disagreement in procedures – referral to CMD(h)” no clock stop is foreseen [62].
On day 0 of the procedure a list of questions is sent to the CMD(h) members. After agreement of the MS the applicant receives the list from the secretariat on day 10 of the timetable [62]. Within

two weeks following receipt of the list of questions the company has to make the decision, if its point of view will be presented orally [53, 64]. It is recommended that this issue is discussed with the RMS, which informs the group whether an oral hearing will take place at the second CMD(h) meeting. Nevertheless the written response to the list of questions always has to be provided and should be sent to all CMD(h) members not later than on day 25 of the procedure [53]. The website of the CMD(h) lists the contact email addresses, as the response should be distributed electronically to the CMD(h) members and to the EMEA [65].
Furthermore one paper copy is necessary for the RMS [53].
It is possible for the CMD(h) to take advice from the CHMP, the HMPC or their working parties and the Homeopathic Medicinal Products Working Group (HMPWG) [62].
It is not expected that new data are presented during the procedure as there is no time for further assessment. The results of new studies have to be distinguished from the clarification of already presented data. As references, e.g. published literature, only interprets the already presented information, these will not generally be considered as new data [53].
Around day 35 the RMS sends an updated assessment report to all CMD(h) members. Seven days before the second meeting the members should outline their view on the response document in writing to all other members of the group [62].
The scientific discussion about the unresolved issues takes place in the second meeting that is scheduled around day 50 [62]. One week before that meeting, the time schedule is sent to the applicant by the CMD(h) secretariat [64].
As already mentioned the applicant has the possibility to present its point of view orally to the coordination group. According to the CMD(h) summary of activities in 2006, 20 oral explanations from applicants took place in 2006 [82].
In the case of such an oral explanation the applicant should send a document to the CMD(h) secretariat and the RMS, which lists maximal five representatives with their affiliation and role in the oral explanation on Wednesday prior to the meeting. Furthermore it should be stated if technical support, e.g. a slide projector, is required for the presentation. At the latest by Friday before the oral hearing the presentation should be send electronically to the RMS, the CMD(h) members and the secretariat [64]. The applicant has to take into account that the presentation should not be longer than 20 minutes and focus on the responses to the most critical issues from the list of questions. If appropriate the impact of the proposed solution on the SPC and PL should be given and also commitments should be taken into consideration as they could be a solution for reaching agreement. At the end the applicant should give a conclusive statement [64].
On the day when the meeting is scheduled, the applicant should hand over 60 paper copies of the handouts and the presentation to the CMD(h) secretariat.
Prior to the oral explanation the RMS summarises the remaining points of disagreement, comments on the new proposed SPC, PL and labelling and presents possible commitments from the applicant [64].
After the presentation of the applicant the MS could raise questions. The duration of the meeting with the applicant, including the oral hearing and the questions and answers should not exceed 40 minutes. Afterwards the applicant has to leave the room for the discussion of the CMD(h) members about the outstanding issues. If possible the agreement on the submission should be reached during the CMD(h) meeting [62, 64].

The RMS informs the applicant about the outcome and of any remaining problems.
If there is no consensus, the procedure continues with the distribution of the final suggestion on the procedure at latest on day 55 by the RMS. In this case the full 60 days can be used to reach agreement between RMS, CMS and the applicant [62].
Article 29 of the Directive 2001/83/EC as amended outlines that all MS within the CMD(h) should use their best endeavours to reach agreement on the discussed issue [6].
If the MS where the application was submitted, including those where the application was withdrawn, reach consensus on refusing or approving the application within the 60 days, the RMS closes the procedure and informs the applicant of the outcome.
Within 30 days the countries shall grant the national marketing authorisation in conformity with the agreed SPC, labelling and PL if the CMD(h) concluded that there is no serious risk to public health [62].
The secretariat provides a database where the points of disagreement and conclusions could be entered, as discussions about the same questions should be avoided in the future [53, 62]. Nevertheless it is possible that potential serious risks are raised again, for example if only a few MS were involved in the first procedure where the problem was already discussed or if new scientific knowledge is available [53].
If the MS fail to reach an agreement within the 60-days period the RMS should immediately inform the Agency and the applicant, with a view to the application of an arbitration procedure according to the articles 32, 33 and 34 of the Directive [62]. Furthermore a detailed statement of the unresolved matters and the reasons for disagreement should accompany the referral to the EMEA [11].
According to article 29(6) of Directive 2001/83/EC as amended the applicant could request the MS that have approved the assessment report, the draft SPC, the labelling and package leaflet to grant the marketing authorisation after the end of the 60 days CMD(h) procedure without waiting for the outcome of the arbitration. In this case, the authorisation granted should be without prejudice to the outcome of the procedure [11].
According to our experience some countries give their consent to grant the marketing authorisation, whereas other MS wait for the outcome of the article 29 referral.

It should be mentioned that the CMD(h) procedure is also applicable to traditional herbal medicinal products that have been registered according to article 16d(1) of Directive 2001/83 as amended [62]. For herbal medicinal products also the HMPC should be informed.
If the CMD(h) is unable to reach consent on issues on traditional medicinal products, the points of disagreement should be referred to the HMPC. For other medicinal products containing herbal substances, the CMD(h) refers the unsolved problems to the CHMP and informs the HMPC [62].
Articles 28 and 29(1) to (3), but not articles 29(4) to (6) apply for homeopathic medicinal products, so that the same procedure as for other medicinal products has to be followed. But if the CMD(h) is unable to reach consensus, the points of disagreement will not be referred to the CHMP for arbitration [62].

9. Article 29 referrals

In case that the CMD(h) is not able to solve an issue in the 60 days procedure, the matter will be referred to arbitration [9]. The RMS should immediately inform the EMEA and the applicant and provide a summary of the unresolved issues and the reasons for the disagreement [13].

The scientific evaluation of human medicinal products is undertaken by the CHMP, one of the scientific committees of the EMEA [66]. The CHMP is composed of one member and an alternate per EU MS, as well as from Iceland and Norway and up to five co-opted members to gain additional expertise in a particular scientific area [67].

For the evaluation a rapporteur and co-rapporteur are appointed from amongst the members or alternate members of the CHMP [68].

Normally the rapporteur should be a CHMP member from the RMS and the co-rapporteur from one of the concerned (divergent) MS, in order to benefit from their knowledge on the application[68].

The CHMP could also appoint additional experts for advice on specific questions [66].

The CHMP considers the points of disagreement and issues an opinion within 90 days after the start of the procedure [66].

At the first meeting of the committee following the referral, the CHMP formulates the question(s) to be addressed to the applicant(s)/MAHs. The CHMP may stop the clock in order to allow the applicant or MAH to prepare the response document [66].

Before issuing an opinion, the committee provides the applicant or MAH with the opportunity to present written or oral explanations.

In comparison to the CMD(h), all members of the CHMP are involved in the evaluation and opinion process, and not only those that are concerned of the application.

Whenever possible the scientific opinion of the committee shall be taken by consensus.

However if agreement cannot be reached, the opinion could be adopted by the absolute majority of the members of the committee, i.e. favourable votes from at least the half of the total number of committee members eligible to vote plus one are necessary [70].

It should be mentioned that the members appointed by the EEA-EFTA states may not vote.

The opinion of the CHMP may have a negative impact for the applicant/MAH, for example if the CHMP finds that the application does not satisfy the criteria for authorisation or that the marketing authorisation should be suspended, varied or withdrawn. It is also possible that the committee recommends that the approval should only be granted with certain conditions or that the SPC has to be changed [66].

After the CHMP has adopted the opinion, the EMEA immediately informs the applicant/MAH [66].

If the CHMP opinion is negative, re-examination could be requested [69]. In this case the applicant/MAH has to notify the EMEA of the intention to appeal within 15 days after receipt of the opinion. The reasons for appeal have to be forwarded to the EMEA within 60 days of the receipt of the opinion. Within 60 days of receipt of the reasons, the CHMP will consider whether its opinion should be revised. For the re-examination a new rapporteur and co-rapporteur are appointed who are responsible for making the assessment of the reasons for appeal [66, 71].

The EMEA opinion is forwarded to the Commission.

The final Commission decision following the arbitration procedure is addressed to all MS. Therefore the countries where the medicinal product is authorised or where an authorisation is pending have to take action within 30 days after the adoption of the Commission Decision. Moreover MS in which the application has not been submitted are also bound by the decision in the case that an application is submitted later.
However, a potential new and therefore not discussed serious risk to public health in repeat use procedures in the MRP could lead to a new discussion in the CMD(h) and, possibly, to a new arbitration procedure [9].
The outcome and duration of the procedure will be discussed in the next statistical section.

10. Statistical evaluation of CMD(h) procedures

The figures of the following statistical analysis are based on the reports from the CMD(h) meetings from December 2006 to January 2007 that are available on the CMD(h) internet page. As already mentioned these press releases include the number of finalised MRPs/DCPs in comparison to new CMD(h) procedures together with the reason for the referral. These reports include the figures of the previous month and therefore the statistical evaluation is based on the procedures from November 2005, i.e. the start of the new legislation, to December 2006. An overview of the analysed 80 CMD(h) referrals from that period is given in the Annex I.
The evaluation of the arbitration procedures is based on the information from the monthly reports of the CHMP and the Commission Decisions.
It should be mentioned, that in some presentations, e.g. in that of Dr. Birka Lehmann on the MRP and DCP and the official CMD(h) statistics of 2006, the figures are slightly different, as the statistical evaluation depends on the counting of the procedures [50, 73]. Furthermore it is sometimes difficult to assign the mentioned reason in a particular category, as the description of the discussed issue is sometimes not detailed enough. But it should be mentioned that the quality of the CMD(h) descriptions has been increased, i.e. the last reports included a more detailed summary than the first press releases after the new legislation came into force.
In the evaluation each procedure counted, i.e. also the procedures referred to the CMD(h) on identical grounds.

10.1 Number of procedures that are referred to the CMD(h)

Since November 2005, i.e. since the new provisions for the MRP and DCP have entered into force, 594 MRPs have been finalised, whereas 114 procedures were referred to the CMD(h).
That means that from November 2005 to December 2006, circa 19 % of all MR procedures had to be discussed in the group due to a potential serious risk to public health raised by one or more MS.
In 2006 only one of the finalised DCPs was referred to the CMD(h) (2%) [82].

The tables 2 and 3 show the number of finalised MRPs and DCPs per month in comparison to the procedures that had to be referred to the CMD(h).

Month	MRP finalised	MRP referred to CMD(h)
Nov 05	38	1
Dec 05	21	9
Jan 06	46	8
Feb 06	24	17
Mar 06	82	7
Apr 06	9	2
May 06	32	3
Jun 06	60	6
Jul/Aug 06	114	14
Sep 06	41	6
Oct 06	9	10
Nov 06	47	13
Dec 06	71	18
Sum	**594**	**114**

Table 2: Finalised MRPs in comparison to MRPs referred to the CMD(h)

Month	DCP finalised	DCP referred to CMD(h)
Nov 05 - Jun 06	0	0
Jul/Aug 06	10	0
Sep 06	4	0
Oct 06	4	0
Nov 06	1	1
Dec 06	38	0
Sum	**57**	**1**

Table 3: Finalised DCPs in comparison to DCPs referred to the CMD(h)

As 402 DCPs are still in progress (status: 31 December 2006) and only 57 procedures have been finalised in 2006, it is likely that the number of negotiations in the CMD(h) concerning DCPs will also increase. It is an interesting question if the percentage of DCPs that are referred to the CMD(h) will be higher, lower or similar as for MRPs. On the one hand, in the DCP the RMS and all CMS are involved from the beginning, so that the time to resolve controversy discussed issues is higher than in the MRP. Moreover in the DCP the CMS do not have to recognise an already granted marketing authorisation and could give their comments and requirements during the complete procedure. But on the other hand there are cases were it is impossible to reach agreement, independent of the available time, as the point of view of some MS are completely different.

