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NOTICE TO APPLICANTS

VOLUME 2A
Procedures for marketing authorisation

CHAPTER 4

Centralised Procedure

April 2006

This Chapter 4 Centralised Procedure will be included in The Rules governing Medicinal Products in the European Community
The Notice to Applicants Volume 2A Procedures for marketing authorisation

CHAPTER 4 Centralised Procedure

April 2006

Note: Since details of the implementation of the new legislation and its impact on the centralised procedure are still being discussed within EMEA, with the Commission, Member States and the scientific Committees, some sections in this chapter are still rather general at this point in time. Further clarification and cross-references to relevant guidelines will be provided as implementation discussions progress.

1. LEGAL BASIS AND SCOPE

Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 ("the Regulation") lays down a centralised Community procedure for the authorisation of medicinal products, for which there is a single application, a single evaluation and a single authorisation allowing direct access to the single market of the Community.

The Regulation establishes a European Medicines Agency (EMEA) which is responsible for co-ordinating the existing scientific resources put at its disposal by the Competent Authorities of the Member States for the evaluation, supervision and pharmacovigilance of medicinal products. Within the EMEA, the Committee for Medicinal Products for Human Use (CHMP) is responsible for preparing the opinion of the EMEA on any question relating to the evaluation of medicinal products for human use.

The Regulation confirms the need to protect public health within the Community whilst at the same time allowing rapid access to the single market for certain medicinal products referred to in its Article 3. The Regulation built upon the experience of the concertation procedure and of the centralised procedure which had been set up under Council Directive 87/22/EEC and Council Regulation (EEC) No 2309/93 respectively, and relies upon the fundamental requirement that the authorisation of medicinal products should be based on objective scientific criteria of quality, safety and efficacy of the medicinal product concerned.

A marketing authorisation granted under the centralised procedure is valid for the entire Community market, which means the medicinal product may be put on the market in all Member States.

The types of product which fall within the scope of the Regulation are set out in Article 3 and the Annex to that Regulation.

For medicinal products falling within the scope of Article 3(1) and of the Annex, applicants are obliged to use the centralised procedure and send their application to the EMEA. For those falling within the scope of Article 3(2) and 3(3), applicants may, at their discretion, also use the centralised procedure.

The EFTA states Iceland, Liechtenstein and Norway have, through the European Economic Area agreement, adopted the complete Community acquis on medicinal products, and are consequently parties to the centralised procedure. The only exemption from this is that legally binding acts from the Community, e.g. Commission Decisions, do not directly confer rights and obligations in Iceland, Liechtenstein and Norway, but first have to be transposed into legally binding acts in these states. According to Decision No. 74/1999 of the EEA Joint Committee, when decisions on approval of medicinal products are taken by the Community,

Iceland, Liechtenstein and Norway will take corresponding decisions on the basis of the relevant acts[1].

1.1 Medicinal products derived from biotechnology

Persons wishing to obtain a marketing authorisation for a medicinal product developed by means of one of the following biotechnological processes:

- Recombinant DNA technology,
- Controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes including transformed mammalian cells,
- Hybridoma and monoclonal antibody methods

must submit the application to the EMEA and the application will be processed via the centralised procedure, as such products fall within the scope of Article 3(1) and point 1 of the Annex to the Regulation.

Any medicinal product in the composition of which there is a proteinaceous constituent obtained by means of recombinant DNA technology, falls under the scope of point 1 of the Annex to the Regulation, irrespective of whether or not the constituent is an active substance of the medicinal product. This also applies where a recombinant DNA technology step is introduced into the manufacture of a proteinaceous product after the granting of a marketing authorisation.

Examples of new biotechnology products which would be considered obligatory for the centralised procedure are given below:

- products intended for gene therapy;
- vaccines from strains developed by means of recombinant DNA technology, including gene deletion;
- any medicinal product for which a monoclonal antibody is used at any stage in the manufacturing process;
- cell therapy products, which are the result of any biotech process referred to in point 1 of the Annex to the Regulation.

1.2 New Active Substances – "mandatory scope"

Applications for medicinal products containing a new active substance[2] must use the centralised procedure in accordance with Article 3(1) and point 3 of the Annex to the Regulation, when such substance has not been authorised in the Community before 20 November 2005 and for which the therapeutic indication is the treatment of:

[1] For Iceland and Norway see "Guidance document to the Industry, with regard to the extension of the centralised procedure, referral procedures, parallel distribution / import and pharmacovigilance requirements to Iceland and Norway" (EMEA/8518/00) as published on the EMEA Website.

[2] New active substance, as defined in Annex III of Chapter 1 Notice to Applicants

- acquired immune deficiency syndrome,
- cancer,
- neurodegenerative disorder,
- diabetes.

'Treatment' of a disease includes interventions that are specifically targeted at modifying the natural course of a disease. Typically, this includes causal or curative treatment of the disease. Thus, treatment of asymptomatic stages of the disease (e.g. in HIV-infection and in diabetes) is included into the compulsory scope of centralised procedure, provided that the known or assumed mechanism of action is disease-specific.

Medicinal products intended for prevention or diagnosis of the diseases are not included in the compulsory scope of the centralised procedure unless they fall under other indents of the Annex to the Regulation. However it is recommended that the centralised procedure be considered by applicants when medicinal products are intended for prevention, or when products, although initially intended for preventive or diagnostic purposes, have a potential for further development into treatment of the diseases mentioned in the Annex.

For precise working definitions of the diseases appearing in the Annex, and for further guidance on the application of this provision, reference is made to the EMEA "Guideline on therapeutic areas within the mandatory scope of the centralised procedure for the evaluation for marketing authorisation applications" published on the EMEA Website (http://www.emea.eu.int/ – Human Medicines – Guidance Documents - 'General Guidance)'

As of 20 May 2008, the centralised procedure will also become mandatory for medicinal products containing a new active substance for the treatment of auto-immune diseases and other immune dysfunctions and viral diseases.

1.3 Orphan medicinal products

Applications for medicinal products designated as orphan medicinal products pursuant to Regulation (EC) No 141/2000, must use the centralised procedure as such products fall within the scope of Article 3(1) and point 4 of the Annex to the Regulation.

1.4 Other medicinal products – "optional scope"

Other new active substances may, at the request of the applicant, be accepted for consideration under the centralised procedure.

In accordance with Article 3(2) of the Regulation, applications for the following categories of medicinal products may, at the request of the applicant, be accepted for consideration under the centralised procedure, when the applicant shows that:

a) a new active substance

or

b) the medicinal product constitutes a significant therapeutic, scientific or technical innovation, or the granting of a Community authorisation for the medicinal product is in the interests of patients at Community level.

These new provisions and in particular the second new provision paves the way for the authorisation, through the centralised procedure, of certain medicinal products that can be supplied without a medical prescription. It could also lead to the authorisation through the centralised procedure of generic medicinal products of nationally authorised products. In all cases, the fact that the authorisation of the product concerned through the centralised procedure is in the interest of patients will have to be shown by the applicant.

For further guidance on the EMEA procedure for confirmation of eligibility, and for examples of medicinal products which may have access to the Centralised procedure based on innovation or patient interest criteria, reference is made to the "Guideline on Article 3(2) of Regulation (EC) No. 726/2004 - Optional scope of the centralised procedure" published on the Commission Website in the NTA Volume 2C http://pharmacos.eudra.org/F2/eudralex/vol-2/home.htm

It has to be stressed that, once granted with a Community marketing authorisation based on Article 3(2) of the Regulation, a medicinal product can no longer be the subject of a subsequent (or previous) national marketing authorisation. In order to maintain coherence, and to preserve the unity of the Community Single Market, where the same marketing authorisation holder wishes to place on the market another medicinal product with the active substance which is already the subject of a Community authorisation, the centralised procedure should be used. In cases where the applicant does not apply for a Community authorisation as described above, the therapeutic indication(s) authorised by the Community should not be part of the national authorisation. In such a context, the Commission will consider the benefit of referring the case to the EMEA through an arbitration procedure in accordance with Article 30 or 31 of Directive 2001/83/EC, in order to preserve the above-mentioned coherence.

Multiple/duplicate or informed consent or generic applications from the same or a different marketing authorisation holder for a medicinal product with an active substance(s) already authorised via the centralised procedure, have 'automatic' access to the centralised procedure.

1.5 Generic and similar biological medicinal products

Generic applications of medicinal products authorised via the centralised procedure may be authorised via the centralised procedure. Alternatively, they may be authorised by the competent authorities of the Member States through a national, mutual recognition procedure or decentralised procedure provided that the conditions, laid down in Article 3(3) of the

Regulation are met (e.g. same summary of product characteristics, same name in all the Member States).

Similar biological ("biosimilar") medicinal products which are developed by means of one of the biotechnological processes listed in the Annex to the Regulation must however be authorised via the centralised procedure.

1.6 CHMP Scientific Opinion in cooperation with the World Health Organisation

According to Article 58 of the Regulation, the EMEA may also give a scientific opinion, in the context of cooperation with the World Health Organisation (WHO), for the evaluation of certain medicinal products for human use intended exclusively for markets outside the Community.

A justification for the product's eligibility for evaluation by the EMEA should be provided and the product should be intended to prevent or to treat diseases of major public interest. The same data requirements and evaluation standards will be adhered to as for EU medicinal products, taking into account possible adjustments as appropriate (e.g. stability).
The evaluation procedure will be an EMEA/WHO partnership, with input from WHO experts as needed.

The CHMP scientific opinion assessment report will contain the conclusions on the quality, the safety and the efficacy of the medicinal product and will take into account appropriate benefit/risk scenarios on the populations and conditions of use as documented with clinical data by the applicant. The CHMP Opinion will be forwarded to the applicant, WHO, the Commission, the Member States, Norway and Iceland.

Article 58(2) of the Regulation also makes provision for obtaining scientific advice on medicinal products intended to be marketed exclusively outside the Community. The procedures for obtaining scientific advice, as outlined in section 2 of this chapter, will apply.

Further information can be found in the EMEA guideline on "Procedural aspects regarding a CHMP scientific opinion in the context of cooperation with the World Health Organisation for the evaluation of medicinal products intended exclusively for markets outside the Community", which is available on the EMEA website (http://www.emea.eu.int/ - – Human Medicines – Guidance Documents - 'General Guidance)'

2. SCIENTIFIC ADVICE AND PROTOCOL ASSISTANCE

2.1 Legal basis and scope

According to Article 57(1)(n) of the Regulation, one of the tasks of the EMEA is, " advising companies on the conduct of the various tests and trials necessary to demonstrate the quality, safety and efficacy of medicinal products.
Scientific advice may be requested for all medicinal products for use in human beings irrespective if eligible for the centralised procedure or not.

Protocol assistance applies to designated orphan medicinal products, in accordance with Article 6 of Regulation (EC) No 141/2000 on orphan medicinal products.

Scientific Advice and protocol assistance are dealing with scientific issues. Regulatory aspects are handled separately by the EMEA. Scientific advice and protocol assistance requests should contain prospective questions concerning quality (chemical, pharmaceutical and biological testing), preclinical (toxicological and pharmacological tests), and clinical aspects (studies in human subjects in either patients or healthy volunteers, including clinical pharmacological trials designed to determine the efficacy and safety of the product for pre or post–Authorisation activities) relating to the proposed future development of the medicinal product.

