European Medicines Agency
Evaluation of Medicines for Human Use

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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

GUIDELINE ON PROCEDURAL ASPECTS REGARDING A CHMP SCIENTIFIC OPINION IN THE CONTEXT OF COOPERATION WITH THE WORLD HEALTH ORGANISATION (WHO) FOR THE EVALUATION OF MEDICINAL PRODUCTS INTENDED EXCLUSIVELY FOR MARKETS OUTSIDE THE COMMUNITY

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This document was applicable till 4 September 2017, when it was superseded by a revised and expanded version of EMA procedural advice for medicinal products intended exclusively for markets outside the European Union under Article 58 of Regulation (EC) No 726/2004 in the context of co-operation with the World Health Organisation (WHO)

Note: * The document of 23 May 2005 has been updated with regard to its scope, to take into account the new fee regulation and aspects of Pharmacovigilance.

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 85 45
E-mail: mail@emea.eu.int http://www.emea.eu.int

GUIDELINE ON PROCEDURAL ASPECTS REGARDING A CHMP SCIENTIFIC OPINION IN COOPERATION WITH WHO

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1. LEGAL BASIS AND SCOPE

Article 58 of Regulation (EC) No 726/2004[1] ("the Regulation") establishes a mechanism whereby the European Medicines Agency (EMEA) may 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. For this purpose, an application shall be submitted to the Agency in accordance with the provisions of Article 6. The Committee for Medicinal Products for Human Use may, after consulting the World Health Organisation, draw up a scientific opinion in accordance with Articles 6 to 9. The provisions of Article 10 shall not apply.

Article 58 of the Regulation responds to the need to protect public health and to give scientific assistance to non-member countries in the context of cooperation with WHO whilst at the same time allowing rapid access to those countries for important new medicinal products.

Article 16(2) of the Commission proposal for a Regulation of the European Parliament and of the Council on compulsory licensing of patents relating to the manufacture of pharmaceutical products for export to countries with public health problems (COM(2004) 737, dated 29.10.2004) makes reference to Article 58:

"Where the application for a compulsory license concerns a medicinal product and the applicant for the compulsory license is not the holder of a marketing authorisation valid within the Community for the product concerned, he may avail himself of the scientific opinion procedure provided for under Article 58 of Regulation (EC) No 726/2004 or any similar procedure provided under national law."

The application for this procedure does not exclude a future application for a marketing authorisation in the Community.

In this Guideline, 'a CHMP scientific opinion' should be understood as a CHMP scientific opinion for the evaluation of medicinal products intended exclusively for markets outside the community in the context of cooperation with WHO. The CHMP scientific opinion assessment report shall contain the conclusions on the Quality, the Safety and 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.

2. ELIGIBILITY FOR A CHMP SCIENTIFIC OPINION

A request for classification as medicinal product qualifying for a CHMP scientific opinion should be made at least six months prior to submission of an application.

In case an applicant considers seeking scientific advice ahead of its application for a CHMP scientific opinion, it is recommended that the eligibility request is already made at that point in time; in this case, the request should be made at least four months prior to the application for scientific advice. If the time gap between the request for scientific advice and the application for a CHMP scientific opinion is large, the applicant may be requested to resubmit the eligibility request at the time of notification of intention to submit.

[1] Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.

For the purpose of a request for classification as medicinal product qualifying for a CHMP scientific opinion, the applicant should provide EMEA with:

- evidence of establishment of the applicant (future Opinion Holder) or a contact point in the European Economic Area (EEA);
- a draft Summary of Product Characteristics (SPC) or a draft product profile;
- a justification for the product's eligibility for a CHMP scientific opinion; the medicinal product for human use intended exclusively for markets outside the Community should be intended to prevent or treat diseases of major public interest[2].
- a statement from the applicant that, for the purpose of this application, the medicinal product is not intended to be marketed in the Community;
- a proposed classification for the supply of the medicinal product;

Further to the provision of the above information, a meeting may be organised in order to clarify outstanding issues prior to the Agency consulting WHO.