The answer to this question will be found in the statistical evaluation of the procedures in 2007.

The diagram 1 shows the number of MRPs referred to the CMD(h) in comparison to finalised procedures. The graphic shows no trend, i.e. an increase or decrease over the analysed period of time.

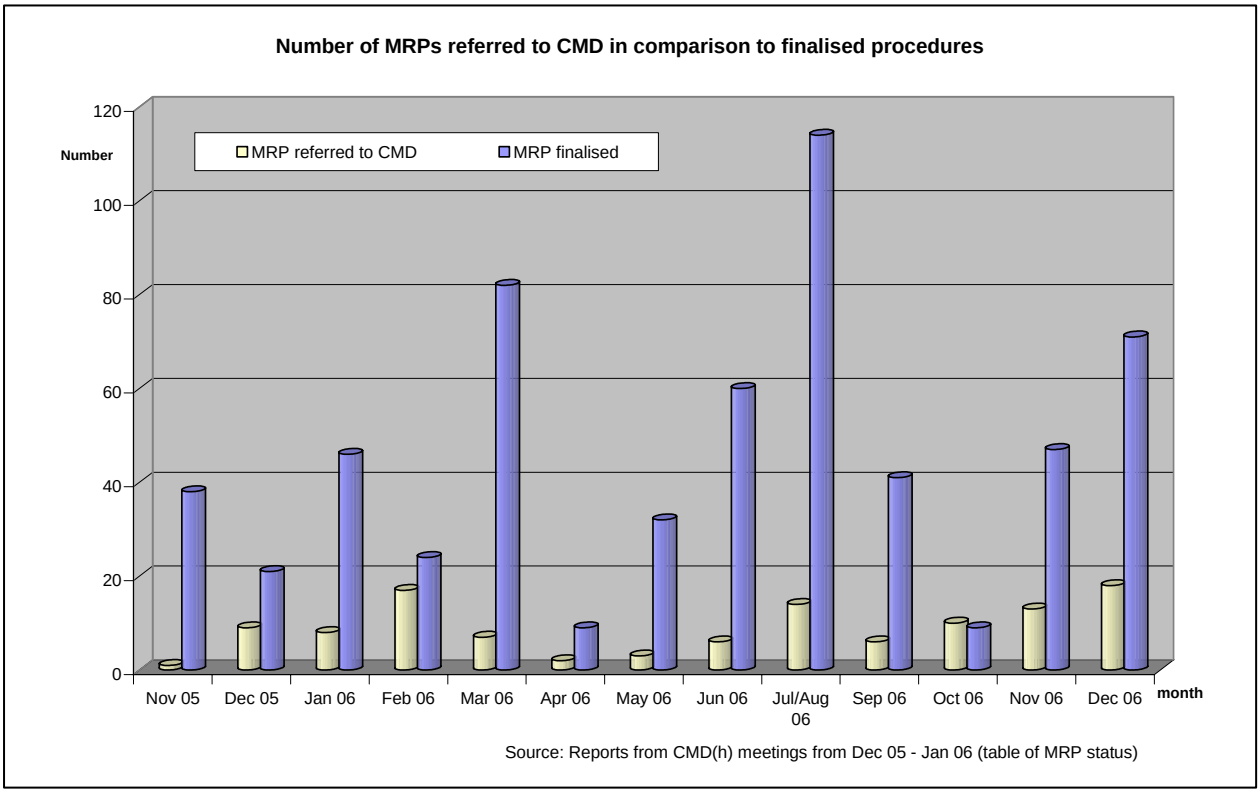


Diagram 1: Number of MRPs referred to CMD(h) in comparison to finalised procedures

10.2 Reasons for referral to CMD(h)

What are the reasons that the MS are unable to reach agreement in the MR procedure?
It should be mentioned that only the grounds for the 80 MRP referrals in 2006 could be evaluated as the information about the first DCP CMD(h) negotiation has not been published yet (status: February 07). Furthermore in some cases several reasons are mentioned in one procedure, so that the sum of all issues that are listed in diagram 2 is more than 80.
According to the CMD(h) reports, the CMS and the RMS have in most of the 60 days procedures divergent opinions on the product information (42 %), i.e. the SPC and the PL. In many of these cases, the difference in the approved indication or posology between innovator SPC in RMS and CMS was discussed. Some CMS were of the opinion that the omission of an indication is a potential serious risk to public health because all information in SCP and PL for interchangeable generic products should be consistent. It is difficult to evaluate the exact percentage of these cases, as the information from finalised CMD(h) procedures in the monthly reports do not always explain the background in detail.
As the MS were in so many cases unable to reach agreement when a generic medicinal product has more or fewer indications than the reference product in the CMS, the CMD(h) released a statement in its monthly report from November 2006, that referral to the coordination group

should only take place in cases with a potential serious risk to public health [14]. The deviation in indications (more or fewer) in the generic product from the national reference product in the CMS should not automatically be considered as a reason for refusing the licensing of a medicinal product. The CMD(h) also developed a document regarding the processing of these generic applications [72].

Three procedures concerning medicinal products for contraception were referred to the coordination group, as the PLs were regarded as being too long and with too many details which are not relevant and not always understandable for women [14]. It is unlikely that this problem will occur in future procedures, as this issue could be avoided with a user test of the PL before the start of the MRP.

The CMD(h) also discussed many bioequivalence and GCP issues (37%). This number includes the four MRP applications with the active substance sumatriptane succinate, that were referred to the CMD(h) procedure due to raised non-GCP compliance of the submitted bioequivalence study. As the applicant has withdrawn the marketing authorisation in the RMS and all applications in the CMS, the CMD(h) decided that no further actions were necessary, as the potential serious risk was not related to the active substance, but to the particular medicinal product [14].

Although the CHMP released a questions and answers document in 2006 that should harmonise the interpretation of the critical parts of the bioavailability and bioequivalence guideline, many issues remain unresolved [83, 84]. Therefore it would be useful to update the questions and answers document after the experience obtained in the CMD(h) referrals and Commission Decisions after arbitration procedures.

Further negotiations in the CMD(h) concerned quality (2%), safety and/or efficacy issues (11%). Last but not least there are a few reasons (8%) for referral to the CMD(h), that could not be grouped in the other areas, e.g. different interpretation of existing bibliographic data , lack of direct comparison versus an active comparator and in the case of oxaliplatine one MS raised a potential risk due to the chosen type of application [14].

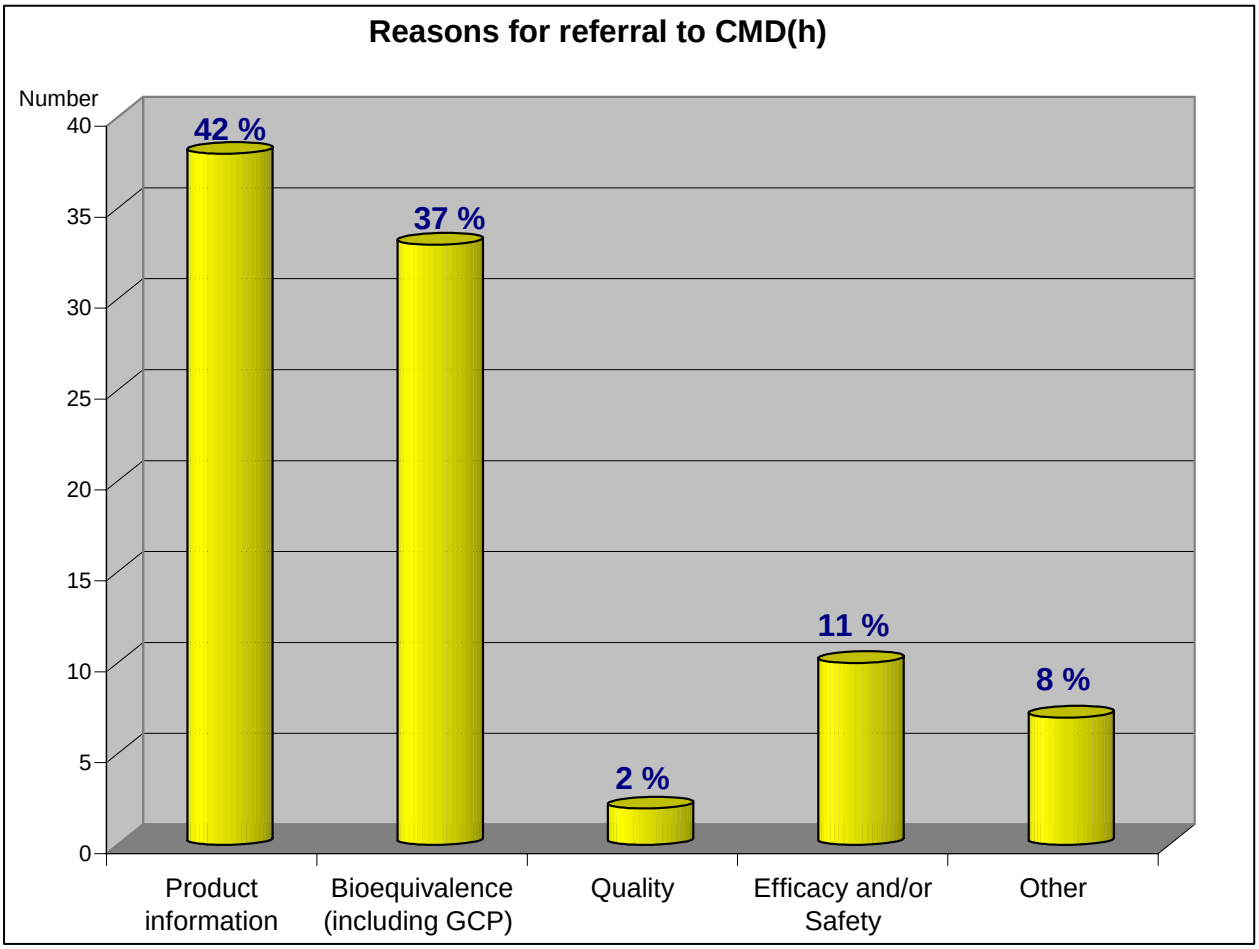


Diagram 2: Reasons for referral to the CMD(h)

10.3 Outcome of the discussion in the coordination group

Is there a chance for finding a solution on the discussed issues in the CMD(h)?
In the first phase after the new legislation came into force, a few industry representatives doubt whether the CMD(h) could solve the problems. In comparison to the CHMP there is no majority vote system on the matter and therefore all involved MS have to agree.
But the statistical evaluation shows, that agreement could be reached in 71% of all cases, whereas 29% of the procedures had to be referred to the CHMP for arbitration (see table 4). Five applications and marketing authorisations with the active substances sumatriptan succinate and opipramole were withdrawn in the RMS and all CMS after referral to the CMD(h).

	Agreement	Arbitration	Withdrawal
Jan 06	1		
Feb 06			
Mar 06	10	7	
Apr 06			4
May 06	9	7	
Jun 06	3	1	
Jul/Aug 06	3	2	
Sep 06	5	2	
Oct 06	8		
Nov 06	9	1	
Dec 06	5	2	1
Sum	53	22	5
%	66	28	6

Table 4: Outcome of the CMD(h) referrals in 2006

The diagram 3 illustrates the figures.