In addition, scientific advice may be requested when designing trials to assess safety and efficacy in a new indication expected to bring significant clinical benefit compared to existing therapies, for the purpose of extending the marketing protection period by one year as defined in Article 14 (11) of the Regulation and for the purpose of obtaining one year of data exclusivity for a new indication as defined in Article 10(5) of the Directive. Scientific advice may also be requested on the criteria determining Conditional Marketing Authorisations, and opinions in the context of co-operation with WHO. Compassionate use as defined in Article 83 of Regulation (EC) No 726/2004 is not a topic for Scientific Advice.
Specifically for protocol assistance, requests may include questions in relation to demonstration of significant benefit, but must remain within the scope of the designated orphan indication.

2.2 Necessity for Scientific advice/Protocol assistance

Scientific advice or Protocol assistance may be given where there appears to be no answer/or lack of appropriate details in the form of:

- EU guidelines/guidance documents or draft documents circulated for Consultation (EMEA guidance documents are available under http://www.emea.eu.int - Human Medicines - Guidance documents or http://pharmacos.eudra.org/F2/eudralex/vol-3/home.htm)

- Pharmacopoeia monographs or draft monographs released for consultation.

However, in case a company chooses to deviate in their development plan from guidance available, it can seek scientific advice from the EMEA.
In addition, a company may also seek advice from the EMEA regarding the applicability of a specific guideline to their product.

It should be noted that any advice given is not binding for the EMEA or the applicant with regard to any future marketing authorisation application of the product concerned. However,

the CHMP would have to provide argumentation during the evaluation of the marketing authorisation application when questioning the design of studies performed following the provision of scientific advice/protocol assistance. The applicant should equally discuss in the marketing authorisation application compliance with Scientific Advice and provide argumentation for any deviation.

The answer given by CHMP is based on the questions and documentation submitted without prejudice to scientific developments; circumstances could change, especially in the case of early advice. In such cases, the EMEA recommends to request a follow-up to the initial scientific advice or protocol assistance. A follow-up request is defined as any subsequent request falling within the same therapeutic indication and initial area(s) as the initial request, (area means quality, preclinical and/or clinical development including pharmacovigilance/risk management aspects).

2.3 Scientific advice/Protocol assistance procedures

The EMEA emphasises the importance of scientific advice/protocol assistance Pre-Submission Meetings with applicants. Pre-Submission Meetings are a unique opportunity for applicants to obtain procedural or regulatory advice from the EMEA.

Scientific advice/protocol assistance requests are validated by a scientific administrator appointed by the EMEA. The scientific administrator is in charge of managing the scientific advice or protocol assistance procedure and will be the contact point for companies for any questions related to the planned/ongoing procedure.

Once validated, the request will be forwarded to Scientific Advice Working Party (SAWP) members and an invoice of the fee to be paid will be sent to the billing address indicated by the applicant. The fee will be payable within 45 days of the date of the notification of the administrative validation to the applicant.
At the start of the procedure, two Co-ordinators will be appointed by the SAWP. For protocol assistance, if the request includes issues relating to demonstration of significant benefit a third Co-ordinator will be appointed.

The scientific advice or protocol assistance provided to companies is the result of a collegial work from the Co-ordinators, the SAWP, the experts, the various Working Parties and Scientific Advisory Groups, the CHMP and the COMP (for questions related to demonstration of significant benefit within the scope of protocol assistance). The answer is prepared by the Co-ordinators and then submitted to the relevant Working Parties for comments and to the SAWP for discussion and adoption of a common position before being forwarded to the CHMP and/or the COMP for formal adoption.

The type of procedures (simplified or standard) will be determined on a case-by-case basis, tentatively at time of appointment of co-ordinators and confirmed at D+30. A 70-day timetable will usually apply. Depending on the nature of the request, this timeframe may be shortened to 40 days.

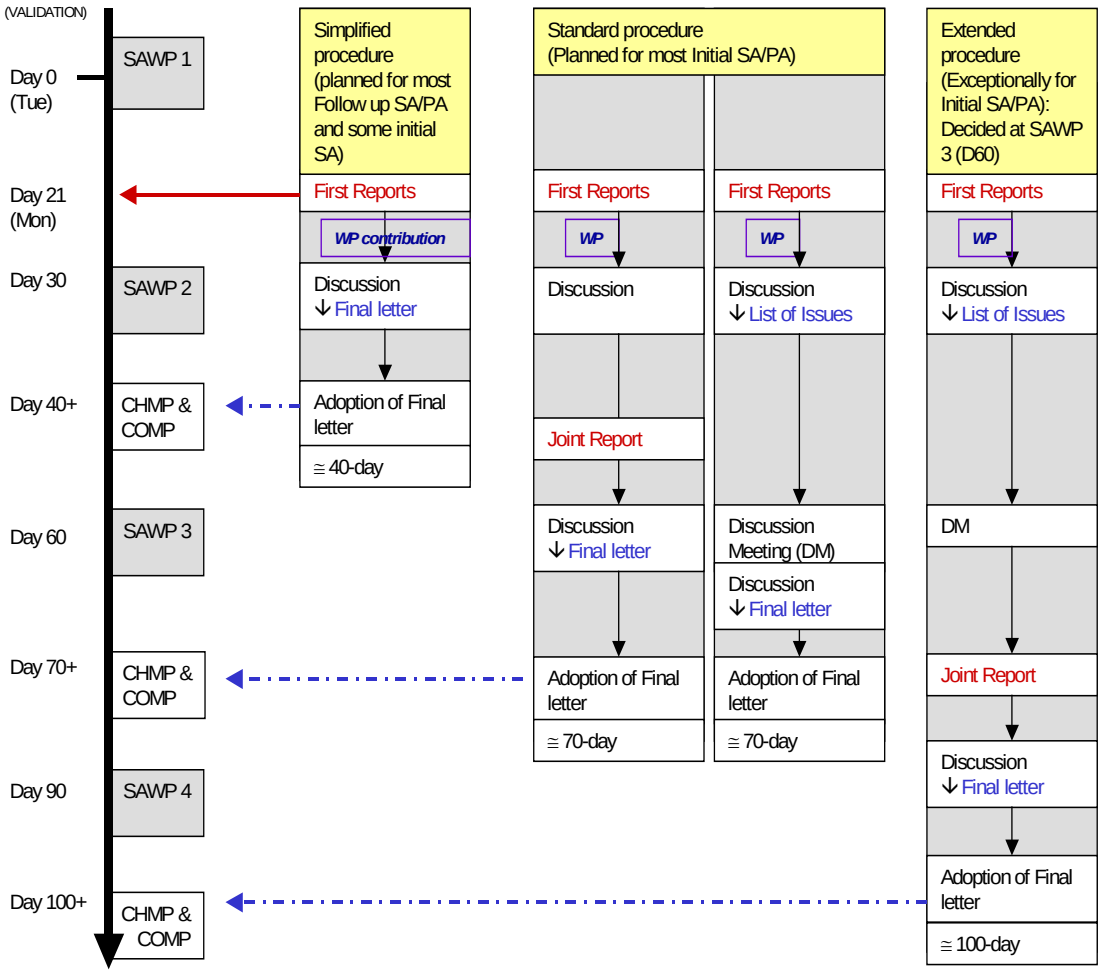
For protocol assistance, in order to achieve a good dialogue, the sponsor will be invited to a discussion meeting in the majority of cases.

For scientific advice, the company may mention its preference for having a discussion meeting in the initial request for scientific advice. However, the decision to invite the company will be made by the SAWP on a case-by-case basis following the identification of the issues, which need to be discussed by the company.

The joint Co-ordinators' report and the draft advice letter to the company are adopted by the SAWP and transmitted to the CHMP (and by the COMP in case of question on significant benefit for protocol assistance). The final advice letter is adopted by the CHMP (and by the COMP If appropriate) and sent to the company.

Further detailed information on the Scientific Advice procedure is available on the EMEA Website (http://www.emea.eu.int/ – Human Medicines - Application Procedures - 'Scientific advice').

Overview of the procedures



3. CHMP OPINION ON COMPASSIONATE USE

According to Article 83 of the Regulation, the CHMP may give an opinion on the conditions for use, the conditions for distribution and the patients targeted for compassionate use of non-authorised products eligible to the centralised procedure. Such medicinal products should be intended for the treatment of patients with a chronically or seriously debilitating disease or whose disease is considered to be life-threatening, and who can not be treated satisfactorily by an authorised medicinal product.

This applies to medicinal products for which clinical trials are ongoing and/or which are the subject of a marketing authorisation application via the centralised procedure.

When a Member State considers the need to make a medicinal product (as defined in paragraph (1) and (2) of Article 83) available for compassionate use, the competent authority of that Member State must notify the EMEA. CHMP opinions are given to Member States who explicitly request recommendations regarding the conditions for compassionate use of a specific medicinal product or when more than one Member State have notified the EMEA of their use of Article 83 for the same compassionate use programme. Applicants should not directly contact the EMEA to request a CHMP opinion.

The EMEA is responsible for keeping an up-to-date list of the opinions given for compassionate use on a public register available on the EMEA website.

Further information can be found in the "Guideline on compassionate use in the European Community", available on the EMEA website (http://www.emea.eu.int - include future path).

4. PROCEDURE FOR SUBMISSION OF THE MARKETING AUTHORISATION APPLICATION

When preparing the submission of a marketing authorisation application, applicants have the opportunity to meet the EMEA to discuss any procedural or regulatory issues on the proposed submission. Experience has shown the usefulness of these "Pre-submission meetings", even where the future applicant has experience with the centralised procedure. Future applicants are strongly advised to avail themselves of such opportunities. Requests for Pre-Submission Meetings should be sent to the EMEA using the "Pre-Submission Meeting Request Form" which is included in the "EMEA Pre-Submission guidance document" on the EMEA Website (http://www.emea.eu.int/ – Human Medicines - Application Procedures - 'Pre-Submission Guidance').

4.1 Pre-submission

At least seven months before submission, applicants should notify the EMEA of their intention to submit an application and give a realistic estimate of the month of submission.
In that notification applicants should include:

- a draft summary of product characteristics;
- a justification of the product's eligibility for evaluation under the centralised procedure (if not already requested at an earlier stage) ;
- in case of a product falling under the scope of Article 3(2), a concise summary document of preferably maximum 2 pages stating why the product should qualify for the granting of a marketing authorisation through the centralised procedure;
- an indication on the number of strengths / pharmaceutical forms / pack sizes (if already known);
- the proposed legal basis of the application according to Articles 8(3), 10, 10a, 10b or 10c of Directive 2001/83/EC;

- in case of 'generic' or 'bio-similar' applications, details of the proposed Reference medicinal product used throughout the quality, safety and efficacy development programme (as appropriate);

- if appropriate, a statement on the appropriateness of the granting of a marketing authorisation under exceptional circumstances (in accordance with Article 14(8) of the Regulation);

- if appropriate, a statement on the intention to request an accelerated assessment procedure (in accordance with Article 14(9) of the Regulation);

- if appropriate, a statement on the intention to request a conditional marketing authorisation (in accordance with Article 14(7) of the Regulation);

- scientific advice received in the past in accordance with Article 57(1)(n) of the Regulation;

- a statement as to whether orphan designation is granted / pending for the medicinal product;

- a proposed classification for the supply of the medicinal product;

- if appropriate, their intention to present a Active Substance Master File for active ingredient(s) prepared in accordance with the guideline on the European Active Substance Master File;

- if appropriate, their intention to present any existing Vaccine Antigen Master File (VAMF) or Plasma Master File (PMF) Certificates in the application;

- proposed Invented Name(s);

- a reference to any request for a CHMP Opinion on compassionate use, which may have been or will be submitted or for which a CHMP Opinion has already been adopted (in accordance with Article 83(4) of the Regulation);

- details of compliance with the requirements of Directive 2001/18/EC on the deliberate release into the environment of genetically modified organisms, if relevant;

- the details of proposed manufacturing and batch release arrangements of finished product and active substance manufacturing (see also Question 17 of the EMEA pre-submission guidance on the EMEA Website (http://www.emea.eu.int/ – Human Medicines - Application Procedures - 'Pre-Submission Guidance');

- whether the quality dossier presents enhanced product and process understanding, and novel manufacturing or control approaches are employed, such as Design Space concepts and Process Analytical Technology (PAT);

- any request for total or partial fee exemptions;

- an indication of any regulatory issues or difficulties already identified which may require clarification or detailed consideration.