After having consulted WHO, EMEA will inform the applicant whether the medicinal product is eligible. The decision (stating the reasons if negative) on eligibility should be available within two months and will be forwarded by EMEA to the applicant. In case the number of applications would be disproportionate to the available EMEA resources, WHO will make a priority list of which the EMEA, according to its resources, will start the ones having the highest priority; applications with lower priority will be postponed.

3. SCIENTIFIC ADVICE

Article 58(2) of the Regulation makes provision for scientific advice on medicinal products intended to be marketed exclusively outside the Community. Scientific advice can be requested during initial development, before an application for a CHMP scientific opinion or in the post-opinion phase.

The existing procedural guidance on scientific advice will also be applied for scientific advice on possible future applications for a CHMP scientific opinion in the context of cooperation with WHO; 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').

The same fee applies; in exceptional cases, total or partial fee exemptions may be granted by the EMEA Executive Director for medicinal products eligible for a CHMP scientific opinion on recommendation from CHMP. Any request should be sent to the Executive Director with the appropriate justification as early as possible, and not later than 3 months prior to the anticipated date of submission of the application for scientific advice.

[2] Such as *(1)* vaccines used or of possible use in the WHO Expanded Programme on Immunization (EPI), *(2)* vaccines for protection against a WHO public health priority disease, *(3)* vaccines that are part of a WHO managed stockpile for emergency response and *(4)* medicinal products for WHO target diseases such as HIV/AIDS, malaria, tuberculosis, lymphatic filariasis (elephantiasis), trachoma, leishmaniasis, schistosomiasis, African trypanosomiasis (sleeping sickness), onchocerciasis (river blindness), dengue fever, Chagas disease, leprosy.

4. PROCEDURE FOR SUBMISSION OF THE APPLICATION FOR A CHMP SCIENTIFIC OPINION

When preparing the submission of an application for a CHMP scientific opinion, applicants have the opportunity to meet the EMEA to discuss any procedural, regulatory or legal issues on the proposed submission. 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'). *[A pre-submission request form will be created.]*

4.1 Before submission

At least six months prior to submission of an application for a CHMP scientific opinion, 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 SPC;
- if already available, the EMEA confirmation of eligibility in consultation with WHO; in absence of this confirmation, the particulars outlined in section 2 should be submitted;
- an indication on the number of strengths / pharmaceutical forms / pack sizes (if already known);
- if applicable, scientific advice received in accordance with Article 58(2) of the Regulation;
- a proposed classification for the supply of the medicinal product;
- if applicable, their intention to present an Active Substance Master File (ASMF) for active substances prepared in accordance with the guidelines on the ASMF which have been published in Volume 3 of the Rules governing medicinal products in the European Union (http://pharmacos.eudra.org/F2/eudralex/vol-3/home.htm);
- if applicable, their intention to present any existing Vaccine Antigen Master File (VAMF) or Plasma Master File (PMF) Certificates.
- any preference regarding rapporteurships (preferably three to four names of CHMP members from three to four different EU Member States, Norway or Iceland);
- details of compliance with the requirements of Directive 2001/18/EC[3], if relevant.
- the details of proposed manufacturing sites for the finished product and active substances (see also section 5.1 Pre-opinion inspections).
- the same fees as for the EU centralised procedure apply; in exceptional cases, total or partial fee exemptions may be granted by the EMEA Executive Director for medicinal products eligible for a CHMP scientific opinion on recommendation from CHMP. Any request should be sent to the Executive Director with the appropriate justification as early as possible, and not later than 3 months prior to the anticipated date of submission of the application.

[3] Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC.

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

A member of staff of the Human Medicines Evaluation Unit of the EMEA will be officially appointed as EMEA Product Team Leader (PTL).