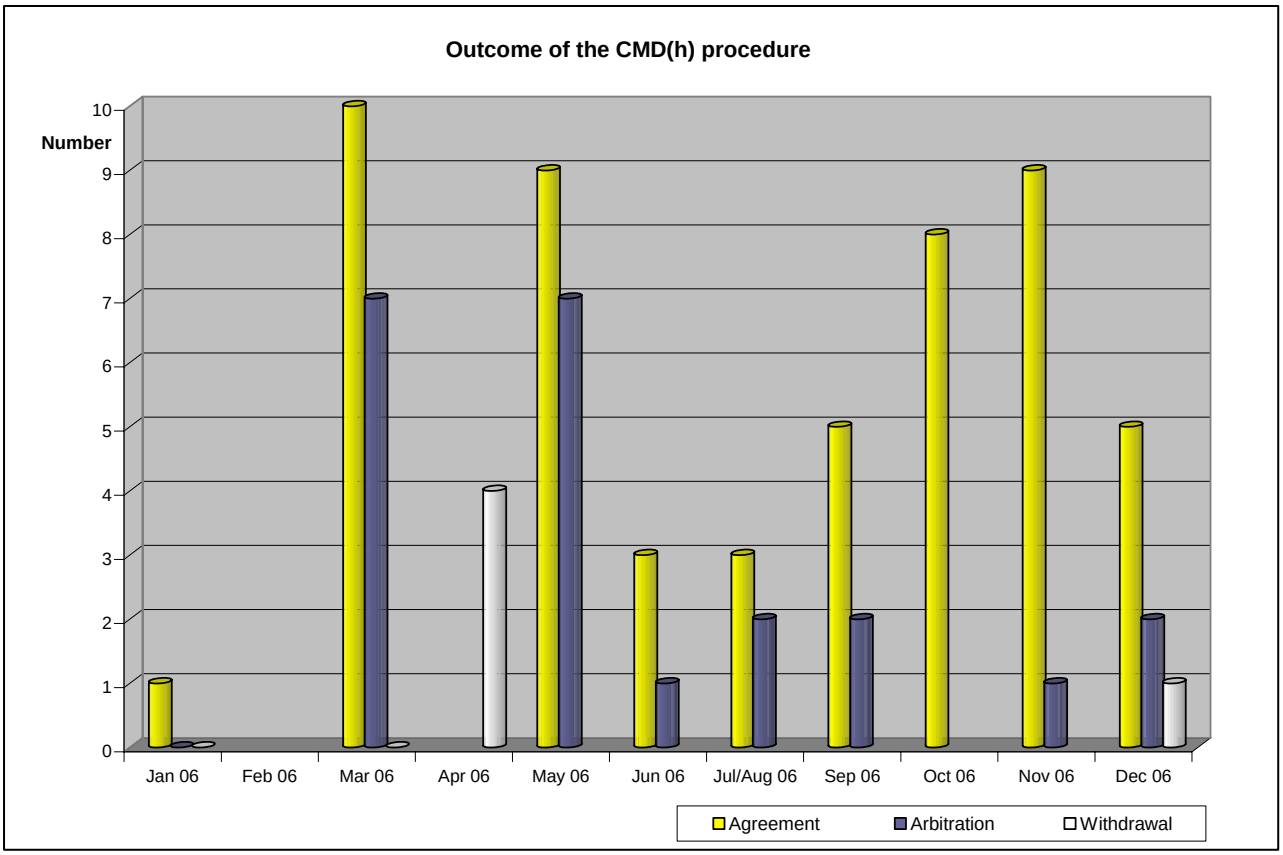


Diagram 3: Outcome of the CMD(h) procedure

10.4 Reasons for arbitration

In which cases is the coordination group unable to achieve a common position?
The diagram 4 illustrates the reasons for referral to the CHMP.
If the bioequivalence study is concerned it is difficult to find an agreement, as a new one could not be submitted during the procedure. Furthermore the bioequivalence guideline is interpreted differently by the MS and does no address all issues, as already mentioned.
It should also be taken into consideration that a national scientific advice from one authority may not be accepted by another national competent authority, as the personal scientific and educational background of the assessors is different [80].
Therefore applications with divergent opinions about the bioequivalence of generic medicinal products often were referred to arbitration (67%). The CHMP also has to discuss many unresolved issues about the product information (29%), but it is more likely that the CMD(h) could find a solution in cases concerning the SPC/PL than in MRPs with study problems.
In one procedure with the active substance glucosamine hydrochloride the CMD(h) could not reach agreement on the existing bibliographic data concerning safety and/or efficacy (4%).

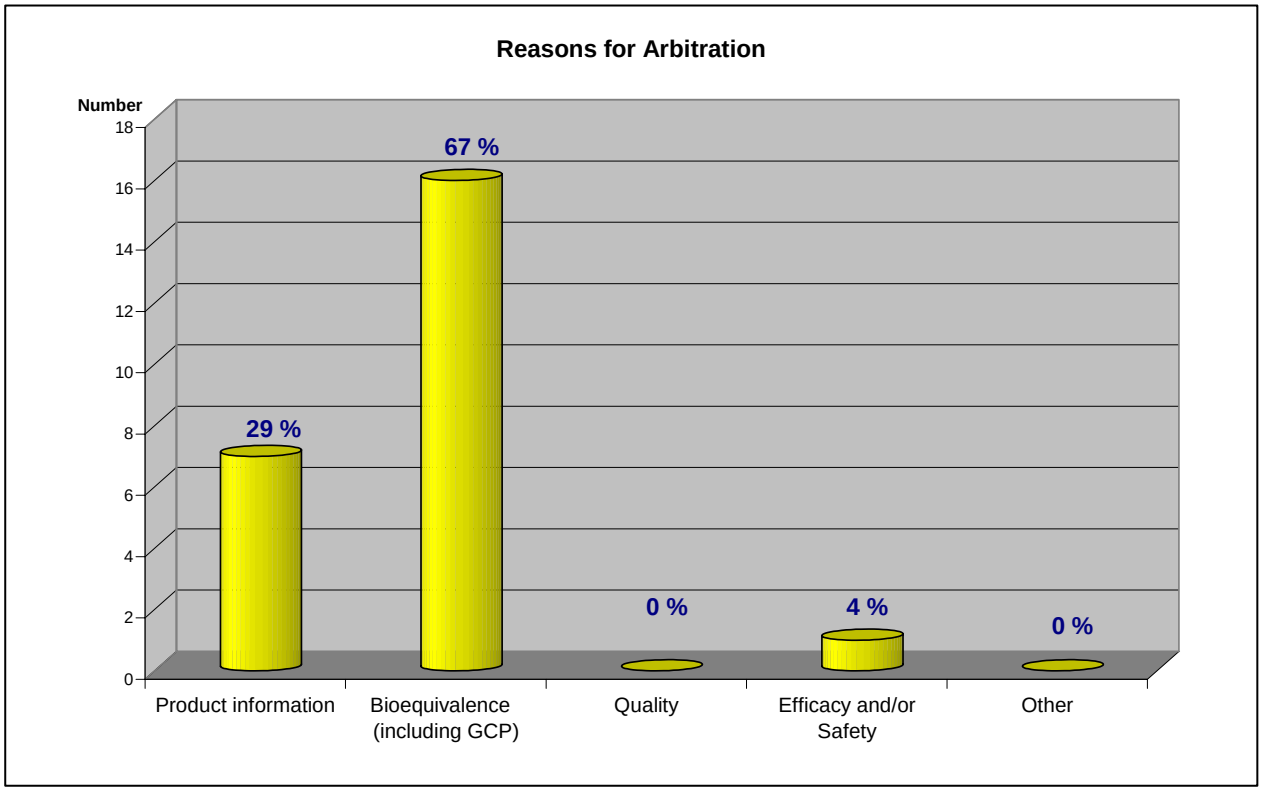


Diagram 4: Reasons for Arbitration

The table 5 compares the reasons for referral to the CMD(h) and to the CHMP.
It shows that the CMD(h) could in most cases find a solution if the involved MS have divergent opinions concerning the product information, quality, efficacy and/or safety, whereas bioequivalence issues often have to be referred to arbitration.

	CMD(h) Referral	CHMP Arbitration
Product information	37	7
Bioequivalence (including GCP)	33	16
Quality	2	1
Efficacy and/or Safety	10	1
Other	7	0
Sum	89	25

Table 5: Comparison of the reasons for referral to the CMD(h) and for CHMP arbitration procedures

10.5 Outcome of article 29 referrals

Last but not least the outcome of article 29 arbitration procedures should be analysed.
The table 6 lists all procedures that have been referred to the CHMP after the new legislation came into force. If possible several procedures with the same active substance and the same issue were grouped together.
The CHMP already gave four positive and two negative scientific opinions. The corresponding Commission Decision is publicly available in three cases.
The positive opinions concerned the product information, safety/efficacy and also the bioequivalence.
Zentiva's Alendros 70, a generic version of Merck &Co's Fosamax tablets (alendronate sodium) was intended for the treatment of osteoporosis in postmenopausal women. The CHMP recommended by majority the refusal of the marketing authorisation in the CMS and the suspension of the RMS approval on the grounds that it has not shown bioequivalence to the originator [74, 75].
The same reason was mentioned in the second negative opinion that concerned metoprolol/felodipine containing medicinal products. In this case the CHMP recommended by consensus that the product should not be placed on the market in the CMS and has also to be suspended in the reference country as bioequivalence with the reference medicinal product (Mobloc/Logimax), that is intended for the treatment of arterial hypertension, has not been demonstrated [76].

Active substance	Reasons	CMD(h) day 60	Number of procedures involved	Outcome	Commission Decision
Doxazosin mesylate	Bioequivalence	03.03.2006; 31.03.2006	5	Positive (CHMP monthly report Jun 06)	11.10.2006
Glucosamine hydrochloride	Safety/Efficacy	31.03.2006	1	Positive (CHMP monthly report Sep 06)	13.12.2006
Alendronic acid	Bioequivalence	31.03.2006	1	Negative (CHMP monthly report Oct 06)	
Ciprofloxacin	Product information	02.05.2006; 09.06.2006; 06.07.2006	3	Positive (CHMP monthly report Nov06/ Jan07)	24.01.2007
Metoprolol/ Felodipine	Bioequivalence	02.05.2006	6	Negative (CHMP monthly report Dec 06)	
Alendronic acid	Product information	06.07.2006	1	Positive (CHMP monthly report Jan 07)	
Cefuroxime	Product information	25.09.2006	1		
Fexofenadin hydrochloride	Bioequivalence	25.09.2006	1		
Lansoprazole	Bioequivalence	23.11.2006	1		
Fentanyl	Product Information, Bioequivalence	18.12.06	2		

Table 6: Overview of all CHMP arbitration procedures

11. Conclusion

In this last part the advantages and disadvantages of the new established CMD(h) should be evaluated and consequences discussed.

First, it should be mentioned that the CMD(h) procedures had an influence on the registration strategy. It could be an advantage to plan smaller duplicate MRPs or DCPs and group together the non-critical countries and those were the likeliness for the referral to the CMD(h) is higher. If agreement could be reached in the "non-critical" procedure, the MRP or DCP is closed and the national phase follows, although a MS of the second duplicate procedure raised a potential risk. Only this last mentioned MRP or DCP will be referred to the CMD(h).
In the finalised procedure the national marketing authorisation could theoretically be granted, but in some cases the MS wait for the outcome of the CMD(h) procedure for the duplicate application.