Admissibility to the centralised procedure

The applicant's request for eligibility for evaluation via the centralised procedure, claiming that the product falls within the scope of the Annex or Article 3(2) of the Regulation, together with a justification and summary of product characteristics/product profile from the applicant, will be presented to all CHMP members at the subsequent CHMP meeting.

Following discussion at CHMP, the EMEA will then inform the applicant of the CHMP position as to whether the product is eligible for evaluation via the centralised procedure.

If the CHMP considers that the product does not fall within the scope of the centralised procedure according to the Regulation, the EMEA shall notify the company that the application is not admissible, stating the reasons.

Selection of Rapporteur/Co-Rapporteur

For any scientific evaluation in respect of a procedure a Rapporteur, and if relevant a Co-Rapporteur, shall be appointed from amongst the members of the CHMP (including co-opted members) or CHMP alternate members. The appointment of the Rapporteur/Co-Rapporteur is made on the basis of objective criteria, which will ensure the provision of objective scientific opinions and will allow the use of the best and available expertise in the EEA on the relevant scientific area.

The role of the Rapporteur is to perform the scientific evaluation and to prepare an assessment report to the CHMP according to the timetable agreed for the evaluation procedure. Where appropriate, the Rapporteur can be supported by a Co-Rapporteur as agreed by the CHMP. The Co-Rapporteur shall prepare a separate full assessment report or prepare a critique of the Rapporteur's report at the discretion of the CHMP.

The appointment process for Rapporteur/Co-Rapporteur is usually initiated at the CHMP meeting following the receipt of the letter of intention to submit. Such appointment is not always connected to a possible earlier request for eligibility for assessment via the centralised procedure. In general, requests for Rapporteur/Co-Rapporteur appointment should optimally be provided seven months before the intended submission date, and should arrive at the EMEA at least 2 weeks in advance of the CHMP meeting.

This will allow EMEA to circulate the request to CHMP members or alternates in advance of the meeting and for CHMP members or alternates to consider at national level a possible (Co-)Rapporteurship.

In the context of quality assurance at CHMP level, CHMP members may be assigned to "peer review" the (Co-)Rapporteurs' scientific evaluation, as well as the validity of the scientific/regulatory conclusions reached, and to improve the quality of the Day 120 List of Questions. At the time of appointment of Rapporteur and Co-Rapporteur, the CHMP will decide on the scope of the peer review (modules 3, 4 and/or 5 of the CTD) and the number of peer reviewers to be assigned to this task.

The peer review will be done in the period between the release of the (Co-)Rapporteur's initial assessment reports (Day 80) and the adoption of the CHMP list of questions (Day 120) – see also section 6.1.

If the intended application is deemed to be admissible and upon appointment of the Rapporteur and Co-Rapporteur, the EMEA shall notify the applicant after the CHMP meeting

of the name of the Rapporteur and the Co-Rapporteur appointed by the CHMP and where to find information on the applicable fees and dossier requirements of the different CHMP members on the EMEA website.

The Rapporteur and Co-Rapporteur choose(s) amongst the experts included in the European experts database available at the EMEA website, those who will form their assessment teams. The names of such experts will be communicated to the applicant as part of the Day-80 Assessment Reports.

The experts, on whom the CHMP can rely when it needs a specific expertise or assessors for the evaluation of applications, are those who have been put at the disposal of the EMEA by the Member States or other experts appointed directly by the EMEA, in accordance with article 62(2) of the Regulation. A database listing all experts involved in EMEA/CHMP activities (for meeting attendance, scientific evaluation, inspections, guidance development, etc) is available on the EMEA website (http://www.emea.eu.int/ - EMEA Structure (European Experts)).
Members of the CHMP and their experts are not permitted to have any direct financial or other interests in the pharmaceutical industry which could affect their impartiality. EMEA has therefore established a procedure and policy on the handling of conflicts of interests for the EMEA scientific committee members and experts, which is also available on the EMEA website.

Estimated submission dates must be reconfirmed at the time of the (Co-)Rapporteurs appointment and must be as realistic as possible. Such information is crucial to the EMEA, to the (Co-)Rapporteurs and their assessment teams for planning purposes. Any anticipated change to the filing date must be notified in advance to EMEA/CHMP. In such case, applicants should be aware that potential re-appointment of (Co-)Rapporteur(s) may become necessary due to other ongoing or planned assessments (see also section 4.3).

Procedure for multiple applications

In certain cases, companies may wish to obtain more than one marketing authorisation for the same medicinal product, either through simultaneous or subsequent applications. In the framework of Article 82(1) of the Regulation, a specific procedure has been agreed between the EMEA and the European Commission. Under this procedure, applicants should inform both the EMEA and the Commission services of their intentions at the latest 4 months prior to submission, in particular providing the Commission with an explanation of the underlying motives for the multiple application and their intentions as far as exploitation of any authorisations granted. The Commission shall authorise that applicant to submit more than one application to the EMEA, when there are objective verifiable reasons relating to public health regarding the availability of medicinal products to health-care professionals and/or patients, or for co-marketing reasons.

Applications for total or partial fee exemptions

A. Under Article 7(2) of Regulation (EC) No 141/2000 on orphan medicinal products, total or partial fee exemptions may be granted by the EMEA, for medicinal products designated as "orphan" by the European Commission on recommendation from the Committee on Orphan Medicinal Products. Any request should be sent to the Head of Scientific Advice and Orphan Drug Sector with the appropriate justification 2 months prior to the anticipated date of submission of the marketing authorisation application.

Applicants will receive an acknowledgement of receipt of the fee reduction request from the EMEA, which will trigger the processing of the fee reduction. Further information on fee reductions for Orphan medicinal products is published on the EMEA website (http://www.emea.eu.int/ Human Medicines – Orphan Medicinal Products – Orphan Incentives – Fees Reductions).

B. Applicants which meet the definition of a micro, small or medium-sized enterprise (SMEs), according to Commission Recommendation 2003/361/EC of 6 May 2003, may request deferral of the fee payable for the application for marketing authorisation or related inspection. SMEs are also eligible for fee reductions for scientific services (including scientific advice and inspections), and fee exemptions for certain administrative services.

C. Fee reductions may also be granted by the EMEA Executive Director in exceptional circumstances and for imperative reasons of public or animal health, after consultation of the competent committee.

D. Where an applicant disagrees on the classification by the EMEA of an application under one of the fee categories described in the Fee Regulation, the following procedure may apply:

- Any disagreement should be sent to the Executive Director accompanied by the appropriate justification, at the latest two weeks after receipt of the invoice indicating the fees payable to the EMEA.
- The Executive Director will take a decision following consultation with the competent committee.

(Invented) Name of products evaluated via the centralised procedure

Applications for medicinal products submitted via the centralised procedure shall include the use of a single name for the product in the Community, except in cases relating to the application of the law on trade marks (see Article 6(1) of the Regulation).

Provided that the medicinal product is eligible for evaluation under the centralised procedure, and where the applicant chooses to use an invented name for their medicinal product, the applicant should submit the proposed invented name(s) at the earliest 12 months and at the latest 4-6 months prior to the planned submission date of the marketing authorisation application.

A specific form (available in the EMEA Pre-Submission Guidance), along with either a draft summary of product characteristics or a product profile, should be sent to the EMEA at the e-mail address: NRG@emea.eu.int.

In order to enable applicants to propose invented names which will be acceptable, it is crucial that the EMEA “Guideline on the acceptability of invented names for human medicinal products processed through the centralised procedure", is followed bearing in mind the paramount criteria of ‘potential safety risk’.

In order to identify, at an early stage, potential difficulties presented by the invented name(s) proposed by an applicant, a satellite group of the CHMP, the invented Name Review Group (NRG), has been set up. The NRG consists of representatives of Member States, the European Commission and the EMEA.

Proposed invented names submitted prior to the CHMP plenary meeting are sent to every NRG contact point nominated by National Competent Authorities (NCA's) of EU-Member States (Norway and Iceland included), the European Commission (EC) and the World Health Organisation (WHO) for their review and will be discussed at the NRG meeting the following month, taking into consideration the relevant objections and comments received on grounds of safety concerns. The conclusions are presented to the subsequent plenary CHMP meeting, after which the applicant will be informed of the outcome.

An **EMEA 'Product Team'** will be set up for each medicinal product intended to be submitted through the centralised procedure. The Product Team consists of a Product Team Leader (PTL) and Product Team Members (PTM) nominated by the EMEA. The applicant will be notified of the appointed PTL. The Product Team is responsible for the handling of all procedural aspects of the application, both in the pre- and post-authorisation stage. The Product Team, under the leadership of the PTL, will in particular be responsible for:

- Provision of procedural guidance concerning all pre authorisation activities and to liaise with the (Co-)Rapporteur in the conduct of such activities;
- Provision of advice to (Co-)Rapporteur/CHMP members/applicant concerning all questions of a regulatory or procedural nature;
- Provision of advice to the applicant in the technical preparation of the marketing authorisation application and subsequent administrative validation of such applications;
- In collaboration with the (Co-)Rapporteur assessment teams production of the List of Questions, List of Outstanding Issues, draft summary of product characteristics proposals to support CHMP discussion/adoption:
- Supporting the (Co-)Rapporteurs with regulatory, technical advice in briefing/debriefing meetings with applicants;
- To support planning and conduct of oral explanations, ad-hoc expert groups, referral to Working Parties, Scientific Advisory Groups etc;
- Managing the timeframe of the procedure to ensure it remains within legal limits;
- Co-ordinating the linguistic check of labelling to ensure consistency and high quality versus the primary reference scientific text;
- Informing the (Co-)Rapporteurs on elements of regulatory and scientific consistency of the application of quality, safety, efficacy and administrative guidelines in the conduct of the evaluation procedure;
- To prepare the CHMP assessment report and consequent Summary of Opinion (SMOP) and European Public Assessment Report (EPAR);
- To act as the primary marketing authorisation holder EMEA contact point for all post authorisation activities and to liaise with the (Co-)Rapporteurs in the conduct of such activities;

The PTL, in close co-operation with the Rapporteur and Co-Rapporteur, will also ensure that the applicant is kept informed of all issues relating to the application. The PTL will serve as the main liaison person between the EMEA, the Rapporteur, the Co-Rapporteur and the applicant. The PTL has a specific supporting role to play as regards the Rapporteur, Co-Rapporteur and their assessment teams and should be systematically involved in all phases of the evaluation preferable directly through participation in all discussions with the applicant.