At least three months before submission, rapporteur/co-rapporteur appointment is made at the CHMP meeting following the receipt of the letter of intention to submit. Further detailed information on the rapporteur/co-rapporteur appointment is available on the EMEA website (http://www.emea.eu.int/ – Human medicines, Application Procedures 'Pre-submission guidance')

To that effect the EMEA shall present the following information to CHMP members:

- EMEA confirmation of eligibility in consultation with WHO, together with the justification given by the applicant;
- the applicant's preference for rapporteurship.

The EMEA notifies the applicant of:

- the name of the rapporteur and the co-rapporteur appointed by CHMP;
- applicable fees;
- dossier requirements of the different CHMP members.

In the 3 months preceding the submission, the rapporteur and the co-rapporteur will notify CHMP of the names of the experts they have nominated for the evaluation of the application.

The experts, on whom CHMP can rely when it needs specific expertise, or assessors for the evaluation of applications, are those who have been put at the disposal of the EMEA in accordance with Article 62 of the Regulation; CHMP may ask WHO to propose experts for certain areas of expertise.

The CHMP members and the experts responsible for evaluating medicinal products rely on the scientific assessment resources available in the national competent authorities and, if requested by CHMP, scientific assessment resources proposed by WHO.

All experts will be entered in the EMEA experts database on the provision that the following completed and signed documents have been submitted to EMEA: (i) Nomination Form, (ii) Public Declaration of Interests and Confidentiality Undertaking form and (iii) Curriculum Vitae. In accordance with the EMEA policy and procedure on the handling of conflicts of interests for EMEA Scientific Committee members and experts (available on the EMEA website (http://www.emea.eu.int/ – General reporting, Executive, EMEA Directorate), the experts will be allowed to participate in the discussions on products under the CHMP scientific opinion procedure to an extent defined by the risk level.

In order to ensure standardisation of the headings listed in the SPC, package leaflet and labelling, the EMEA provides the applicant with a template of what must be included in these documents. This template is available in paper and electronic format, as well as on the EMEA website (http://www.emea.eu.int/ – Human medicines, Application Procedures 'Product Information Templates').

4.2 Submission of the application and payment of fees

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 cannot 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 rapporteur and co-rapporteur, and may require in exceptional cases the appointment of a new rapporteur and/or co-rapporteur.

In order to accelerate and facilitate the procedure, applicants are invited to submit, in parallel to the EMEA, copies of the dossier to both the rapporteur and the co-rapporteur.

The address for submission of the application is given in the EMEA website (http://www.emea.eu.int/ – Human medicines, Application Procedures 'Pre-submission guidance').

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 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. Where more than one procedure is processed in a given month a summary invoice or statement will be issued at the end of each month for payment within 30 days of the end of the month.

4.3 Dossier to be submitted

The dossier should be submitted in the Common Technical Document format (CTD)[4], except for EU dossiers with the edition 1998 of the Notice to Applicants (NTA) format that have been the basis of a marketing authorisation application and for which no CTD dossier exists[5].

Regarding the EMEA requirements on dossier copy numbers, applicants should consult the EMEA website (http://www.emea.eu.int/ – Human medicines, Application Procedures 'Pre-submission guidance').

In those cases where a ASMF exists, the applicant should ensure that the Active Ingredient Manufacturer's (AIM's) restricted part of the ASMF is submitted by the AIM to the EMEA, rapporteur and co-rapporteur at 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 of compliance to Community legislation and accompanying evaluation reports together with the respective VAMF or PMF data.

In the case of a medicinal product containing or consisting of genetically modified organisms within the meaning of Article 2(1) and 2(2) of Directive 2001/18/EC, as amended, the application must also be accompanied by:

[4] see Volume 2B of the Rules Governing Medicinal Products in the European Union (http://pharmacos.eudra.org/F2/eudralex/vol-2/home.htm)

[5] e.g. expired licenses

- 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, as amended,
- the complete technical dossier supplying the information requested in Annexes III and IV to Directive 2001/18/EC, as amended, and the environmental risk assessment resulting from this information; the results of any investigations performed for the purposes of research or development.