What are the advantages of the new group?
The new legislation leads to harmonisation of decisions, as it is not longer possible to withdraw a MS that raised a potential risk to public health in the MRP and in the DCP after day 120, without any consequences. In the subsequent CMD(h) procedure the issue will be discussed and if no agreement could be achieved the application will be referred to the CHMP for arbitration. The final Commission Decision leads to a single ruling on the area of disagreement, which is binding on the MS concerned [6]. This new procedure makes sense, as if a potential serious risk to public health exists, the medicinal product should not be placed on any market in the EU. Furthermore if the CHMP and the European Commission consider that the benefit-risk ratio is favourable and the objections raised should not prevent the granting of a marketing authorisation, the countries could not hind the launch of products and therefore the free movement of safe goods.
In some cases the divergent position of some MS is based on the decision of national advisory committees, national safety or pharmacovigilance decisions and/or national court cases [80]. Therefore it is not possible for the CMD(h) representative of that country to change his/her opinion. In this case the decision of the European Commission is necessary that the national authority is able to move [80].
For example the applications with the active substance glucosamine were referred to the CHMP and received positive opinions by majority. As a consequence the borderline between medicinal product and food supplement was established, as the CHMP was of the opinion that the discussed strength is a medicinal product and not a food supplement. The Commission Decision overruled previous negative national decisions and (ongoing) court cases [80].
Before the new legislation came into force many applications were withdrawn to avoid the time-consuming arbitration procedures. This withdrawal of disagreeing MS led to expensive back-up solutions for getting a marketing authorisation for a specific medicinal product in that country.

One possibility was the repeat use, i.e. the reapplication to the CMS withdrawn from the first procedure. Sometimes a potential health issue could be solved by providing additional data before the reapplication, as it is not acceptable to submit additional data during a MRP [40].
That solution was costly and very time-consuming. Furthermore it was unclear if the issue could be solved in the meantime and that the critical CMS could really be persuaded to grant the marketing authorisation.
Another possibility was to licence a marketing authorisation from another pharmaceutical company or developer in that MS that had to be withdrawn in the own procedure to avoid arbitration. Also this solution was very expensive.
It should be mentioned here that the withdrawal of the MS that raised a potential serious risk could nevertheless be an option to avoid arbitration. In one case the RMS gave the advice to withdraw the application during the CMD(h) procedure in a specific country, as the disagreeing state signalised that they would agree if the medicinal product will not be placed on their market.
However in most cases the withdrawal of the disagreeing country does not make sense, as consensus has to be reached by the MS concerned by the application, which also includes CMS where the application was withdrawn. Moreover if agreement could be reached the applicant has to submit a repeat use application for getting the marketing authorisation in the withdrawn MS.

What are the negative aspects of the new provision that the withdrawal of the disagreeing MS is no longer possible in the MRP and DCP (after day 120) without any consequences?
We should not forget that time to market is very important for generic medicinal products. Therefore the 60 additional days for the discussion in the coordination group could be a long time, if other pharmaceutical companies are able to launch their products directly after patent expiry. An early market entrance for generics is important as a higher market share and therefore significant economic returns for being first could be achieved [77]. If a physician prescribes a generic medicinal product instead of the original one for the first time, it is very likely that he or she will not change to another generic. That is mainly the case for medicinal products that have to be taken regularly, for example for the decrease of blood pressure [77].
If no agreement could be reached in the CMD(h), an arbitration procedure will follow. With the duration of approximately 7-12 months, it is unlikely that the product could be placed on the market on time, i.e. after the expiry of patent and data exclusivity.

Moreover the CMD(h) procedure could have another negative impact for pharmaceutical companies.
Even if the coordination group is able to reach consensus on the product information, the outcome can have serious consequences for reimbursement [81]. Unlike in Germany an authorised generic medicinal product will not automatically be reimbursed by the statutory health insurance in many countries.
For example in Spain a generic medicinal product does not get the so-called EFG status if the generic and the original national SPC are different. Without that status reimbursement of the concerned medicinal product is not possible. Therefore compromises in the CMD(h) procedure could lead to reimbursement issues.

To improve this situation the coordination group already published a list of medicinal products for which the SPC should be harmonised across the Community. But these article 30 procedures are very time-consuming, especially as the interest of the originator companies to finish this forced procedures early is low.
But is should also be mentioned that the number of companies using the CP for the approval of medicinal products with new active substances has increased in the last years. As these products have the same product information in all MS, the issue concerning different SPCs in the countries will decrease in the future.

A few positive and negative aspects of the new CMD(h) have been discussed. So, what could be improved from an industry perspective?
First, the applicant has no possibility to appeal against a CMD(h) decision if the outcome of the procedure is not satisfying, for example if the medicinal product will not be reimbursed due to a compromise of the group concerning the product information.
Second, the guideline does not include the provision, that a MR or DC procedure could be referred to the CMD(h) before day 90 and 210, respectively. But in many cases the positions are clear and are unlikely to be changed. Therefore it would be an advantage if the CMD(h) referral could start earlier if all involved MS agree that this timeline could be shortened [81].
Sometimes only one MS raises a potential serious risk to public health whereas all other countries are willing to grant the marketing authorisation. Unlike the majority vote system in the CHMP the CMD(h) has to achieve a common position, i.e. every opinion has to be taken into consideration. This is a clear disadvantage in the viewpoint of the pharmaceutical industry. Clarification of the controversial issue between authorities in the 60 days CMD(h) procedure should be preferred over the clarification via arbitration procedure [29]. The number of arbitration procedures has increased since the new legislation came into force, as the referral to the CHMP is the last tool to achieve common position. Therefore it would be an advantage, if the CMD(h) would be able to vote instead of a decision by consensus.
Furthermore in some procedures MS raised issues that are not in line with the corresponding guideline on the definition of a potential serious risk to public health in the context of article 29(1) and (2) of Directive 2001/83/EC as amended. A more harmonised interpretation would minimise the procedures that are referred to the CMD(h). To improve this situation a check by the RMS and the CMD(h) members if the raised potential serious risk to public health is valid before the initiation of the referral would be an advantage.

Last but not least a few questions remain.
So, particular MS often raise potential serious risks to public health, even if all other involved countries are willing to grant the marketing authorisation. Will theses MS change their evaluation, if they recognise that the recommendations of the CHMP are contrary to their point of view? Furthermore will the European Commission try to influence MS that in most cases do not agree with the evaluation of all other MS?

With the new legislation the MS have to reach agreement in the procedures for getting a marketing authorisation. As already mentioned in the statistical part, the new established CMD(h) is in many cases able to solve the issues within the 60 days and so time-consuming article 29 referrals could be avoided. Although there are still many issues and procedures that could be improved, the new CMD(h) is a chance to increase the harmonisation in the EU and therefore for reaching agreement in MRP and DCP.

12. Summary

The Mutual Recognition Facilitation Group (MRFG) was established in 1995 to coordinate and facilitate the operation of the MRP (Mutual Recognition Procedure) and was regarded as a major player in the European system. However the lack of a legal basis and the fact, that the group could not discuss scientific problems related to individual applications were recognised as a clear disadvantage for solving issues in MRPs.

With the revision of the legislation, the already existing cooperation group MRFG became an official status and was renamed Coordination Group for Mutual Recognition and Decentralised Procedures (human) (CMD(h)).

The new CMD(h) is composed of one representative per EU member state, who is appointed for a period of three years. The MRFG was chaired by the country which held the presidency of the EU and therefore a new person was appointed every six months. For a better consistency of decisions this procedure has been changed with the new legislation and so the chairperson of the CMD(h) is elected by and from amongst its members for a period of three years which could be renewed once.

It should also be mentioned that the new legislation established many new transparency measures for the procedures and also for the CMD(h). Therefore the group published its “rules of procedure” and also the membership and professional qualifications of each member.

According to Article 27 of Directive 2001/83/EC as amended the coordination group is “set up for the examination of any question relating to the marketing authorisation of a medicinal product in two or more member states” in the MRP and DCP (Decentralised Procedure) and is, according to the Notice to Applicants, “responsible for the smooth functioning and good outcomes of the MRP and DCP with a mix of regulatory and scientific work”.

This definition covers a variety of tasks, for example the 60 days CMD(h) procedure.

If a member state raises grounds for supposing that the authorisation of the medicinal product concerned may present a potential serious risk to public health, the procedure will be referred to the CMD(h).

Based on Article 29(2) of Directive 2001/83/EC as amended the European Commission adopted a guideline that defines in which exceptional cases a member state can refuse to recognise a marketing authorisation (MRP) or a positive assessment (DCP) on the basis of a potential serious risk to public health.

The involved countries should use their best endeavours to find a solution in the 60 days CMD(h) procedure. In the exceptional case that the CMD(h) is unable to reach agreement an arbitration procedure will be initiated, leading to a single decision on the area of disagreement and binding on the member states concerned. The goal of the coordination group is to solve the majority of issues and avoid article 29 referrals.

The 60 days CMD(h) procedure is applicable for new MRP and DCP applications, repeat use submissions, extensions and renewals. It should be mentioned that variations are excluded, as they are not covered by the legislation, but could be discussed in the regular work of the coordination group.

This thesis gives an overview of the tasks, composition and transparency measures of the CMD(h) and the difference to its predecessor MRFG. After a short description of the procedures that lead to referral to the coordination group and the 60-days CMD(h) procedure itself, a statistical evaluation of the number and reasons of new CMDs, outcome of the 60 days procedure and the cases that have to be referred to arbitration, will follow. Last but not least the advantages and disadvantages of the new group will be discussed and also proposals for improvement considered.

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Annex I: Overview of all evaluated CMD(h) procedures

	CMD Day 60	Name Product	Active substance	Legal basis	Procedure number	Reason CMD	Reason CMD (class)	Outcome CMD	Reason Arbitration
1	30.01.06	Omperazol 10, 20, 40 mg capsules	Ome-prazole	Generic	UK/H/799/01 -03	Different interpretation with regard to existing guidelines on the required bioequivalence data for the formulations	BE (bio-equivalence)	Agreement	
2	03.03.06	Epra-tenizide plus 600/12,5 mg	Eprosartan, hydro-chloro-thiazide	Fixed combi-nation	DE/H/538/01	Efficacy of the combination product in comparison to eprosartan as monotherapy. Inconsistent information in SPC in section 4.6 in comparison to other medicinal products with angiotensin-II antagonists in combination with hydrochlorothiazide	Efficacy, PI (product information)	Agreement	
3	03.03.06	Cardoreg	Doxazosin mesylate	Generic	DK/H/429/01 /E01	Different view on the clinical consequences of deviation from the existing bioequivalence guideline	BE	Referral	BE
4	03.03.06	Doxa-gamma			DK/H/624/01 /E01		BE		BE
5	03.03.06	Doxastad			SE/H/469/01		BE		BE
6	03.03.06	Formoterol Novolizer 6µg, 12µg	Formoterol	Last para-graph	DE/H/571/01 -02	Different interpretation of the submitted data concerning safety and efficacy of the medicinal product (last paragraph)	Safety/ Efficacy	Agreement	
7	03.03.06	Lanso-prazole Vetiquima 15 mg, 30mg	Lanso-prazole	Generic	PT/H/113/01 -02	Choice and composition of meal content used in the fed bioequivalence study and risk of dose dumping related to food intake. Discussion on clinical relevance of a lower Cmax for the test product.	BE	Agreement	
8	03.03.06	Lanso-prazole Suprazol 15, 30mg		Generic	PT/H/114/01 -02		BE		
9	03.03.06	Nurofen Junior Zäpfchen 60 mg	Ibuprofen	Biblio-graphic	DE/H/0433/0 1	Different interpretation of the existing bibliographic data.	Other	Agreement	