4.2 Submission of the application

The date and time of delivery of the dossier to the EMEA should be arranged between the applicant and the EMEA. The EMEA will inform future applicants well in advance of the program of scheduled CHMP meetings in order to be able to identify preferred optimal submission dates. Target dates for submission of the application are published on the EMEA Website (http://www.emea.eu.int/ – Human Medicines - Application procedures - 'Pre-Submission Guidance').

As soon as the applicant is aware that the original indicated submission date can not be met he should inform the EMEA, Rapporteur and Co-Rapporteur immediately, since a delayed submission can have consequences for already planned activities of the assessment teams of the Rapporteurs and Co-Rapporteurs. It may even be the case that assessment capacity is not immediately available at the moment a delayed submission is received and that therefore Rapporteur and/or Co-Rapporteur may in exceptional cases request the appointment of a new Rapporteur and/or Co-Rapporteur.

The address for submission of the application is given in Chapter 7.

4.3 Dossier to be submitted

The EMEA requires from the applicant:

- one full copy of the dossier (modules 1-5 according to the EU-CTD format), including the applicant's part of the Active Substance Master File , if any;

- two additional copies of Modules 1 and 2 including the draft summary of product characteristics, labelling and package leaflet in English;

- one electronic copy of module 1 and 2 (at least 2.1-2.5) in WORD.

In addition, applicants must submit the dossier to both the Rapporteur and the Co-Rapporteur in parallel to the EMEA. Otherwise there may be a delay in the start of the procedure because of the time lapse between the validation by the EMEA and the confirmation from the Rapporteur and the Co-Rapporteur that they have received the dossiers.
Detailed and up-to-date requirements for submission of the application to EMEA and Rap/Co-Rap and CHMP members are given on the EMEA website (http://www.emea.eu.int/ – Human Medicines - Application procedures - 'Pre-Submission Guidance').

In order to ensure standardisation of the headings and certain sections of the summary of product characteristics, package leaflet and labelling, the EMEA provides the applicant with a template of what must be included in these documents. This template is available on the EMEA website (http://www.emea.eu.int/ – Human Medicines - Application Procedures - Product Information Templates').

In those cases where a Active Substance Master File exists, the applicant should ensure that the Active Substance Master File is submitted by the active substance manufacturer to the EMEA, Rapporteur and Co-Rapporteur at around the same time as the main application.
In case the applicant wishes to use existing VAMF or PMF Certificates in the application, the applicant will be required to provide the valid VAMF or PMF Certificate and accompanying evaluation reports together with the respective VAMF or PMF data.

Applicants should provide with their application one English mock-up of the outer and inner packaging for each pharmaceutical form of the medicinal product in the smallest pack-size. A mock-up is a copy of the flat artwork design (computer generated) in full colour, providing a replica of both the outer packaging and immediate labelling/packaging. It is generally advised that a "worst-case" mock-up of a multi-lingual pack (e.g. Belgian) is also provided in the application, in the smallest pack size of each pharmaceutical form so that the feasibility of multiple languages on the smallest labelling is tested (see also Chapter 7 for further information on mock-up submission).

In the case of a medicinal product containing or consisting of genetically modified organisms within the meaning of Article 2 of Directive 2001/18/EC, the application must also be accompanied by:

- a copy of any written consent or consents of the competent authorities to the deliberate release into the environment of the genetically modified organisms for research and development purposes where provided for by Part B of Directive 2001/18/EC or of Directive 90/220/EEC;

- the complete technical dossier supplying the information requested in Annexes III and IV to Directive 2001/18/EC;

- the environmental risk assessment resulting from this information in accordance with the principles set out in Annex II to Directive 2001/18/EC;

- the results of any investigations performed for the purposes of research or development.

Applicants must include evidence of establishment in the European Economic Area (EEA), as well as documents showing their capacity to perform all the responsibilities required of the Marketing Authorisation Holder under Community pharmaceutical legislation, whether he does it himself or via one or more persons designated to that effect, in particular:

- a document identifying the qualified person responsible in the EEA for pharmacovigilance within the meaning of Article 23 of the Regulation and Article 8 (n) of Directive 2001/83/EC, together with a curriculum vitae and the address, 24h telephone and fax number;

- a document describing the scientific service in the EEA in charge of the information about the medicinal product within the meaning of Article 98 of Directive 2001/83/EC, including the address, the telephone and fax number of one contact person in the EEA;

- a document identifying the qualified person in the EEA responsible for batch release and the contact person for product defects and product recalls (within the meaning of Article 48 of Directive 2001/83/EC), including their address, 24h telephone and fax number;

- a document describing in detail the pharmacovigilance system and, where appropriate, the risk-management system, as required in Article 8 (ia) of Directive 2001/83/EC of the Regulation;

In addition the submission of complete copies using electronic storage media is encouraged. Details should be discussed beforehand with the EMEA through the Product Team Leader.
At a minimum, the applicant should submit an electronic (WORD) copy of Modules 1 and 2, including the English version of summary of product characteristics, labelling and package leaflet. However, applicants are encouraged to submit to the EMEA one full copy of the marketing authorisation application on a suitable PC-compatible medium, e.g. CD-ROM/DVD, together with 3 additional paper copies of Modules 1 and 2 only.

Applicants wishing to use this option must give a written undertaking to supply a full paper copy of the marketing authorisation application within 48 hours upon request and confirm that the data on CD-ROM/DVD supplied is identical to that in any written submission. Applicants should also liaise with Rapporteur, Co-Rapporteur and any other member of the CHMP who has requested a full or partial copy of the dossier to determine if they wish to receive the application on a suitable PC-compatible medium.

Format for Marketing Authorisation Applications

EU-Common Technical Document (CTD)

Since 1st July 2003, all applications to the EMEA should be made entirely in accordance with the EU-CTD (Common Technical Document) presentation outlined in Volume 2B of the NTA published on the Commission Website (http://pharmacos.eudra.org/F2/eudralex/vol-2/home.htm).

The CTD is an internationally agreed format for the preparation of a well-structured applications to be submitted to regulatory authorities in the three ICH (International Conference on Harmonisation) regions of Europe, USA and Japan. It is intended to save time and resources and to facilitate regulatory review and communication. The CTD gives no information on the content of a dossier, but provides for a harmonized format of presentation of the necessary data to support the application in accordance with the legal/scientific requirements of each region.

The EU-CTD is organised in five modules: Module 1 contains the specific EU administrative and prescribing information. The structure of Modules 2, 3, 4, and 5 is common for all regions and will contain the high level summaries and quality, non-clinical and clinical documentation respectively.

Electronic Common Technical Document (eCTD):

Applicants have the option of submitting an Electronic Common Technical Document (eCTD) in alongside the paper CTD. Applicants are advised that where an eCTD is submitted, the paper CTD remains the formal submission, and therefore both paper and electronic submissions must comply fully with the Common Technical Document as regards presentation and content of the dossier.

Applicants should liase with the EMEA if intending to submit an eCTD in addition to paper.
In case of eCTD submission, 2 copies of the eCTD should be provided to the EMEA.

The EMEA will transfer the data onto its internal system, perform a computer validation testing, and on successful completion of this, perform the regulatory validation procedures (See section 3.4 Validation).

The latest version of the ICH M2 eCTD Specification can be found at http://www.ich.org. Further information and guidance on eCTD submissions can be found on the EMEA e-submission website (http://esubmission.eudra.org).

4.4 Validation by the EMEA

The EMEA will complete its validation by the starting date of the procedure, as published on the EMEA website (http://www.emea.eu.int/ – Human Medicines - Application procedures - 'Pre-Submission Guidance').

During validation the EMEA PTL may consult the Rapporteur and Co-Rapporteur, on the need for action relating to matters such as GMP inspection, ad-hoc expert groups, Scientific Advisory Groups, GCP inspections, and completeness of data. If relevant, the Commission Services will be consulted on points of interpretation of EU legislation.

In the event that the EMEA requires additional data, information or clarification in order to complete its validation of the dossier, it will contact the applicant requesting supply of this data, information or clarification within a specific time limit. When supplying the EMEA with this information, the applicant should also send a copy of this information to the Rapporteur and Co-Rapporteur. In this case, the validation can only be completed after receipt and verification of the information submitted. If the Rapporteur and the Co-Rapporteur have not received their copies of the dossier and/or additional validation information on the day where the dossier is validated by the EMEA, the start of the procedure may be delayed until the procedural starting date of the next month. Applicants should provide a proof of delivery to Rapporteur, Co-Rapporteur to the EMEA before start of the procedure.

4.4.1 Positive outcome of the validation

In case of a positive outcome, the EMEA shall notify the applicant in writing that the validation has been successfully completed, together with the names of CHMP members to whom full or partial copies of the dossier should be sent. The applicant should also send a copy of any additional data or information supplied during the validation phase to these CHMP members. The timetable for evaluation adopted by the CHMP will be attached to the letter confirming the positive outcome of the validation.

The EMEA, CHMP members and the appointed experts who have received full or part dossiers, are required to fully protect the confidentiality of the data submitted to them based on Article 63 of the Regulation, and the EMEA Code of Conduct EMEA/MB/15314/2004 on the EMEA Website (http://www.emea.eu.int/– General Reporting - Administration).

The EMEA will publish the International Non proprietary Name (INN) of Orphan Medicinal Products when a marketing authorisation application is submitted, as well as the designated orphan indication and the name of the sponsor.

4.4.2 Negative outcome of the validation

Failure to provide the data, information or clarification requested, failure to adhere to the EU-CTD format will result in a negative validation, of which the applicant shall be informed in writing.

The applicant will be invited to either collect the dossier or have it destroyed by the EMEA. Individual arrangements should be made with the Rapporteur and Co-Rapporteur concerning copies in their possession.

The applicant will be required to submit a new dossier to the EMEA should a new application be initiated in the future.

4.4.3 Payment of fees

The fee shall be due on the date of the administrative validation of the application.

The EMEA will issue an invoice on the date of the notification of the administrative validation to the applicant and fees will be payable within 45 days of the date of the said notification. The invoice will be sent to the billing address indicated by the Applicant and will contain clear details of the product and procedures involved, the type of fee, the amount of the fee, the bank account to where the fee should be paid and the due date for payment.

The EMEA should receive the full application fee in Euro in accordance with Council Regulation (EC) No 297/95 as amended, net of all bank charges (see also Chapter 7).

If the application cannot be validated, the EMEA will issue an invoice on the date of the notification of the administrative non-validation to the applicant for an administrative charge to cover administrative costs.

4.4.4 Management of applications

Once validated, details of the product will be entered into the EMEA tracking system (SIAMED). The numbering system allows for a clear identification of any application for the granting, the extension, the variation, the transfer, the renewal of a Community marketing authorisation for any product and for any of its presentations throughout its life cycle.

In the EMEA, applications for a marketing authorisation for a medicinal product are primarily identified by the name and the active substance(s) of the product. However for administrative purposes, each application is also given a core-number composed of four sections: EMEA/H/C/..., where H stands for Human, C for centralised procedure with the dots corresponding to a sequential and unique number for each product (six digits). The applicant will be informed of the procedure number in the EMEA validation letter. Such number should be included in all future correspondence with the EMEA on the application.

4.5 Need for samples and sample analysis

Samples for testing the proposed medicinal product are not required at time of submission of the application.