In addition, applicants must provide evidence of establishment of the applicant (future Opinion Holder) or the contact point in the EEA, as well as documents showing their capacity and commitment to perform all the responsibilities required of the Opinion Holder, in particular:

- a document identifying the person for pharmacovigilance who will be the contact person for any specific pharmacovigilance issues (as described in section 11), together with a curriculum vitae and contact details
- a document identifying the contact person responsible for any quality issues including its contact details

In addition the submission of complete copies using electronic storage media is encouraged. Details should be discussed beforehand with the EMEA through the PTL. At a minimum, the applicant should submit an electronic (WORD) copy of the SPC, labelling and package leaflet in English.

4.4 Validation by the EMEA

The EMEA will send the applicant an acknowledgement of receipt of the dossier and, within 10 working days following such receipt, will complete its validation.

During validation, the EMEA PTL may consult the rapporteur and co-rapporteur, on the need for action relating to matters such as GMP inspection, samples for analysis, ad-hoc expert groups, GCP inspections, liaison with environmental agencies and completeness of data.

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.

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, and provide 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 CHMP will be attached to the letter confirming the positive outcome of the validation.

The EMEA, CHMP members and the appointed experts as well as observers appointed by WHO, are required to fully protect the confidentiality of the data submitted to them (see also EMEA Code of Conduct EMEA/D/37674/99 on the EMEA website (http://www.emea.eu.int/ – General reporting, Administration 'Statutory Documents').

4.4.2 Negative outcome of the validation

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

If the application cannot be validated, an administrative fee will be invoiced and 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 initiate a new procedure should a new complete dossier be submitted in the future to the EMEA.

4.4.3 Management of applications

Once validated, details of the product will be entered into the EMEA tracking system. The numbering system allows for a clear identification of any application for the CHMP scientific opinion, the extension, the variation, the transfer, the renewal of a CHMP scientific opinion for any product and for any of its presentations throughout its life cycle.

Applications for a CHMP scientific opinion for a medicinal product can be identified by either the invented name, if available[6], or the international non-proprietary name (INN)/common name of the active substance(s) of the product in combination with the name of the applicant, where appropriate. However for administrative purposes and in the context of this opinion, each application is also given a core-number composed of four sections: EMEA/H/W/..., where H stands for Human, W for WHO and the three dots correspond to a sequential number for the product identification. The applicant will be informed of the procedure number in the EMEA validation letter.

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 constituents during the assessment of the application in accordance with the provisions of Article 7(b) of the Regulation. Such a request is adopted by CHMP at Day 90 or at the latest by Day 120.

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 CHMP will carry out the required testing.

The results of the tests are reported to the EMEA, rapporteur and co-rapporteur and subsequently to CHMP for consideration in finalising the CHMP Assessment Report.

5. PRE-OPINION INSPECTIONS: GMP INSPECTIONS

The legal basis for pre-opinion inspections of manufacturers of medicinal products in connection with the CHMP scientific opinion is laid down in Article 8.2 of the Regulation, which provides that:

"Where it considers it necessary in order to complete its examination of an application, the said Committee may require the applicant to undergo a specific inspection of the manufacturing site of the

[6] The use of an EU registered trade mark is not a prerequisite for the use of this procedure.

medicinal product concerned. Such inspections may be made unannounced. The inspection shall be carried out within the time-limit laid down in the first subparagraph of Article 6(3) by inspectors from the Member State holding the appropriate qualifications; they may be accompanied by a rapporteur or an expert appointed by the Committee".

The EMEA has a coordinating role for these inspections whilst the responsibility for carrying them out rests with a Competent Authority. For applications where the manufacturer of the product is located inside the EEA, the Supervisory Authority (defined by legislation as the Competent Authority of the Member State that granted the manufacturing authorisation in respect of the medicinal product) is responsible for the inspection.