	CMD Day 60	Name Product	Active substance	Legal basis	Procedure number	Reason CMD	Reason CMD (class)	Outcome CMD	Reason Arbitration
10	03.03.06	Alfuzosin Stada	Alfuzosin	Generic	SE/H/559/01	Deficiencies in the study design to fully evaluate the influence of food on the formulation.	BE	Agreement	
11	31.03.06	Fostimon 75, 150 IU/ml	Uro-follitropin	Full dossier	FR/H/282/01 -02	Efficacy in the clamined indication and safety (immunogenicity)	Efficacy/ Safety	Agreement	
12	31.03.06	Glucomed 625 mg tablet	Gluco-samine hydro-chloride	Biblio-graphic	SE/H/560/01	Different interpretation of the submitted quality data and existing bibliographic data concerning safety and efficacy.	Quality, Safety/ Efficacy	Referral	Safety/ Efficacy
13	31.03.06	Alendros 70	alendronic acid	Generic	CZ/H/115/01	Different views on the clinical consequences of deviation from the existing bioequivalence guideline.	BE	Referral	BE
14	31.03.06	Doxazosin NM Pharma	Doxazosin mesylate	Generic	SE/H/465/01	Different views on the clinical consequences of deviation from the existing bioequivalence guideline.	BE	Agreement	
15	31.03.06	Doxazosin Retard Arrow 4 mg prolonged release tablets	Doxazosin mesylate	Generic	DK/H/431/01 /E/01	1. Different views on the clinical consequences of deviation from the existing bioequivalence guideline. 2. One CMS for Doxazosin Retard “Arrow” raised concerns over the indication “Essential Hypertension”. Agreement was reached in the CMD(h) on the wording of the indication.	BE, PI	Referral	BE
16	31.03.06	Doxazosin Retard Winthrop 4 mg prolonged release tablets	Doxazosin mesylate	Generic	DK/H/694/01 /E/01		BE	Referral	BE

	CMD Day 60	Name Product	Active substance	Legal basis	Procedure number	Reason CMD	Reason CMD (class)	Outcome CMD	Reason Arbitration
17	31.03.06	Ramipril Capsules 1.25, 2.5, 5, 10 mg	Ramipril	Generic	UK/H/830/01 -04	1. Difference in approved indications between RMS SPC and CMS, such that the following indications are not included in the UK SPC: • Treatment of manifest non-diabetic glomerular nephropathy • Treatment of incipient diabetic nephropathy (microa-lbuminuria) in patients with type 2 diabetes mellitus and hypertension The CMS considered that omission of these indications was a public health concern because all information in SPC and PIL for interchangeable generic products should be consistent. 2. One CMS raised concern over interpretation of criteria for extra-polation of results from a bioequi-valence study conducted with the 10mg strength capsules to the 1.25mg strength, based on linearity of ramipril/ramiprilat pharmacokinetics over this dose range.	PI (Harmoni-sation), BE	Agreement. Further action in the Sub-group on harmonisation of SPCs.	
18	31.03.06	Lamo-trigine 25, 50, 100, 200mg	Lamotrigine	Generic	UK/H/827/01 -04	Difference in approved indications between innovator SPC in RMS and CMS, such that the indication for bipolar disorder is not included in the RMS SPC. One CMS considered that omission of this indication was a PSRPH because all of the information in the SPC and PIL for interchangeable generic products should be consistent.	PI (Harmoni-sation)	Agreement. Further SPC activity proposed.	

	CMD Day 60	Name Product	Active substance	Legal basis	Procedure number	Reason CMD	Reason CMD (class)	Outcome CMD	Reason Arbitration
19	--	Sumatriptan Basics 50/100 mg	Suma-triptane succinate	Generic	DE/H/0530/001-2	Non-GCP compliance of the submitted bioequivalence study.	BE (GCP)	Withdrawal of the marketing authorisation and applications in the RMS and CMS. No further actions were deemed to be necessary by the CMD(h), as the PSRPH raised was not related to the active substance, but to the specific medicinal products.	
20		Sumatriptan Basics F 50/100 mg			DE/H/0545/001-2		BE (GCP)		
21		Sumatriptan Basics A 50/100 mg			DE/H/0591/001-2		BE (GCP)		
22		Sumatriptan Basics B50/100 mg			DE/H/0592/001-2		BE (GCP)		
23	02.05.06	TerbiLich 250 mg	Terbinafin	Generic	DE/H/0555/01	Different interpretation of the available clinical and toxicological data with regard to the inclusion of paediatric indications to the product information	PI	Agreement. Current product information will not extented; wait of outcome of the evaluation of paediatric data for terbinafine in peadiatric worksharing project of HMA.	

	CMD Day 60	Name Product	Active substance	Legal basis	Procedure number	Reason CMD	Reason CMD (class)	Outcome CMD	Reason Arbitration
24	02.05.06	Cipro-floxacin 2mg/ml solution for infusion	Cipro-floxacin	Generic	UK/H/848/01	The procedure highlighted differences in approved posology between national 'brand leader' SPCs. Specifically, the referring CMS objected to the RMS approved posology for urinary tract infections, UTI (100mg twice daily) and considered that the maximum recommended daily dose (800mg) should be increased up to 1200mg daily. Referring CMS consider that the experience of UTI posology of 200-400mg twice daily in a number of EU Member States, together with available published data from open post marketing studies, would justify amendment to the RMS approved posology (UTI). Furthermore, referring CMS were concerned that the SPC should include an optimal dosage regimen because, in their view, the RMS approved posology may risk sub-therapeutic dosing and lead to development of resistance. The RMS considered that the available information was insufficient to justify amendment to the posology and in the absence of data in favour or against the different options under discussion a consensus could not be reached.	PI (Harmoni-sation)	Referral	PI (Harmoni-sation)
25	02.05.06	Estradiol 2mg film-coated tablets	Estradiol	Generic	NL/H/685/01	The indication "Prevention of osteoporosis in postmenopausal women at high risk of fractures who are intolerant or contraindicated for other medicinal products approved for the prevention of osteoporosis" is beyond the indications approved for the reference product in one CMS.	PI (Harmoni-sation)	Agreement. Procedure is finalised without the osteoporosis indication. The applicant commits to submit a type II variation to introduce this indication.	
26	02.05.06				NL/H/686/01		PI (Harmoni-sation)		

	CMD Day 60	Name Product	Active substance	Legal basis	Procedure number	Reason CMD	Reason CMD (class)	Outcome CMD	Reason Arbitration
27	02.05.06	Modafinil 100mg Tablets	Modafinil	Generic	UK/H/834/01	Concerns were raised on the GCP documentation for the bioequivalence study. Concerns were raised that the deletion of the indication for Obstructive sleep apnoea, which is authorised in some CMS, might result in inadequate information being provided to some patients. The applicant addressed all the concerns. Some changes were made to the Patient Information Leaflet	BE (GCP), PI (Harmoni-sation)	Agreement	
28	02.05.06	Equasym 10, 20 and 30mg Capsules	Methyl-phenidate hydro-chloride	Last paragraph	UK/H/819/01 -03	There were concerns that the once daily treatment with Equasym XL would not give sufficient therapeutic cover relative to the immediate release (IR) formulations. There were concerns that treatment with Equasym XL would provide less control of symptoms after the school day than a conventional twice daily regimen of IR methylphenidate and hence that patients using Equasym XL would be more likely to require additional IR methylphenidate to control ADHD, resulting in increased overall exposure to methylphenidate. There were concerns regarding initiating methylphenidate treatment with Equasym XL in the treatment of naive patients. Finally the applicant was requested to provide a risk management plan (RMP). The applicant addressed all the concerns. Some alterations were made to the SPC to clarify some of the above issues and a RMP has been agreed.	PI	Agreement	

	CMD Day 60	Name Product	Active substance	Legal basis	Procedure number	Reason CMD	Reason CMD (class)	Outcome CMD	Reason Arbitration
29	02.05.06	Metoprolol/ Felodipin Yes	Felodipine/ metoprolol tartrate	Generic	DK/H/853/01	Different interpretation of the submitted study to establish therapeutic equivalence.	BE	Referral	BE
30	02.05.06	Metafelosan			DK/H/854		BE		BE
31	02.05.06	Mefelor			DK/H/884/01		BE		BE
32	02.05.06	Mefesan			DK/H/885/01		BE		BE
33	02.05.06	Mefecur			DK/H/886/01		BE		BE
34	02.05.06	Mefecomb			DK/H/887/01		BE		BE
35	02.05.06	Yasminelle	Dros-pirenone, ethinyl estradiol	Full dossier	NL/H/701/01	The proposed PL is not in accordance with the Directive 2001/83/EC, which states that "the package leaflet must be written and designed to be clear and under-standable, enabling the user to act appropriately". The proposed PL is too long, repetitive and alarming for women, with too many details, which are not relevant and not always understandable for women. The text in the paragraph on liver tumours under section *Yasminelle and cancer* is not agreed, like the recommendations on the shift/delay of menstrual period.	PI (PL)	Agreement. MAH commits to perform user consultation in two MS, amongst France.	
36	02.05.06	Belanette			NL/H/702/01		PI (PL)		
37	02.05.06	Yasminelle 28			NL/H/704/01		PI (PL)		
38	02.05.06	Paroxetine Ranbaxy 20mg	Paroxetine	Generic	DE/H/0574/01	The bioequivalence data submitted with the application have been regarded by CMS as not in agreement with the criteria given in the 'Note for Guidance on the Investigation of Bioavailability and Bioequivalence'.	BE	Agreement .The CMD(h) and the MS concerned have noted, that not all criteria mentioned in the Note for Guidance on the Investigation of Bioavail-ability and Bioequivalence are fulfilled. However, due to the nature of the product, these deviations are not of clinical relevance and therefore not a risk to public health. The CMD(h) has agreed to forward questions with regard to the scientific methodology to the PK Study Group of the Efficacy Working Party of the CHMP for further discussion.	

	CMD Day 60	Name Product	Active substance	Legal basis	Procedure number	Reason CMD	Reason CMD (class)	Outcome CMD	Reason Arbitration
39	09.06.06	Loratadine 10mg tablets	Loratadine	Generic	UK/H/829/01 /MR	The application was referred to CMD(h) as the company were unable to resolve all of the CMS concerns in relation to product quality during the 90 day procedure. Further clarification of data was provided during the referral to CMD(h) and consensus was reached.	Quality	Agreement	
40	09.06.06	Cipro-floxacin Kabi 100mg/ 50ml; Cipro-floxacin Kabi 200mg/100 ml, 400mg/200 ml	Cipro-floxacin	Generic	NL/H/695/01 /MR; NL/H/695/02 -03/MR	The procedure highlighted differences in approved posology between national 'brand leader' SPCs. Specifically, the referring CMS objected to the RMS approved posology for urinary tract infections, UTI (200-400 mg twice daily) and considered that the maximum recommended daily dose (1200mg) should be decreased to 800mg daily. The referring CMS considered that the available information was insufficient to justify amendment of the posology. The other MS were concerned that lowering the dose will result in a suboptimal dosage regimen. In their view, the lower dosing may risk sub-therapeutic dosing and lead to development of resistance. In the absence of data in favour or against the different options under discussion a consensus could not be reached.	PI (Harmoni-sation)	Referral	PI (Harmoni-sation)

	CMD Day 60	Name Product	Active substance	Legal basis	Procedure number	Reason CMD	Reason CMD (class)	Outcome CMD	Reason Arbitration
41	09.06.06	Lamo-trigine 25, 50, 100, 200mg Tablets	Lamotrigine	Generic	UK/H/835/01 -04/MR	The application was referred on the basis of the acceptability of the design and conduct of the comparative bioequivalence studies with reference to the Note for Guidance for claiming essential similarity of all strengths; the omission of an additional indication in the summary of product characteristics; agreement of safety information concerning use in pregnancy; and agreement of the patient information. Further clarification of data was provided and agreement of the SPC reached.	BE, PI	Agreement	
42	09.06.06	Lamo-trigine 2, 5, 25, 50, 100, 200mg Dispersible Tablets			UK/H/836/01 -06/MR		BE, PI		
43	06.07.06	Uvadex	Metho-xasalen	Full dossier	UK/H/397/01 /E/01	One CMS was concerned at the evidence supporting dose and irradiation conditions for photoactivation and characterisation of photoactivated cells in relation to clinical efficacy. CMS were reassured by clarification from the company along with a commitment to completion of further characterisation studies.	Efficacy	Agreement	