The CHMP may, however, request the testing of samples of the medicinal product and/or its ingredients during the assessment of the application in accordance with the provisions of Article 7(b) of the Regulation. In this case the Rapporteur and/or Co-Rapporteur will specify a test protocol (type of samples, number of samples, number of batches, testing to be performed and methods and specifications to be used) and agree with the EMEA which laboratory e.g. Official Medicines Control Laboratory (OMCL) or other laboratories designated for this purpose by the Member States will carry out the required testing.

The results of the tests are reported to the EMEA, Rapporteur and Co-Rapporteur and the CHMP for consideration when finalising the CHMP Assessment Report.

The EMEA implements every year a post authorisation sampling and testing programme, according to Article 57(1)(r) of the Regulation, aimed at monitoring the quality of Centrally Authorised Products. This programme is done in close collaboration between the marketing authorisation holders, the (Co-) Rapporteurs and institutional partners (OMCL, national authorities and inspections services). All centrally authorised products on the European Market could be tested, except human medicinal products that are subject to Official Batch Release (e.g. blood products and vaccines). More information about this monitoring programme is available on the EMEA website (http://www.emea.eu.int/ - Inspections – Sampling and Testing).

5. PRE-AUTHORISATION INSPECTIONS (GMP, GCP AND GLP)

Inspection(s) requested in connection with an application for a marketing authorisation must be adopted by the CHMP. It should be pointed out that pre-authorisation inspections, where requested by the CHMP, should be carried out within the 210 days set out in the legislation for the scientific evaluation of the application and that applicants therefore are required to ensure that the sites to be inspected (manufacturing and quality control sites and/or non-clinical study sites and/or clinical trials sites) are ready for inspection from the time of submission of the application.

5.1 Legal basis

According to article 57(1)(i) of the Regulation, the EMEA is responsible for the co-ordination of pre-authorisation Good Manufacturing Practice (GMP), Good Clinical Practice (GCP), Good Laboratory Practice (GLP) and Pharmacovigilance inspections in connection with the granting of a marketing authorisation by the Community.

- GMP Inspections: the legal basis for pre-authorisation inspections of manufacturers of medicinal products is laid down in Article 8(2) of the Regulation.

- GCP Inspections: GCP inspections are conducted in accordance with article 15 of Directive 2001/20/EC. The reference standard for these inspections is set out in the requirements that the legislation places on clinical trials included in marketing authorisations, in particular recital 16 and Article 6(1) of the Regulation. Article 6(1) of the Regulation also refers to Directive 2001/83/EC which provides additional legal framework in sections 4 and 8 of Annex I- Introduction and general principles.

- GLP Inspections: Introduction and general principles, section 9, of Annex I to Directive 2001/83/EC, indicates that non-clinical studies mentioned in marketing authorisation applications should have been performed in compliance with the principles of GLP as laid down in Directive 2004/9/EC and Directive 2004/10/EC, and hence should be "inspection ready" at the time of submission of the application and throughout the assessment.

5.2 Type of Inspections

GMP Inspections: these inspections may be carried out to verify compliance with European Community Good Manufacturing Practice Principles and Guidelines (contained in Volume IV of the Rules Governing Medicinal Products in the European Union) and/or an inspection may

be requested to cover product or process related issues arising from the assessment of the application. In this case the Rapporteur and/or Co-Rapporteur will provide the inspection team with a list of questions/issues, which should be addressed during the inspection.

More detailed information on this type of inspections can be found in the "EMEA Pre-Submission guidance document" on the EMEA Website (http://www.emea.eu.int/ – Human Medicines - Application Procedures - 'Pre-Submission Guidance').

GCP Inspections: routine inspections are carried out as a routine surveillance of GCP compliance, and not all applications would necessarily give rise to a routine GCP inspection. The applications, clinical trials and sites are selected to cover a range of different situations (e.g. size of sponsor company, origin of pivotal data, target population etc.).

The assessment of the dossier may however identify a need for a specific GCP inspection(s) (triggered inspection). These triggered inspections should be given priority due to their nature of investigating an established concern.

GLP inspections: these are normally study related audits that are requested when it is necessary to assess in retrospect specific issues related to the assessment of the application. Exceptionally, a general GLP inspection covering general GLP compliance could be requested to verify compliance with Good Laboratory Practice Principles and Guidelines in accordance with Directives 2004/10/EC and 2004/09/EC.

5.3 Inspection Team

The responsibility for performing GMP, GCP and GLP inspections rests with the inspection services of the Competent Authorities of the EU Member States and, where appropriate, the countries of the EEA. On the advice of the Rapporteur and/or Co-Rapporteur the Inspection Team may include scientific experts and/or a Rapporteur.

GMP Inspections: the responsibility for carrying out GMP Inspections rests with the Supervisory Authority of the Member State in which the product is either manufactured or imported, controlled and released for sale within the EEA. When the Supervisory Authority is not able to inspect in a third country, the Rapporteur and the Supervisory Authority together designate another Competent Authority as the "Leading Inspection Service" for the inspection (this is the only difference between EU/EEA and foreign inspections).

GCP Inspections: one EU/EEA Inspectorate is designated as the "Reporting Inspectorate", usually from the same country as the CHMP Rapporteur or Co-Rapporteur unless the site(s) to be inspected are located in a single EU/EEA state (or small number (3 or less) of EU/EEA states), in which case that Inspectorate is usually designated as the Reporting Inspectorate.

In addition to the Reporting Inspector, one Lead Inspector is designated per site to be inspected. The Lead inspector is usually from the Inspectorate in the Member State where the site(s) to be inspected is located (for inspections in the EU/EEA). The Reporting Inspector may also be the Lead Inspector for one or more sites.

In the case of third country inspections, the Reporting inspectorate and the inspectors are usually from the Rapporteur/Co-Rapporteur country inspectorates.

GLP Inspections: if the site is located within the EU the team will be drawn from the GLP Monitoring Authority of the Member State where the test facilities are located. If the test facility is located in third countries, the CHMP will nominate the monitoring authority in the

inspection request. Normally, the monitoring authority of the member state of the Rapporteur or Co-Rapporteur will be responsible for these inspections.

5.4 Procedural Aspects

5.4.1 Validation

Detailed information on the documentation that will be reviewed from a GMP and GCP perspective during validation can be found in the EMEA pre-submission guidance.

5.4.2 Timetable for inspections

Inspection request(s) may be adopted by CHMP at any stage of the assessment. However, they are usually requested for adoption by CHMP at Day 90 or at the latest by Day 120. In the case of GCP inspections, they will always be addressed in the List of Questions, except in those situations when a GCP inspection is requested later in the procedure. For inspections covering specific aspects of the application, issues to be checked during the inspection will be detailed in an attachment to the Day 80 assessment report(s) or discussed with the assessors.
Once an inspection request is adopted by the CHMP the Inspection Sector of the EMEA will write within 5 working days to:

The applicant, explaining that an inspection(s) will take place, giving details (target date for carrying out the inspection, inspection team, scope of the inspection, contact person in the relevant authority responsible for arranging the inspection)

The Contact Person in the relevant authority responsible for arranging the inspection

Inspections usually take place in parallel with the “clock stop” period and will approximately be conducted within two months from the adoption of the inspection request.

More detailed information on the timelines for these inspections can be found on the different SOPs for coordinating centralised GMP, GCP and GLP inspections, as published on the EMEA website (http://www.emea.eu.int - Inspection)

5.4.3 Inspections Reports

The inspectors will prepare a report(s) which will be provided to the inspectee for comments on major factual errors or omissions within 15 days, and where needed for submission of a Corrective action plan. The final report(s) is then sent to the EMEA inspection sector by Day 180 at the latest, and circulated to the Rapporteur and Co-Rapporteur and CHMP. The Inspection Report should however be available at EMEA earlier, when responses are required as part of the answers to the List of Questions.

The timing of any further discussions, further actions and/or the request for and provision of additional information arising from the inspection will be agreed with the Inspectors, and communicated by the Inspectors to the Rapporteur, the Co-Rapporteur and the EMEA.

In the case of GCP Inspections, when more than one site is inspected per inspection request, the Reporting Inspector compiles an Integrated Inspection Report. This report will summarise the major and critical findings and contain an evaluation of the quality of the data submitted and compliance with the principles of GCP based on the findings at all inspected sites. The report will also contain a conclusion on whether the quality of the data inspected as a whole or in parts may be used for the evaluation by the assessors regarding acceptance/non-

acceptance of the trial data and should recommend any follow-up to be requested of the applicant or even further inspection if considered necessary.

5.5 Inspection Fees

The basis for charging fees for inspections is provided by Council Regulation (EC) No 297/95, as amended. Article 3(4) refers in broad terms to the fee that may be charged for "any inspection". Fees will be payable within 45 days of the date on which the inspection is carried out. Fees payable to the EMEA for Inspections are published on the EMEA website (http://www.emea.eu.int/ Inspection - Fees).

6. SCIENTIFIC EVALUATION OF AN APPLICATION BY THE COMMITTEE

6.1 Timetable for the evaluation

Once the application is validated and provided the Rapporteur and Co-Rapporteur have confirmed that they have received the dossier (including any additional information requested during validation phase), the EMEA starts the procedure at the monthly starting date published on the EMEA website. If the Rapporteur and the Co-Rapporteur have not received their copies of the dossier and/or additional validation information on the day where the dossier is validated by the EMEA, the start of the procedure may be delayed until the procedural starting date of the next month.

If, within a month from the start of the procedure, any other member of the CHMP has not received the requested parts of the dossier from the applicant, the EMEA will stop the clock until confirmation is received that each member of the CHMP has been delivered the requested documentation.

It is therefore important that applicants are able to provide a proof of delivery to Rapporteur, Co-Rapporteur and to CHMP members (upon request) to the EMEA.

Having taken into consideration the standard timetable agreed by the CHMP for the evaluation of a centralised application, a timetable is prepared by the EMEA in consultation with the Rapporteur and the Co-Rapporteur. This timetable is then proposed to the CHMP for adoption.

The EMEA shall ensure that the opinion of the CHMP is given within 210 days (less any clock-stops for the applicant to provide answers to questions from the CHMP).

Article 56(2) of the Regulation allows the CHMP to establish scientific advisory groups (SAG) in connection with the evaluation of specific types of medicinal products or treatments. CHMP may also consult its working parties (standing or temporary) on any scientific issues or during a marketing authorisation application evaluation.

The role of the SAGs is to provide, on request from the CHMP, an independent recommendation on scientific and technical matters relating to products under evaluation or any other scientific issues relevant to the work of the CHMP. While views expressed by the SAGs are taken into account, the ultimate responsibility for final opinions rests with the CHMP.

So far, the CHMP has set up SAGs to provide expertise on oncology, diagnostics, anti-infectives, HIV/viral diseases, cardiology, CNS/psychiatry and endocrinology/diabetes. Each SAG is composed of experts selected from the European experts list according to their specific expertise. The SAG opinion will be forwarded to the Chairperson of the CHMP according to the timetable established in order to ensure that legal deadlines for evaluation of application are met.

More information on the CHMP interaction with its SAGs and working parties can be found in the CHMP Rules of Procedure (EMEA/CHMP/111481/2004) published on the EMEA website (http://www.emea.eu.int/ – Human Medicines – General guidance - General reporting), as well as in the published Mandates of each SAG.