	CMD Day 60	Name Product	Active substance	Legal basis	Procedure number	Reason CMD	Reason CMD (class)	Outcome CMD	Reason Arbitration
44	06.07.06	Cipro-floxacin Hikma	Cipro-floxacin	Generic	UK/H/397/01/E/01	The procedure highlighted differences in approved indications, posology and contra-indications between national 'brand leader' SPCs. Specifically, the referring CMSs objected to the RMS approved posology for complicated urinary tract infections, UTI (200-400 mg twice daily) and considered that the maximum recommended daily dose (1200mg) should be decreased to 800mg daily. In the absence of data in favour or against the different options under discussion a consensus could not be reached on the posology. Consensus was reached on the other grounds of referral, which means that the indications treatment of osteomyelitis and complicated skin infections was accepted by all MS, like as the contraindication for the concomitant use with tizanidine, and the inclusion of a special warning for use in patients with pre-existent significant renal disorders. All CMD members were of the opinion that the organisms listed in the breakpoints and susceptibility table should be relevant to the indications exclusively. It was decided to add this point to the request for an article 29(4) referral as a remark.	PI (Harmoni-sation)	Referral	PI (Harmoni-sation)
45	06.07.06	Alendronat Hexal	Alendronic acid	Generic	SE/H/517/E 01	The indication "Prophylaxis of glucocorticoid-induced osteoporosis" was initially not accepted by one member state, but was accepted during the CMD(h) referral. The indication "Treatment of osteoporosis in men" is not acceptable to two CMS.	PI	Referral	PI
46	04.08.06	Protamin-sulfat Leo Pharma	Protamine sulfate	Bibliog.	SE/H/562/01/MR	PSRPH concerns were raised by one CMS, especially relating to the posology and the declaration of the strength.	PI	Agreement	
47	04.08.06	Matrifen	Fentanyl	Generic	SE/H/568/01-05/MR	PSRPH concerns were raised by one CMS regarding the wording of the indication.	PI	Agreement	

	CMD Day 60	Name Product	Active substance	Legal basis	Procedure number	Reason CMD	Reason CMD (class)	Outcome CMD	Reason Arbitration
48	01.09.06	Fentanyl ratiopharm 25, 50, 75, 100 mcg/h Matrixpflaster	Fentanyl	Generic	DE/H/634/01-04/MR	Potential serious risk to public health concerns were raised by one CMS regarding the wording of the indication.	PI	Agreement	
49	01.09.06	Fentanyl CT 25, 50, 75, 100 mcg/h Matrixpflaster			DE/H/635/01-04/MR		PI		
50	01.09.06	Ribo-fentanyl 25, 50, 75, 100 mcg/h Matrixpflaster			DE/H/636/01-03/MR		PI		
51	25.09.06	Tarka Tablets	Trandolapril/ verapamil hydro-chloride	Fixed Combi-nation	NL/H/107/05-06/MR	One of the MS is of the opinion, that the clinical program submitted cannot support the proposed indications. Demonstration of a superior blood pressure lowering of the 240/2 and 240/4 mg dose strengths compared to the approved 180/ 2 mg dose strength has not been demonstrated.	PI	Agreement (It was noted that the NfG on clinical investigation of medicinal products in the treatment of hypertension – Fixed combinations, does not address line extensions of fixed-combinations and does not require demonstration of a superior blood lowering pressure effect to the approved fixed combination. The clinical studies performed demonstrated superiority of the fixed combination over placebo and the individual compounds. This is reflected is a new wording of the indication)	

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52	25.09.06	Cefuroxim-axetil 125,250, 500 mg	Cefuroxime	Generic	NL/H/556/01-03/E01	One CMS could not accept the indication 'Uncomplicated gonorrhoea: urethritis and cervicitis' and two CMS could not accept the indication 'Treatment of early stage Lyme disease (stadium 1) and subsequent prevention of late complications in adults and children above 12 years of age'.	PI	Referred to CHMP for arbitration for the indication 'Uncomplicated gonorrhoea: urethritis and cervicitis'. The CMD(h) was able to reach agreement on the approval of the indication 'Treatment of early stage Lyme disease (stadium 1) and subsequent prevention of late complications in adults and children above 12 years of age'.	PI
53	25.09.06	Fexo-fenadin Teva	Fexofenadine hydrochloride	Generic	DK/H/0911/01-02/MR	Referring CMSs considered that bioequivalence of the test and reference formulations has not been demonstrated given that the bioequivalence study does not meet the conventional 90% confidence interval acceptance limits of 80-125% for Cmax.	BE	Referred to CHMP for arbitration	BE
54	25.09.06	Grazax	Standardised allergen extract of grass pollen from Timothy (Phleum pratense)	Full dossier	SE/H/612/01/MR	PSRPH concerns were raised by one CMS which questioned the immunomodulatory effect of the product since efficacy was shown only over one season.	Efficacy	At the CMD(h) meeting the RMS presented their view and the company was invited for an oral hearing. The general opinion of CMD(h) was that the outstanding issue could be solved by appropriate changes to the SPC and a post-approval commitment to provide yearly results from the already ongoing GT-08 extension study which will be concluded after the pollen season 2009. Agreement was reached based on the revised SPC and the commitment given by the applicant.	

	CMD Day 60	Name Product	Active substance	Legal basis	Procedure number	Reason CMD	Reason CMD (class)	Outcome CMD	Reason Arbitration
55	27.10.06	IG VENA	Human normal immuno-globulin	Full dossier	IT/H/0130/01/MR	A CMS raised doubts on the existence of sufficient evidence on the viral safety of this product with respect to non-enveloped viruses, as the safety of the product relies exclusively on the partitioning process. Though the effectiveness of this process is acknowledged, the introduction of a specific second step for non-enveloped viruses has been requested, and its absence has been considered as a major concern.	Safety	Agreement: As the major objection was based mainly on a national interpretation of the relevant Guideline, it was agreed that IG Vena should be regarded as safe and that this product does not carry any PSRPH.	
56	27.10.06	Tobrineb	Tobramycin	Hybrid	IT/H/0132/01/MR	One CMS suggested a direct comparison versus an active comparator	Other	Agreement reached. Consensus was reached on the Applicant's post-approval commitment to perform the requested study.	
57	27.10.06	Actitob			IT/H/0133/01/MR		Other		
58	27.10.06	Prexige	Lumiracoxib	Full dossier	UK/H/887/01-03/MR	Several CMS considered that the safety and efficacy of lumiracoxib was not established in all indications sought and proposed that the indications be limited to osteoarthritis. There was also debate regarding the duration of treatment. The indication "relief of dental pain or pain after dental surgery" was not acceptable to referring CMSs.	PI	At CMD(h) meeting the RMS presented their view and the main points for discussion. The company was subsequently invited for an oral hearing. The majority opinion at CMD (h) was that the indication for treatment of osteoarthritis of knee and hip would be acceptable with the proviso that the treatment should be for the shortest duration and with the lowest dose. The dental pain indication and with it the 200 and the 400mg strength tablets were withdrawn. The applicant agreed to a commitment to provide an appropriate Risk Management Plan in consultation with PhVWP. Agreement was reached based on the revised SPC and post approval commitment provided by the applicant regarding the Risk Management Plan.	
59	27.10.06	Frexocell			UK/H/888/01-03/MR		PI		
60	27.10.06	Stellige			UK/H/889/01-03/MR		PI		
61	27.10.06	Hirzia 100, 200 & 400mg			UK/H/890/01-03/MR		PI		

	CMD Day 60	Name Product	Active substance	Legal basis	Procedure number	Reason CMD	Reason CMD (class)	Outcome CMD	Reason Arbitration
62	27.10.06	Imodium Plus Caplets	Lo-peramide/ Simeticone	Fixed Combi-nation	UK/H/0241/02/MR	Serious public health concerns were raised with regard to the lack of adequate proof of comparable bioavailability and problems in data collation together with inconsistencies in the analyses of bioequivalence studies presented by the applicant.	BE	At the CMD(h) meeting the RMS presented its view and the company was invited for an oral hearing. The general opinion of CMD(h) was that the grant of a marketing authorisation was appropriate even though strict bioequivalence with the authorised chewable tablets used as the comparator had not been demonstrated. This is a locally acting product on the gut wall and a pharmacodynamic study would have been more appropriate to prove safety and efficacy for this line extension rather than a bioequivalence study. Nevertheless given the absence of local exposure biomarkers, bioequivalence studies have been accepted as a surrogate. In addition, the company has provided a commitment to undertake a post-authorisation comparative efficacy and safety study, and to provide other appropriate safety data on the use of the product in the UK and US in order to confirm clinical equivalence and the on-going risk-benefit evaluation of the product. CMD(h) reached a consensus agreement that because this application is for a line extension and both actives have a well known safety and efficacy profile there is no potential serious risk to public health. It must be recognised however that this case does not serve as precedent for post-hoc deviation from the relevant guidelines.	

	CMD Day 60	Name Product	Active substance	Legal basis	Procedure number	Reason CMD	Reason CMD (class)	Outcome CMD	Reason Arbitration
63	23.11.06	Oxaliplatin Medac	Oxaliplatin	Biblio-gra-phic	FI/H/584/01/MR	The bibli. applic. of oxaliplatin was accepted by all MS except one involved in this procedure. According to the disagreeing MS non-clinical and clinical data were considered in-sufficient to provide adequate evidence of safety and efficacy.	Other	After the responses by the Applicant and the final discussion in CMD(h), it was concluded that the well-established use of oxaliplatin has been demonstrated and that the bibliography of this application is both extensive and of high quality. Thus, the application fulfils the requirements for a well established use and no potential serious public health concern exists. Following the CMD(h) meeting at EMEA on 14 November 2006, the disagreeing MS concurred with the majority view of the other 17 Concerned MS in these procedures and the view of the RMS that the dossier submitted under “well-established use” comprised data that demonstrated systematic, documented and extensive evidence of use over a period of 10-years. Agreement was reached.	
64	23.11.06	Oxaliplatin Ratio-pharm			FI/H/585/01/MR		Other		
65	23.11.06	Oxali			FI/H/587/01/MR		Other		
66	23.11.06	Oxamed			FI/H/589/01/MR		Other		
67	23.11.06	Lanso-prazole Teva 15, 30mg	Lanso-prazole	Ge-neric	UK/H/884/01-02/MR	A serious public health concern was raised by three MS who considered that bioequivalence in the fed state had not been established for registration in the national market concerned. Bio-equivalence had been demonstrated only under fasting conditions	BE	At the CMD(h) meeting the RMS presented its view and the applic. written and oral explanation were discussed. The Company explained the absence of any pot. risk to public health resulting from the findings of the fed study (90% CI for AUCinf. 78-110%). Lansoprazole’s bio-availability is not only markedly reduced (by approx. 70%) when taken with food, but its absorption, in the presence of food, can be quite erratic as shown by the large intra-subject variability (70-82%). This is parti-cularly so following a high fat high calorie meal as is the case with the applicant’s fed study. The SPC and PIL are amended to make it clear that the product should be ad-ministered on an empty stomach. The final proposed wording was: The capsules are swallowed whole with liquid. The capsules may be emptied, but the contents may not be chewed or ground. Concomitantly taken food slows down and reduces the absorption of lansoprazole. This medicine has the best effect when taken into empty stomach. This is consistent with the outcome of the Article 29 referral for generic lansoprazoles (which was converted to Commission Decision on 21 February 2006). However, the proposal was not acceptable to the CMS and the application was therefore referred to CHMP for arbitration.	BE