Standard timetable for the evaluation of a centralised application

DAY	ACTION
1	Start of the procedure
80	Receipt of the Assessment Report(s) or critique from Rapporteur and Co-Rapporteur(s) by CHMP members and EMEA. EMEA sends Rapporteur and Co-Rapporteur Assessment Report/critique to the applicant making it clear that it only sets out their preliminary conclusions and that it is sent for information only and does not yet represent the position of the CHMP.
100	Rapporteur, Co-Rapporteur, other CHMP members and EMEA receive comments from Members of the CHMP (incl. peer reviewers).
115	Receipt of draft list of questions (including the CHMP recommendation and scientific discussion) from Rapporteur and Co-Rapporteur, as discussed with the peer reviewers, by CHMP members and EMEA.
120	CHMP adopts the list of questions as well as the overall conclusions and review of the scientific data to be sent to the applicant by the EMEA. Clock stop. At the latest by Day 120, adoption by CHMP of request for GMP/GLP/GCP inspection, if necessary (Inspection procedure starts).
121*	Submission of the responses, including revised summary of product characteristics labelling and package leaflet texts in English, and restart of the clock.

* Target dates for the submission of the responses are published on the EMEA Website (http://www.emea.eu.int/ – Human Medicines - Application Procedures - 'Pre-Submission Guidance').

After receipt of the responses, the CHMP will adopt a timetable for the evaluation of the responses. In general the following standard timetable will apply:

DAY	ACTION
150	Joint response Assessment Report from Rapporteur and Co-Rapporteur received by CHMP members and the EMEA. EMEA sends joint Assessment Report to the applicant making it clear that it only sets out their preliminary conclusions and that it is sent for information only and does not yet represent the position of the CHMP. Where applicable, Inspection to be carried out. EMEA/QRD sub-group meeting for the review of English product Information with participation of the applicant (optional).
170	Deadline for comments from CHMP Members to be sent to Rapporteur and Co-Rapporteur, EMEA and other CHMP Members.
180	CHMP discussion and decision on the need for adoption of a list of "outstanding issues" and/or an oral explanation by the applicant. If an oral explanation is needed, the clock is stopped to allow the applicant to prepare the oral explanation. Submission of final inspection report to EMEA, Rapporteur and Co-Rapporteur by the inspections team (at the latest by Day 180).
181	Restart the clock and oral explanation (if needed).
181 to 210	Final draft of English summary of product characteristics, labelling and package leaflet sent by applicant to the Rapporteur and Co-Rapporteur, EMEA and other CHMP members.
By 210	Adoption of CHMP Opinion + CHMP Assessment Report (and timetable for the provision of product information translations)

After adoption of a CHMP opinion, the preparation of the annexes to the Commission Decision is carried out in accordance with the following timetable:

DAY	ACTION
215 at the latest	Applicant provides the EMEA with summary of product characteristics, Annex II, labelling and package leaflet and Annex A in the 20 languages (All EU languages including Norwegian). EMEA circulates draft translations to Member States for review.
232 at the latest	Applicant provides EMEA with final translations of summary of product characteristics, Annex II, labelling and package leaflet in the 20 languages, taking account comments received from Member States by Day 229.
By 237	Transmission of Opinion and Annexes in all EU languages to applicant, Commission, and Members of the Standing Committee, and Norway and Iceland.
By 246	Applicant provides EMEA with one final full colour 'worst-case' mock-up of outer and inner packaging for each pharmaceutical form.

Further details on the post-opinion review of translations and forms to be used, are available In the EMEA "New linguistic review process of product information in the centralised procedure" as published on the EMEA website (http://www.emea.eu.int/ – Human Medicines - Application procedures - Product Information Templates - reference documents)

Once the medicinal product is authorised and in all cases BEFORE the medicinal product is placed on the market, specimens of the final outer and immediate packaging and the package leaflet of all product presentations must be submitted to the EMEA within a timeframe agreed between the EMEA and the marketing authorisation holder.

6.2 Accelerated Assessment

When a marketing authorisation application is submitted for a product which is of major public health interest, in particular from the viewpoint of therapeutic innovation, the applicant may request an accelerated assessment procedure in accordance with Article 14(9) of Regulation (EC) 726/2004.

The applicant should justify their expectation that the medicinal product is of major public health interest particularly from the point of view of therapeutic innovation.
The applicant should notify the intent to submit a request for an accelerated assessment procedure as part of the "letter of intent" (see section 3.1). The request itself for accelerated assessment can be submitted at any time prior to the submission of the marketing authorisation application. Where possible, the applicant should submit the request at least 10 working days in advance of the CHMP plenary meeting preceding the intended start of the evaluation procedure.

The applicant's request shall be duly substantiated and shall be sent to the PTL, (Co-) Rapporteur and all CHMP members.

The outcome of the assessment of the request by the CHMP will be communicated to the applicant.

If accepted by the CHMP, the above-mentioned standard timetable will be reduced to 150 Days.

For further details on the documentation required to substantiate a request for accelerated assessment, and on the reduced timetable, reference is made to the EMEA "Guideline on the procedure for Accelerated Assessment pursuant to article 14 (9) of Regulation (EC) 726/2004" published on the EMEA website (include future path).

6.3 Liaison between the applicant and the EMEA

For general information regarding the procedure, the applicant is advised to liaise with the PTL. When during the course of the scientific assessment, clarification regarding specific issues relating to the data submitted is necessary, the applicant and the (Co-)Rapporteur(s) may liaise directly, and inform the PTL of the outcome of their discussions.

Whenever meetings between the (Co-)Rapporteur with the applicant or marketing authorisation holders take place, minutes of all contacts shall be made available to the (Co-)Rapporteur and the EMEA. Contacts by other CHMP members and alternates with the applicant are not considered appropriate and should be avoided during assessment procedures. Should such contacts take place, these shall be reported to the Rapporteur, the Co-Rapporteur and to the EMEA.

6.4 Committee's request for additional information

The CHMP will consider the preliminary Assessment Reports or critique from the Rapporteur and Co-Rapporteur. From these, the peer review comments, and the comments of other members of the CHMP the outstanding issues which the applicant should address will be identified. A consolidated list of questions, identifying "major objections" and/or "other

concerns" may be adopted. These will be sent to the applicant together with the CHMP recommendation and scientific discussion. The clock will be stopped at this point.
The CHMP recommendation will state whether:

- the product could be approvable provided satisfactory answers are given to the "other concerns" and the indications, other elements of the summary of product characteristics or other conditions for the marketing authorisation are amended as outlined in the list of questions;

- the provisional view of the CHMP is that the product is not approvable since there are "major objections" which have been identified in the detailed questions.

The applicant is expected to respond within the time frame agreed by the CHMP (3 months) from the date of receiving the questions. Applicants may request an additional 3-month period by writing to the CHMP chairman outlining their reasons. This time period is felt to be an adequate time for companies to prepare the answers to the list of questions, including new data generated as a result of issues raised in the list of questions. If the applicant is unable to respond in the time frame, then careful consideration should be given to withdrawing the application and resubmitting, if necessary after obtaining scientific advice, when the full information is available. The applicant is advised to consult with the Rapporteur, the Co-Rapporteur and the PTL if clarification is required on any of the questions. The applicant may also wish to consult the Rapporteur, Co-Rapporteur and the PTL regarding the strategy for the response and revision of indications, other elements of the summary of product characteristics or other conditions for the marketing authorisation (see also the EMEA guidance document on Rapporteur meetings with applicants on the list of questions, published on the EMEA website: http://www.emea.eu.int/pdfs/human/regaffair/227002en.pdf). Applicants should inform the EMEA/CHMP preferably one month in advance of the submission of the responses. Target dates for submission of the responses are published on the EMEA Website.

Further guidance on the response time is provided in the EMEA guidance “Time allowed for applicants to respond to questions and issues raised during the assessment of new marketing authorisation applications in the centralised procedure” as published on the EMEA Website (http://www.emea.eu.int/pdfs/human/regaffair/7540106en.pdf.)

6.5 Oral (or written) explanation

The CHMP will discuss the joint Assessment Report and the comments of other CHMP members on the report. The CHMP may then identify outstanding issues, which the applicant will be asked to address in writing and/or during an oral explanation.

In addition to the written responses to the issues raised by the CHMP, applicants may also avail themselves of an oral explanation to the CHMP. The time limit set out in Article 6 of the Regulation shall be suspended for the time allowed to the applicant to prepare an oral (or written) explanation. Applicants should normally respond (or prepare for an oral explanation) within 1 month. In exceptional circumstances a 1 or max. 2 months extension may be granted upon provision of appropriate scientific justifications, which will be reviewed and agreed by CHMP.

Further guidance on the response time is provided in the EMEA guidance “Time allowed for applicants to respond to questions and issues raised during the assessment of new marketing authorisation applications in the centralised procedure” as published on the EMEA Website (http://www.emea.eu.int/pdfs/human/regaffair/7540106en.pdf.).

Applicants or any relevant third party may also be invited by the CHMP for an oral explanation.

Further details on oral explanations are available in the EMEA "Guidance to applicants on CHMP Oral Explanations in relation to Centralised Applications" on the EMEA Website (http://www.emea.eu.int/– Human Medicines - guidance documents - general guidance)'.

After the oral explanation and the subsequent CHMP discussion, the (Co-)Rapporteur/PTL will provide feedback to the applicant on the general orientation of the CHMP before any formal vote takes place. In case of a positive trend, a discussion on key amendments to the summary of product characteristics and draft follow-up measures or conditions to the marketing authorisation may be held. In case of a negative trend, the possible procedural options will be discussed with the applicant.

Oral Explanation

Oral explanations will be provided at the request of either the applicant or the CHMP. The CHMP may also invite on its own initiative or consider a request of any relevant third party for an oral explanation.

When the applicant wishes to have the opportunity of an oral explanation, they should present a written request to the CHMP preferably one month before the anticipated date of the oral explanation and certainly prior to Day 180.

The CHMP may also invite the applicant to provide oral explanations on aspects of the dossier requiring clarification. A list of outstanding issues, to be addressed at the oral explanation will be adopted by the CHMP (usually at Day 180) and sent to the applicant. The applicant would then liaise with the Rapporteur and the EMEA PTL regarding details of the presentation.

In order to maximise the benefit of an oral explanation, it is important that applicants preparing for and attending oral explanations bear in mind that they are held to only allow clarification of outstanding issues.

The applicant should remember:

That the oral proceedings of the CHMP are in English. For the presentation, slide projectors, overhead projectors and computerised systems are available at the EMEA. Applicants should consult in advance with the EMEA PTL on the facilities they would like to use.

A concise information package to support and elaborate on the outstanding issues to be addressed during the oral explanation, as well as the draft updated summary of product characteristics/package leaflet and any proposal for follow-up measures/specific obligations, risk minimisation actions, should be received by the EMEA PTL and all CHMP members at least 10 working days before the CHMP meeting.

At least one week before the oral explanation, the applicant should provide the PTL with the definitive list of names and a short curriculum vitae of the persons who will be attending the oral explanation. The applicant's delegation attending the hearing should be limited to a maximum of 10 persons. In addition, the draft presentation must be sent to the (Co-Rapporteur and the PTL.

At least 2 hours before the oral explanation, the applicant should provide the PTL with 60 hard copies of the handouts of the final presentation and an electronic version.

Oral explanations will usually be conducted in the following sequence:
The Chairman will invite the applicant's representatives to briefly introduce themselves; to confirm that all pertinent data have been submitted to the CHMP, whether favourable or unfavourable to the case and whether there is any further or additional information to be given to the CHMP.

The Chairman will invite the applicant representatives to make their presentation (usually not more than 30-40 minutes) and will then ask the Rapporteur to put any outstanding questions to the applicant.

An opportunity will also be given to all members of the CHMP to raise questions or comments.

At the conclusion of the oral explanation, the representatives of the applicant will be invited to leave and the CHMP will discuss and provide a preliminary recommendation on the acceptability of the application.

The applicant will be informed of the trend at CHMP level at the end of the scientific discussion ahead of any formal vote to conclude the evaluation process.

6.6 Withdrawal of the application

Where an applicant decides to withdraw their application before an Opinion has been adopted by the CHMP or during the appeal process, the applicant shall communicate its reasons for doing so to the EMEA. The EMEA shall make this information publicly accessible and shall publish the assessment report, if available, after deletion of all information of a commercially confidential nature (as justified by the applicant). Withdrawal of the application after adoption of the opinion will not prevent that this information is made publicly available.

Further guidance on the withdrawal information to be published is provided in the EMEA "Reflection paper on publication of withdrawals", as published on the EMEA website (include future link).

7. THE COMMITTEE'S OPINION

On or before Day 210, the CHMP adopts its opinion in the light of the final recommendation of the Rapporteur and Co-Rapporteur and further evidence presented at the oral explanation. In case of an oral explanation and where the procedural timetable allows, the CHMP Opinion will be adopted at the following CHMP meeting, allowing applicant, (Co-)Rapporteur and CHMP members to finalise the product information and Assessment Report as appropriate. The applicant should liaise with the PTL on the practical arrangements in connection with the adoption of the opinion.

Details about adoption of opinions by the CHMP are available in the Committee's "Rules of Procedure", as published on the EMEA website:
(http://www.emea.eu.int/pdfs/human/regaffair/ 11148104en.pdf).

The draft opinion is prepared by the EMEA and then adopted by the CHMP.
The CHMP opinion, which may be favourable or unfavourable, is, wherever possible, reached by scientific consensus.

If such consensus cannot be reached, the Opinion shall be adopted by an absolute majority of the members (i.e. favourable votes by at least half of the total number of CHMP members eligible to vote plus one). When divergent positions have been expressed, they will be referenced in the CHMP Opinion. Members expressing such divergent positions shall state clearly the reasons on which they are based. The divergent positions will be appended to the Opinion. The reasons for the divergent opinions shall be publicly available together with the documentation made publicly available in relation to the evaluation of applications.

Where the Opinion is adopted by a majority vote, the number of votes shall be clearly mentioned in the Opinion. In the absence of an absolute majority position the CHMP Opinion is deemed to be negative.

The position of the Norwegian and Icelandic CHMP members, who do not take part in the CHMP vote as such, is nevertheless recorded in the opinion.

The Rapporteur and the Co-Rapporteur, in co-ordination with the PTL, taking account of the full scientific debate within the CHMP and the conclusions reached, prepares the final assessment report, which, once adopted by the CHMP, becomes the CHMP assessment report and is appended to the CHMP opinion.

7.1 Favourable opinion

In the event of an opinion in favour of granting the relevant authorisation to place the medicinal product concerned on the market, the following documents must be annexed and/or appended to the opinion (Article 9(4) of the Regulation).

- A draft summary of product characteristics as referred to in Article 11 of Directive 2001/83/EC;
- Manufacturing and/or importing information;
- Conditions or restrictions regarding supply and use, including the conditions under which the product may be made available to patients in accordance with Title VI of Directive 2001/83/EC;
- Conditions or restrictions with regard to the safe and effective use of the medicinal product. In addition, CHMP may recommend in its opinion conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States, in accordance with Article 127a of Directive 2001/83/EC;
- A draft labelling and package leaflet presented in accordance with Title V of Directive 2001/83/EC;
- The CHMP assessment report;
- Where relevant, divergent positions of Committee Members with signatures and with their grounds for not supporting the opinion.

Should the CHMP want to record any follow-up measures they will be included in the Assessment Report and referenced in a “letter of undertaking” signed by the applicant which will be annexed to it.

7.2 Conditional Marketing Authorisation and Marketing Authorisation under Exceptional Circumstances

7.2.1 Conditional Marketing Authorisation

In accordance with Article 14(7) of the Regulation, following consultation with the applicant, the CHMP may adopt an Opinion recommending a marketing authorisation to be granted subject to certain specific obligations to be reviewed annually. The list of these obligations shall be made publicly accessible.

Article 14(7) equally provides that the provisions for granting such authorisation shall be laid down in a Commission Regulation.

The granting of a conditional marketing authorisation will allow medicines to reach patients with unmet medical needs earlier than might otherwise be the case, and will ensure that additional data on a product are generated, submitted, assessed and acted upon.

The applicant should notify the EMEA about its intention to request a conditional marketing authorisation as part of the "letter of intent" (see also section 3.1).

Conditional marketing authorisations will be valid for 1 year, on a renewable basis.
Before expiry, the marketing authorisation holder shall apply for the renewal of the marketing authorisation.

For further guidance on the criteria for conditional marketing authorisation, justifications to be provided and the procedure to be followed, reference is made to the implementating Commission Regulation (EC) No 507/2006 on the Commission website (http://pharmacos.eudra.org/F2/eudralex/vol-1/reg_2006_507/reg_2006_507_en.pdf) and EMEA guidance documents published on the EMEA website (include future link).

7.2.2 Marketing Authorisation under Exceptional Circumstances

In accordance with Article 14(8) of the Regulation, in exceptional circumstances, and following consultation with the applicant, an authorisation may be granted subject to a requirement for the applicant to introduce specific procedures, in particular concerning the safety of the product. Such authorisation must be based on one of the grounds set out in Part II.6 of Annex I to Directive 2001/83/EC. Continuation of the authorisation shall be linked to the annual reassessment of these conditions.

The applicant should include a statement on the appropriateness of the granting of a marketing authorisation under exceptional circumstances as part of the "letter of intent" (see also section 3.1).

The applicant may request advice from the EMEA about the appropriateness of applying for a marketing authorisation under exceptional circumstances. This should preferably occur in the context of the pre-submission meeting between the EMEA and applicant and occur at least 4-6 months before the marketing authorisation application submission.

For further guidance on the conditions and procedures for the granting of a marketing authorisation under exceptional circumstances, reference is made to the EMEA "Guideline on procedures for the granting of a marketing authorisation under exceptional circumstances" published on the EMEA Website (include future path)

7.3 Specific obligations and follow-up measures

7.3.1 Specific obligations

When a conditional marketing authorisation is granted, the marketing authorisation holder is obliged to submit post authorisation data to the Rapporteur, Co- Rapporteur, CHMP Members and the EMEA, within an agreed timeframe. A marketing authorisation under exceptional circumstances may also include such an obligation. These additional data, known as 'specific obligations', are set out in Annex II.C of the Commission Decision and are detailed in the Letter of Undertaking of the marketing authorisation holder as adopted at the time of the CHMP Opinion.

The specific obligations are to be reviewed at the intervals indicated and at the longest annually (at the time of the annual re-assessment). The annual review includes a re-assessment of the benefit/risk profile. For conditional marketing authorisations, such review will occur at the one-yearly renewal of the marketing authorisation.

Two paper copies of the documentation relating to specific obligations as well as an electronic copy should be sent by the marketing authorisation holder to the EMEA. One paper and electronic copy should be simultaneously be sent to the (Co-)Rapporteur. After validation, an electronic copy of the submitted documentation should be provided to all CHMP members. The documentation will be reviewed in accordance with a 60-day timetable.

7.3.2 Follow-up measures

For all opinions of the CHMP (whether or not for conditional approval or under exceptional circumstances) it might be necessary to establish post-authorisation follow-up measures. Follow-up measures can be requested at the initial CHMP opinion or further to the CHMP assessment of any submitted additional data/applications.

The same dossier submission requirements and assessment timetable as for specific obligations apply (see above).

Marketing authorisation holders will be informed of the outcome of CHMP discussions on the specific obligation / follow-up measure by the EMEA.

7.3.3 Resulting variation applications

When submitting data relating to a follow-up measure or specific obligation for centrally authorised medicinal products, marketing authorisation holders should review whether these data would require changes to the product information or to the marketing authorisation (e.g. changes to the Quality Module) of the medicinal product. If such changes are identified, the marketing authorisation holder should submit the follow-up measure or specific obligation data within the framework of the appropriate variation/extension procedure(s). This will minimise the processing and review time and will allow quicker implementation of the required changes.

7.3.4 Non-fulfilment of specific obligations or follow-up measures

Marketing authorisation holders must indicate realistic target dates for the submission of the post-authorisation data in their Letter of Undertaking.

If no documentation is received in order to fulfil the specific obligations or follow-up measures before the deadline previously agreed by the CHMP and after having received reminder letters from the EMEA, the matter will be put by the EMEA on the Agenda of the following CHMP meeting.

In case of non-fulfilment of the specific obligations the CHMP will formulate an opinion, on the basis of Articles 14(7), 14(8) of the Regulation, recommending the "variation/ suspension/revocation" of the marketing authorisation.

In case of non-fulfilment of follow-up measures the CHMP will have to consider the possibility to recommend a "variation/revocation/suspension" of the marketing authorisation based on the re-assessment of the benefit/risk profile of the product in accordance with Article 5 of the Regulation and with Article 116 of Directive 2001/83/EC.

7.4 Unfavourable opinions

In addition to the applicant briefing following the CHMP trend vote, the EMEA immediately informs the applicant when the opinion of the CHMP is that the application does not satisfy the criteria for authorisation set out in the Regulation.

The following documents shall be annexed and/or appended to the opinion:

- the appended CHMP assessment report stating the reasons for its negative conclusions.
- where appropriate, divergent positions of Committee Members with their grounds for not supporting the opinion.

Information about unfavourable opinions / refusals, incl. divergent positions if applicable, and the reasons for such opinion shall be made publicly accessible, even if the application has been withdrawn.

8. FOLLOW-UP TO THE CHMP OPINION

8.1 Translations of the CHMP opinion

Within 5 days after the CHMP opinion, the applicant will provide the EMEA members with the translations of the Annex A, summary of product characteristics, Annex II (Conditions of the marketing authorisation), labelling and package leaflet in all EU languages (including Icelandic and Norwegian). Throughout the evaluation procedure, a cumulative review of the quality of the product information will be carried out by the EMEA in co-operation with the Member States.

By Day +22 after adoption of the Opinion, final (revised) translations of all texts for summary of product characteristics, Annex II, labelling and package leaflet should be provided to the EMEA taking account comments received from Member States by Day +19. One final full colour 'worst-case' mock-up of outer and inner packaging for each pharmaceutical form should be provided to the EMEA by Day +36 after adoption of the Opinion.

8.2 Transmission of the CHMP opinion

The EMEA will prepare a "Summary of Opinion" (for favourable as well as unfavourable opinions) in liaison with the applicant. Such Summaries will be published on the EMEA Website after the adoption of the CHMP Opinion (http://www.emea.eu.int/ – Human Medicines - 'Summaries of Opinion').