	CMD Day 60	Name Product	Active substance	Legal basis	Procedure number	Reason CMD	Reason CMD (class)	Outcome CMD	Reason Arbitration
68	23.11.06	Ondan-setron 2mg/ml solution for injection	Ondan-setron	Generic	UK/H/850/01 /MR	A serious public health concern was raised by a Member State regarding the lack of concomitant therapy with dexamethasone in protecting against delayed or prolonged emesis in section 4.2 of the SPC.	PI	The RMS gave a presentation on the procedure. The RMS was of the view that the changes to the posology section would have implications on other ondansetron SPCs, including oral and suppository formulations and did not consider it appropriate to substitute the current text with a recommendation to combine dexamethasone with ondansetron, since evidence for this particular combination had not been formally assessed. However, the RMS acknowledged that important issues had been raised and that the text under discussion could be improved and proposed to include the following under section 4.2: “Prescribers intending to use ondansetron in the prevention of delayed nausea and vomiting associated with chemotherapy or radiotherapy in adults, adolescents or children should take into consideration current practice and appropriate guidelines”. This proposal was accepted by all CMS. Agreement was therefore reached.	
69	23.11.06	Ramipril HCT 2.5/12.5mg tablets	Ramipril/ hydro-chloro-thiazide	Generic	NL/H/721/01 -02/MR	Two MS have the opinion that, due to the lack of an add-on study in non-responders to HCT, the add-on indication for the treatment of essential hypertension in patients whose blood pressure is not adequately controlled on HCT alone cannot be granted.	PI	All Concerned Member States are in agreement that the add-on effects of ramipril to non-responders to HCT have been adequately demonstrated by results from appropriately designed parallel group comparative studies of the combination with the individual components. The CMD(h) forwarded a request for further discussion of the CHMP NfG hypertension (CPMP/EWP/2238/95 Rev 2) to the cardiovascular group of EWP, in relation to the statements in section 7.2.1 and addendum, section 3.3 which could be regarded as slightly contradictory. Therefore the following two questions were posed to the EWP for clarification regarding the assessment of combination medicinal products: Is it possible to further specify when one pivotal add-on study is sufficient? Should omission of the add-on trial on the second component be the exception or the rule? Agreement reached.	
70	23.11.06	Ramipril HCT 5/25mg tablets			NL/H/723/01 -02/MR		PI		

	CMD Day 60	Name Product	Active substance	Legal basis	Procedure number	Reason CMD	Reason CMD (class)	Outcome CMD	Reason Arbitration
71	23.11.06	Sertra-line 50, 100mg tablets	Sertraline	Ge-neric	UK/H/863/01 -02/MR	A serious public health concern was raised by a MS who considered that bioequivalence of the application product to an adequate comparator had not been established for registration in the national market concerned. Bioequivalence had been demonstrated between the applicant's sertraline tablets and Lustral 100mg tablets (the reference product authorised in the RMS). A biostudy was requested with the relevant 100mg capsule formulation of the reference product.	BE	At the CMD(h) meeting the RMS presented its view and the applicant's written explanation was discussed. The applicant had submitted the justification that in accordance with the guidance notes for the Investi-gation of Bioavailability and Bioequivalence any product is considered essentially similar to the reference product when it satisfies the criteria of the same qualitative and quantitative composition in terms of the active substance and having the same pharmaceutical form. Differences in the excipients for the tablets and capsules were not expected to cause any significant differences in efficacy or safety and dissolution data were provided to support similar bioavailability of the test and reference products. The company asserted that article 10.2(b) of the amended directive 2001/83 allows various oral immediate release dosage forms, such as tablets and capsules to be considered to be the 'same pharmaceutical form'. The view of the CMD(h) was that this has to be substantiated for each pharmaceutical form. The CMD(h) was of the opinion that it was the task of the Applicant to demonstrate bioequivalence against the relevant RMP, if there are different pharmaceutical forms available in different MS and agreed that authorisation of the medicinal product could represent a serious public health concern in the CMS. In this case the RMP was available in alternative dosage forms. The applicant made the commitment to submit the results of a bioequivalence study between the test product and the capsule formulation of the RMP to accompany a further application. This was accept-able to CMS and resolution on the referral completed.	
72	23.11.06	In-fusiflux	Fluconazole	Ge-neric	SE/H/605/01 /MR	Potential serious risk to public health concern was raised by one CMS regarding the posology for the treatment of systemic candida infections.	PI	Agreement was reached based on the following posology: The dose in candidaemia and other invasive Candida infections is 400-800 mg on the first day and 200-400 mg daily thereafter. The dose depends on the type and severity of the infection. In most cases a loading dose of 800 mg on the first day followed by 400 mg daily thereafter may be preferable. The duration of treatment, often up to several weeks, is determined by the clinical response.	

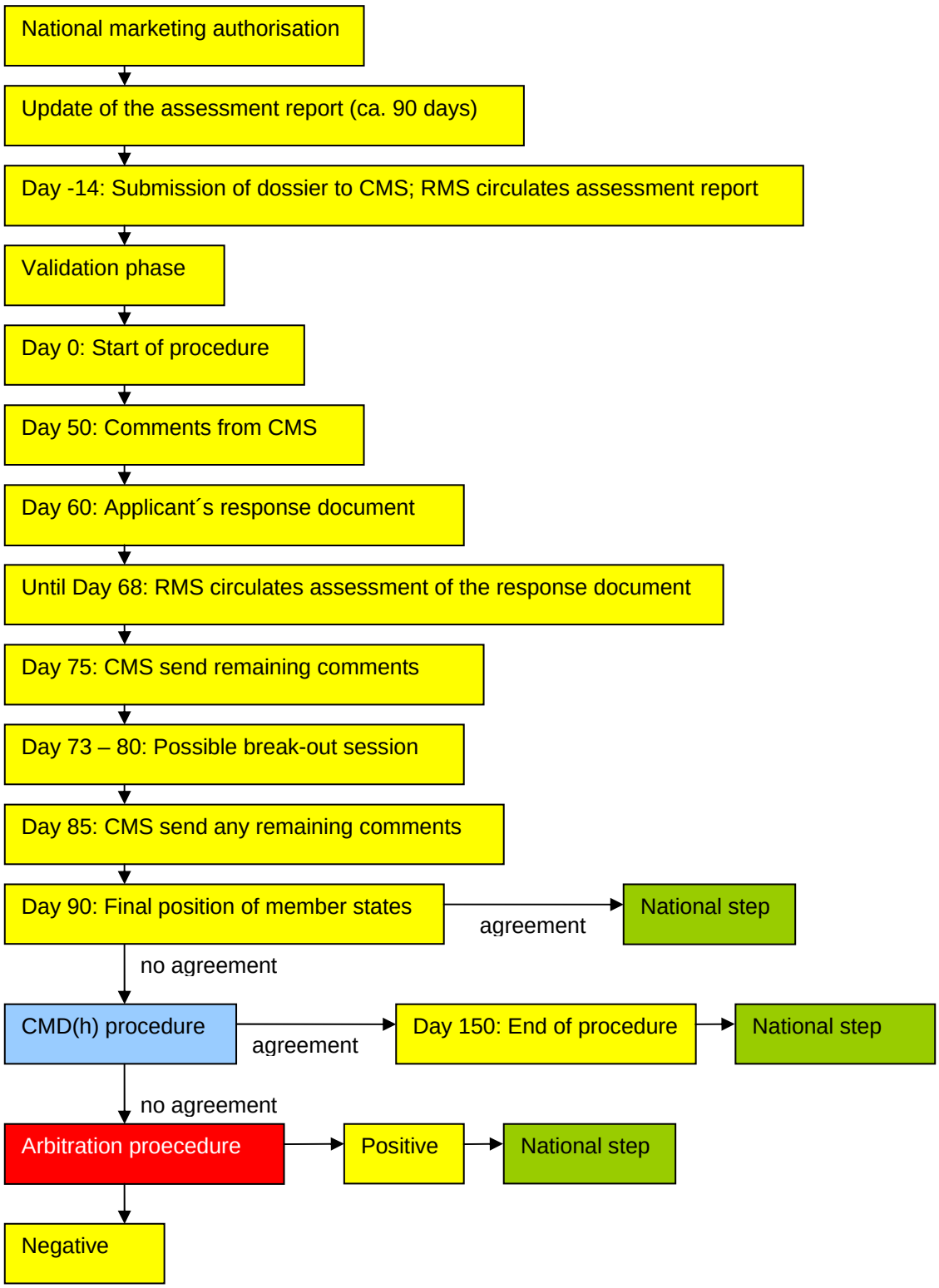
	CMD Day 60	Name Product	Active substance	Legal basis	Procedure number	Reason CMD	Reason CMD (class)	Outcome CMD	Reason Arbitration
73	18.12.06	Cipro-floxacin Mayne 2 mg/ml	Ciprofloxacin	Generic	FI/H/609/01/ MR	A serious public health concern was raised by one Member State regarding the following: 1) Should the dosage in the indication “Complicated urinary tract infections” in adults be 100 mg twice daily or 200-400 mg twice daily. 2) Should the maximum daily dose in adults be 800 mg or 1200 mg. 3) Should sections 4.4 and 4.8 of the Summary of Product Characteristics include warnings about ciprofloxacin and QTc prolongation.	PI	After the written responses by the Applicant and the final discussion in CMD(h), it was concluded that: 1) The dosage in the indication “Complicated urinary tract infections” in adults should be 200-400 mg twice daily. 2) The maximum daily dose in serious, life threatening and recurrent infections should be 1200 mg. 3) The warning about ciprofloxacin and QTc prolongation should be included in sections 4.4 and 4.8 of the Summary of Product Characteristics. All Concerned Member States approved the aforementioned conclusions. Agreement was reached.	
74	18.12.06	Paro-xetine 10, 20, 30, 40mg	Paroxetine	Generic	NL/H/831/01 -04/MR	Two CMSs have raised public health objections to the bioequivalence study with the 40 mg strength. The size of biobatch (5.000 units / 40 mg strength) is not in accordance with the Note for Guidance published in 2001, while the biobatch was produced in 2002. The *a posteriori* justification for deviation to the minimum requirements was not considered acceptable.	BE	It was acknowledged, that there was a deviation of the guidelines. However, according to the RMS, the applicant has adequately argued that the biobatches are representative for the product on full production scale and it is not expected that the bioavailability of the biobatch will differ from a batch of tablets that would have been produced from the full amount of bulk blend. Nevertheless, to finalise the procedure and not to deviate from generally accepted standards, the applicant committed to perform a new BE in line with the European guidelines and to report on the results within 6 months. Agreement reached with a commitment of the applicant.	

	CMD Day 60	Name Product	Active substance	Legal basis	Procedure number	Reason CMD	Reason CMD (class)	Outcome CMD	Reason Arbitration
75	21.12.06	Fina-sterid Jacob-sen	Finasteride	Generic	SE/H/636/01 /MR	A PSRPH concern was raised by one member state who considered it necessary to include a statement in section 4.6 of the SPC that small amounts of finasteride have been recovered from the semen in subjects receiving finasteride 5 mg/day and since there may be a possibility that a male foetus could be adversely affected if his mother is exposed to such semen, a man treated with finasteride should avoid exposure of his partner to semen, e g by use of a condom, or discontinue finasteride.	PI	At the CMD(h) meeting the RMS gave a presentation of the procedure. The RMS considered that a condom warning was not scientifically justified, based on two human studies and on a reproductive toxicity study in Rhesus monkeys, and would impose an unnecessary restriction on peoples lives. All MS agreed, except one, who considered the risk to a male foetus not to be negligible and therefore proposed a warning in the SPC. Agreement was reached to refer the scientific question to the Pharmacovigilance Working Party whether exposure to semen from a man treated with finasteride 5 mg/day could risk to cause malformations in a male foetus exposed in utero to such semen. In addition, additional information was included in the SPC sections 5.2 and 5.3 concerning studies performed but the condom warning proposed for section 4.6 of the SPC by one member state was not included. The Applicant has committed to follow the outcome of the PhVWP discussion by submitting a Type II variation afterwards if necessary.	