If within 15 days of receipt of the opinion, the applicant does not inform the EMEA of any intention to request a re-examination of the opinion, the EMEA will then forward the opinion (and the required annexes) to the Commission, the Member States, Norway and Iceland and the applicant together with the CHMP assessment report.

The opinion and its annexes are sent either by electronic mail or by courier (if electronic mail is not available). The Decision-Making Process of the Commission described in chapter 6 starts once the opinion with the Assessment Report has been received.

8.3 Re-examination

The applicant may notify the EMEA/CHMP in writing of their intention to request a re-examination of the opinion within 15 days of its receipt (after which if such a request is not made, the opinion becomes final).

The detailed grounds for the request must be forwarded to the EMEA within 60 days after receipt of the opinion. If the applicant wishes to appear before the CHMP for an oral explanation, this should also be requested at this stage.

The EMEA will publish in the CHMP Press Release/'Monthly Report' a short statement on the re-examination request.

The CHMP will appoint a new Rapporteur and where necessary (a) new Co-Rapporteur(s), different from those appointed for the initial opinion, to co-assess the grounds for the re-examination of the opinion. . The re-examination may deal only with the points of the opinion initially identified by the applicant and may be based only on the scientific data available when the CHMP adopted the initial opinion. The applicant may request that the CHMP consult a Scientific Advisory Group (SAG) in connection with the re-examination of the opinion. In case of such a request, the CHMP will systematically consult the relevant SAG or of an ad-hoc expert group meeting in case no SAG is established in the therapeutic area concerned. Within 60 days from the receipt of the detailed grounds for re-examination, the CHMP will re-examine its opinion. If considered necessary, an oral explanation can be held within this 60 days timeframe. No clock-stops apply to this procedure.

Once the CHMP adopts a final opinion, it is forwarded (with the required annexes) within 15 days of its adoption, to the Commission, the Member States, Norway and Iceland and the applicant. The reasons for the CHMP conclusions will be annexed to the final opinion/assessment report.

At the end of the re-examination procedure, the Summary of Opinion (SmOp) or the Questions and Answers document on the initial CHMP Opinion will be revised to reflect the outcome of the re-examination procedure, and will be published at the time of the CHMP Monthly Report. The EPAR/Refusal EPAR will be published once the Commission Decision has been issued.

For further guidance on the re-examination procedure, CHMP timetable for assessment and possible scientific advisory group consultation, reference is made to the EMEA "Guideline on the procedure for re-examination of CHMP opinions" published on the EMEA Website (include future path).

8.4 European Public Assessment Report

In accordance with Article 13 of the Regulation, the EMEA shall publish the CHMP assessment report on the medicinal product which includes the reasons for its opinion in favour of granting authorisation, after deletion of any information of a commercially confidential nature. This document is called the European Public Assessment Report (EPAR).

Article 13(3) of the Regulation further states that the EPAR shall include a summary written in a manner that is understandable to the public. The summary shall contain in particular a section relating to the conditions of use of the medicinal product.

The objective of such a patient-friendly summary is not only to be a non-technical version of the EPAR information, but also to include additional information that is considered useful for patients.

EPARs and their summaries are published on the EMEA website (http://www.emea.eu.int/ – Human Medicines - List of authorised products (EPARs)).

8.4.1 Operating approach to the preparation of the EPAR

Since the EPAR will be made available by the EMEA after the Commission has made the decision to authorise the product, it is prepared in parallel to the decision-making phase.

The responsibility of preparing the EPAR rests with the EMEA and will be co-ordinated by the PTL. The preparation of the EPAR is required in cases where the CHMP formulates positive final opinions.

In accordance with Article 9(4) of the Regulation, applicants will receive the assessment report of the CHMP. Applicants are then required to identify within a short period of time those issues which they consider to be commercially confidential. Such issues should be notified and justified by the applicant to the PTL, together with supportive justification or documentation.

Upon receipt of the applicant's response with those issues which the applicant considers to be commercially confidential, the PTL will prepare a draft of the EPAR, taking into account the obligations of the Regulation, transparency and confidential considerations. Any proposed deletion that is not considered duly justified will not be implemented by the EMEA. Deletion of information other than that of a commercially confidential nature will not be accepted.

The draft EPAR will then be circulated to members of the CHMP at a subsequent meeting. If there are any controversial issues that are not resolved and draft of the EPAR is not adopted, a meeting with the Rapporteur(s), and the concerned party(ies) can be organised by the EMEA. The adopted draft EPAR is sent to the applicant for information.

8.4.2 Availability of the EPAR

Once the CHMP has agreed on the text and after the Commission Decision has been issued, the EPAR will be sent to the applicant.

The EPAR shall be made available on the EMEA Website from the date of the Commission Decision to grant the marketing authorisation.

8.5 Negative decision

Following a Commission Decision on the refusal to grant a marketing authorisation, which, in accordance with Article 12(2) of the Regulation, constitutes a prohibition to place on the market the medicinal product concerned throughout the Community, the EMEA shall make information about such refusal and the reason for it publicly accessible ("Refusal EPAR").

9. MARKETING OF THE MEDICINAL PRODUCT IN THE COMMUNITY

In accordance with Article 13(4), the marketing authorisation holder shall inform the EMEA of the dates of the actual marketing of the product in all Member States, taking into account the various presentations authorised. The marketing authorisation holders shall also notify the EMEA if the product, or any of its presentations, ceases to be marketed in any of the Member States, either temporarily or permanently. Such notification shall normally be notified to the EMEA no less than 2 months before the marketing interruption.

Any authorisation, which is not followed by the actual marketing in the Community within 3 years after authorisation, shall cease to be valid. Similarly, when a product previously marketed in the Community is no longer actually present on the market for 3 consecutive years, the authorisation shall cease to be valid. However, the Commission in exceptional circumstances may grant exemptions from these provisions on duly justified public health grounds.

For more details on this provision, please refer to Chapter 1 section 2.4.2 and to Questions and Answers on this topic included in the EMEA Post-Authorisation Guidance (include future path).

10. POST-AUTHORISATION INSPECTIONS (GMP, GCP AND PHV)

Marketing authorisation holders are reminded that the following routine or specific inspections may occur in the post-authorisation phase:

GMP Inspections:
The legal basis for post-authorisation (re-)inspections of manufacturing sites is provided by Article 8(2) and 19(3) of the Regulation. The purpose of GMP re-inspections is to verify that manufactures continue to comply with EU GMP and with the requirements of the marketing authorisation as accepted by the CHMP. These inspections are systematic and every site located in a third country, which does not have an operational MRA, will be inspected every three years. The CHMP may also request a GMP re-inspection of any manufacturing site due to concerns arising from reports of product defects or if GMP non-compliance is suspected.

Pharmacovigilance Inspections:
The legal basis is set out in Article 19(1) of the Regulation and Article 111(1)(d) of Directive 2001/83/EC. Such inspections may be routine or may be triggered (by risk factors or by concerns relating to product safety, compliance with regulatory requirements). The CHMP

may request a pharmacovigilance inspection due to issues arising from the monitoring of specific products, or in order to be assured about the pharmacovigilance system in place in a company which is marketing authorisation holder for one or more centrally authorised products (or as a consequence of a referral for other products). The scheduling and conduct of these inspections will be driven by risk analysis criteria.

Data submitted as a result of specific obligations/follow-up measures, variations, extensions or other information received post-authorisation (e.g. in relation to safety updates, risk management plan etc…), may trigger a GCP, GMP or pharmacovigilance inspection request.

More information on the conduct of such inspections can be found in the EMEA Post-Authorisation Guidance Document on the EMEA website (http://www.emea.eu.int/ - Human Medicines - Application Procedures)

11. TRANSFER OF A COMMUNITY MARKETING AUTHORISATION

The transfer of a marketing authorisation granted under the centralised procedure is regulated in Commission Regulation (EC) No. 2141/96, of 7 November 1996.

In accordance with that Regulation, the marketing authorisation holder should submit an application to the EMEA supported by the documents mentioned in the Annex to that Regulation. The EMEA will issue an invoice on the date of the notification of the administrative validation to the applicant and fees will be payable within 45 days of the date of the notification.

In addition evidence should be provided of the establishment in the EEA of the person to whom the transfer is to be granted (transferee), as well as a proof that an agreement for the transfer of the marketing authorisation has been reached.

Within 30 days as from the submission of the valid application with the required documentation, the EMEA will adopt an opinion, which will be sent to the marketing authorisation holder, the transferee and to the Commission.
The opinion will be unfavourable if the documents submitted in support of the application are incomplete or if it appears that the transferee is not established in the EEA.

In the case of a favourable opinion, the Commission will amend the decision granting the marketing authorisation. The transfer is authorised from the date of notification of the amendment of the Commission decision granting the marketing authorisation.

For the transfer of a marketing authorisation covering medicinal products already marketed by the marketing authorisation holder, the EMEA, by mutual agreement with the marketing authorisation holder and the transferee, will set the date by which the transfer will actually take place ('implementation' date), i.e. the date on which the transferee will start to release batches on the market with the name of the new marketing authorisation holder and the transferee takes full responsibility for the old and new batches of the medicinal product concerned.

The EMEA will inform the Commission of this 'implementation' date.
For the transfer of a marketing authorisation covering medicinal products not yet marketed by the marketing authorisation holder, the proposed implementation date should refer to the day on which the Commission Decision on the transfer will be issued.

When transferring the marketing authorisation of a designated Orphan medicinal product, the marketing authorisation holder must also transfer the Orphan designation of the product concerned in accordance with Article 5(11) of Regulation (EC) No 141/2000, in order to maintain the orphan status.

Further details on the handling of transfer procedures, documentation to be provided and choice of 'implementation' date can be found in the EMEA Post-Authorisation Guidance Document on the EMEA website (http://www.emea.eu.int/ - Human Medicines - Application Procedures)

12. RENEWAL OF MARKETING AUTHORISATION

According to Article 14 of the Regulation, a marketing authorisation for a medicinal product shall be valid for five years, except when a conditional marketing authorisation has been granted (see section 7.2). The marketing authorisation may be renewed after five years on the basis of a re-evaluation by the EMEA/CHMP of the benefit-risk balance of the product, upon application by the holder at least six months before expiry.

This application should be supported by a dossier containing a consolidated version of the dossier, including all variations introduced since the marketing authorisation was granted. The EMEA will issue an invoice on the date of the notification of the administrative validation to the applicant and fees will be payable within 45 days of the date of the notification.

The assessment will consist of a re-evaluation of the benefit-risk balance, on the basis of a consolidated version of the file, making use of the PSUR data and any relevant new information affecting the benefit-risk for the product. The CHMP will adopt an opinion on the renewal of the marketing authorisation after 90 (or maximum 120) days.

Once renewed, the marketing authorisation shall be valid for an unlimited period, unless the Commission upon recommendation of the CHMP decides on justified grounds relating to pharmacovigilance, to proceed with one additional five-year renewal. However, the CHMP may assess the benefit-risk balance of a medicinal product at any time the CHMP deems appropriate.

More detailed information on the format and content of the renewal application and the procedure is provided in the "Guideline on the processing of renewals in the centralised procedure", which is published in Volume 2C of the Notice To Applicants, as well as in the EMEA Post-Authorisation Guidance Document on the EMEA website (http://www.emea.eu.int/ - Human Medicines - Application Procedures).

Marketing authorisations, which have already been renewed under the system in force before the application of the new Regulation (20 November 2005), should be renewed once more under the new system before the authorisation may gain unlimited validity.