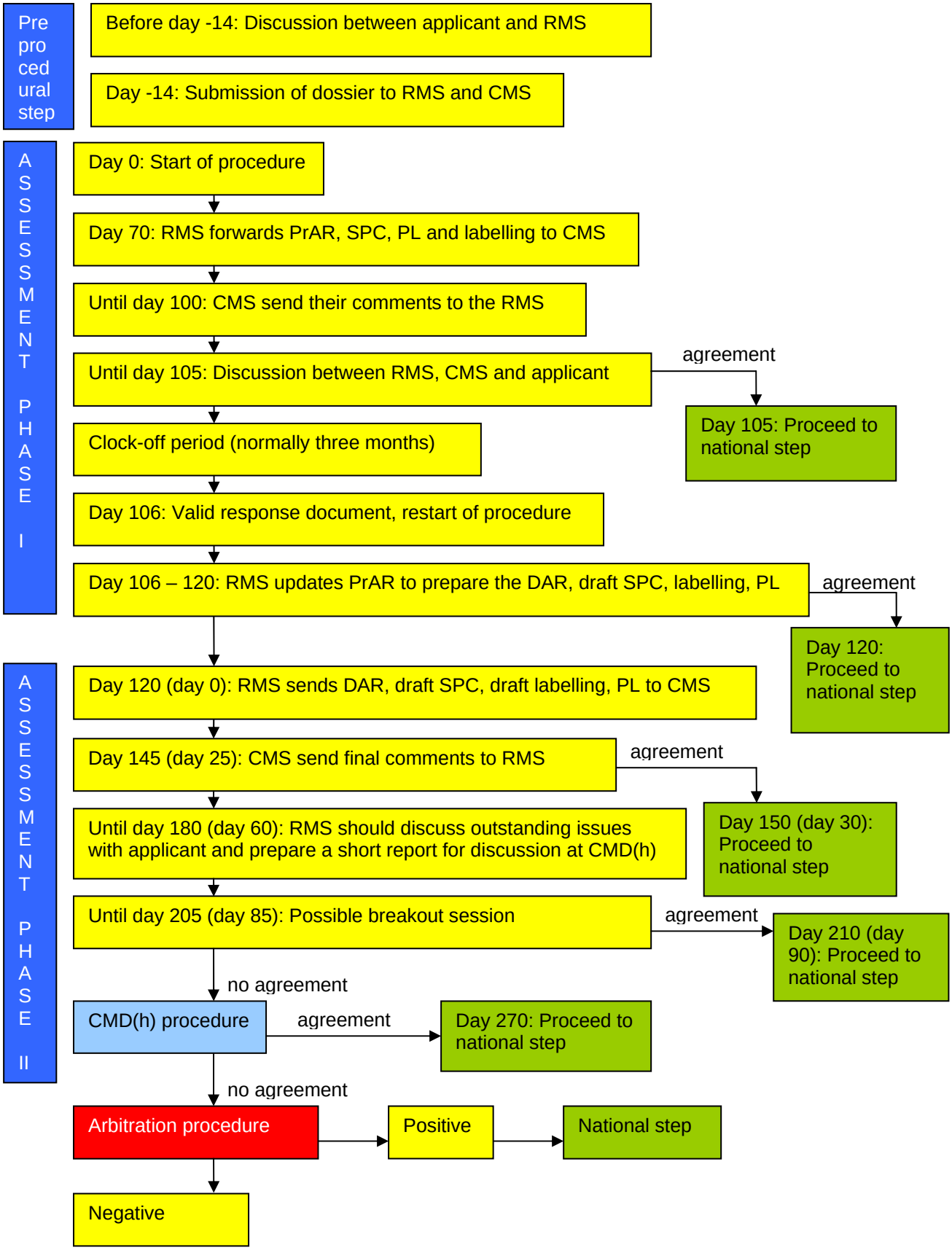
	CMD Day 60	Name Product	Active substance	Legal basis	Procedure number	Reason CMD	Reason CMD (class)	Outcome CMD	Reason Arbitration
76	18.12.06	Fen-tanyl-ratio-pharm 25, 50, 75, 100 µg/h Matrixpflaster	Fentanyl	Generic	DE/H/739/01-04/MR	The CMD(h) referral was raised by one CMS with regard to a number of concerns regarded as a PSRPH: - Indication needs to be restricted in view of the available data; - a starting dose of 12 µg/h needs to be supported; - Information on the use in a paediatric population is to be added as post approval procedure only; - With regard to the patient population proposed the conversion table morphin to fentanyl is not sufficiently justified; - The Bioequivalence studies submitted in support of the application are not deemed appropriate in design and choice of strength being compared; - For safe use, the SPC and PL need to be amended in relevant sections; e.g. contraindications as concerns concomitant drug treatment, use while breast feeding.	PI, BE	At CMD(h) and during the final phase of the referral a number of issues could be resolved by proposing amended text in the Product information, respectively agreement by the applicant to extend the application to include use in a paediatric population at a later stage only. Though, no consensus could be achieved with regard to the indication, proper conversion table, bioequivalence, concomitant treatment with other opioids and use during breast-feeding. The matters were referred to CHMP for arbitration.	PI, BE
77	18.12.06	Fen-tanyl-ratiopharm 25, 50, 75, 100 µg/h TTS			DE/H/740/01-04/MR		PI, BE		PI, BE
78	21.12.06	Opratifi 50mg	Opipramol	Biblio-graphic	DE/H/659/01/MR	CMS questioned that the bibliographic data submitted sufficiently supported the claim of 'well-established use' for this medicinal product leaving certain aspects on the dose finding, efficacy and safety open, thus not allowing to draw a final conclusion on the risk-benefit ratio.	Efficacy, Safety	During the CMD(h) meeting the RMS clarified that opipramol has been extensively used since 1962 resulting in a substantial number of publications in support of the efficacy and safety of the drug substance. However, it was noted that the use, which is based on the history of the active substance, has been limited to some MSs predominantly in Germany and that most of the literature is older one in German language. As no agreement could be reached at the CMD(h) discussion, the applicant decided to withdraw the marketing authorisation and applications in the RMS and CMS.	

	CMD Day 60	Name Product	Active substance	Legal basis	Procedure number	Reason CMD	Reason CMD (class)	Outcome CMD	Reason Arbitration
79	21.12.06	Caber-gonicht	Cabergoline	Generic	SE/H/651/02-04/MR	Potential serious risks to public health were raised by two MS who considered that efficacy of cabergoline for the indication Parkinson's disease had not been sufficiently demonstrated, and that cardiac valvulopathy and subsequent cardiac pathology as a class effect of ergot derived dopamine agonists is a serious safety issue which has consequences for the benefit risk of the product.	Safety, Efficacy	At the CMD(h) meeting the RMS presented its view and the applicants written explanation was discussed. The objection concerning the efficacy of cabergoline for treatment of Parkinson's disease was resolved during the referral procedure. The issue of cardiac valvulopathy was discussed by the PhVWP at their meeting in December 2006 before the CMD(h) meeting. In a PhVWP report to the CMD(h), the PhVWP concluded that the increased risk of cardiac valvulopathy associated with cabergoline was at least equivalent to pergolide. The SmPC for cabergoline products should therefore be updated in line with the SmPC for pergolide products i.e. restricted second line indication, contraindications and warnings for use and monitoring requirements. The SmPC for Kabergolin IVAX/Cabergonicht was subsequently revised in line with the SmPC for pergolide products, and circulated to CMS. The proposal for a revised SmPC was accepted by all CMS. Agreement was therefore reached.	
80	21.12.06	Kaber-golin IVAX			SE/H/570/02-04/MR		Safety, Efficacy		

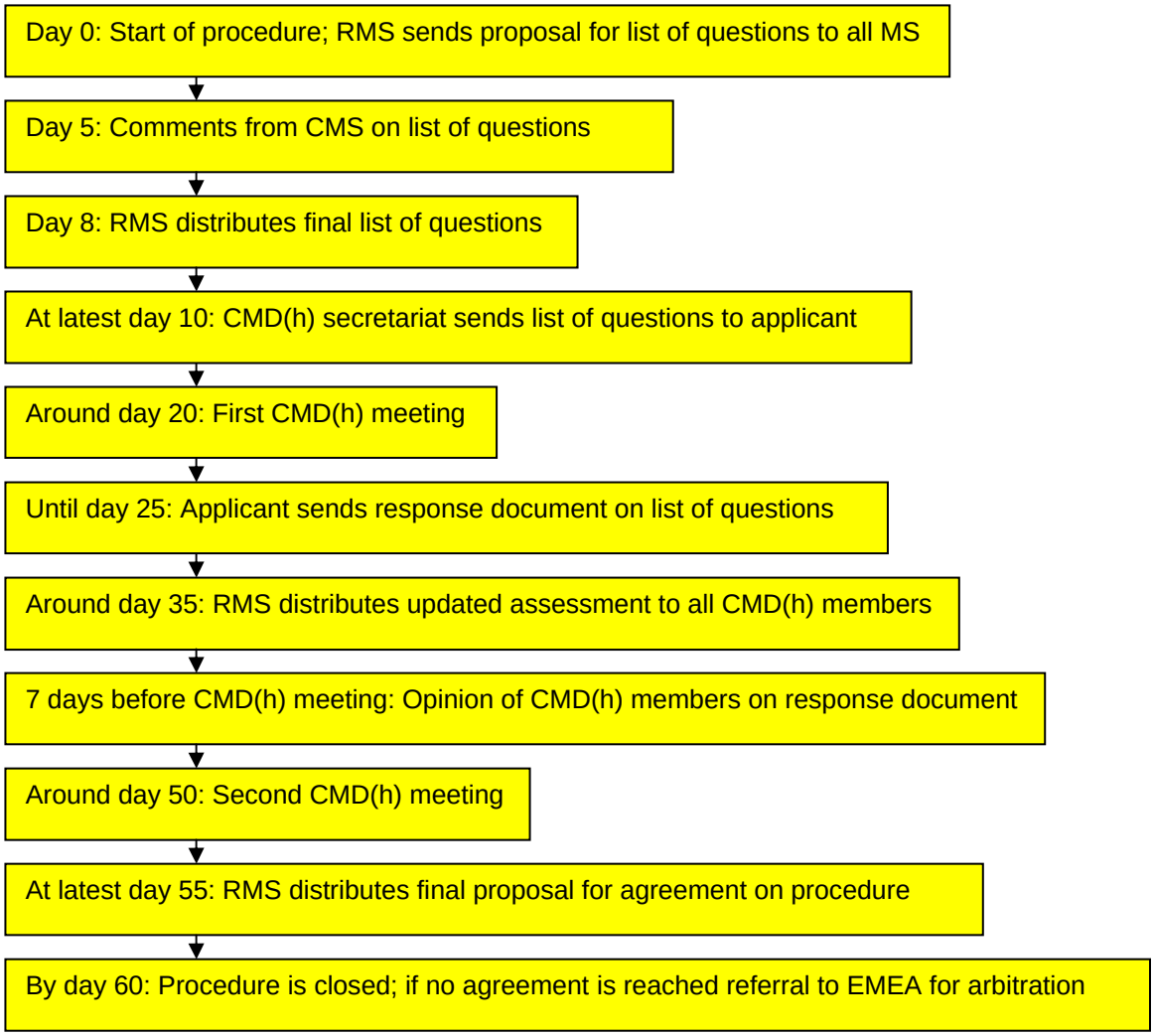
Annex II Flow Chart of the Mutual Recognition Procedure



Annex III Flow Chart of the Decentralised Procedure



Annex IV Flow Chart of the 60 days CMD(h) Procedure



Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

Ulm, den 10.03.07 _____