For applications where the manufacturer of the product is located outside the EEA, and since the product is not intended for import to the EEA, no Supervisory Authority by definition will exist and so the responsibility for inspection will be the Competent Authority of the rapporteur's Member State.

5.1 Pre-submission notification by the applicant for a CHMP scientific opinion

In their notification of intention to submit (see section 4.1), applicants should mention the name (including contact point) and the address of the proposed manufacturer of the active substance(s) and finished product. The sequence of all different sites involved should be clearly described (as a flowchart).

5.2 Designation of an inspection team and preparation for the inspection

Once the application is received, the EMEA determines whether or not the manufacturing and control site(s) concerned have already been inspected, by whom, and if satisfactory inspection reports from the last 2-3 years are available. Where a satisfactory report is not available, the EMEA contacts the rapporteur and co-rapporteur, and a decision is made whether or not to ask CHMP to make a request for an inspection in connection with specific aspects of the application and/or, in the case of manufacturers in third countries, for general GMP compliance. Such request is adopted by CHMP at Day 90 or at the latest by Day 120. For an inspection covering specific aspects of the application, issues to be checked during the inspection will be detailed in an attachment to the Day 70 assessment report(s).

When the Competent Authority of the Member State of the rapporteur is not able to inspect in a third country, the rapporteur will designate another Competent Authority as the "Replacement Inspection Service" for the inspection consulting, through EMEA, the ad hoc GMP Inspection Services group as necessary.

Each request for inspection must be adopted by CHMP. Inspections, where requested by CHMP, should be carried out and finalised within the 210 days set out in the legislation for the scientific evaluation of the application. Companies therefore, should be required to be ready for inspection from the time of submission of the application and be in compliance with EU Good Manufacturing Practice (GMP)[7]. Manufacturers located in third countries must comply with equivalent standards.

[7] see Volume 4 of the Rules Governing Medicinal Products in the European Union (http://pharmacos.eudra.org/F2/eudralex/vol-4/home.htm).

5.3 Contacts with the applicant and the manufacturer(s) to be inspected

Once CHMP has requested an inspection and the inspection team has been agreed, the EMEA notifies the applicant that an inspection will take place, gives details of the inspection team and asks for the inspection fees to be paid.

The inspectors make the arrangements with the manufacturer and set an inspection date. In preparation of the inspection, the manufacturer(s) or the applicant may be asked to provide information about the site and operations to be inspected (the most convenient format for this information is a "Site Master File" in the format currently in use in the European Union). The applicant may be requested to supply a copy of Module 3 of the application to the members of the inspection team.

Prior to the inspection, the Module 3 assessor(s) liaises with the inspection team on any points for special consideration during the inspection and whether or not any aspect of the manufacture of the starting material(s) is critical to ensure the quality of the finished product, in which case an inspection of the starting material(s) will also be considered.

5.4 Inspection and transmission of the report

At the end of the inspection, the inspectors make a report of the main findings to the management of the site or company inspected.

Inspection reports, in accordance with the agreed Community format, are provided by the inspection team within 15 days of each inspection.

The draft inspection report is sent by the inspectors to the management of the site or company with a request for comments on major factual errors, points of disagreement or remedial actions to be provided within 15 (calendar) days of receipt. The timing of any discussions or the provision of additional information will be agreed and communicated to the rapporteur and the EMEA.

5.5 Submission of the final report to the rapporteur and the EMEA

One month after transmission of the inspection report to the manufacturer, the inspection team send their report to the rapporteur and the EMEA indicating whether or not the report has been agreed by the company inspected and, if not, the reason. A copy of the comments from the manufacturer is included. In all cases the inspection team will include their final conclusions.

This must be completed by Day 180 of the assessment procedure.

Any further pre-opinion inspections that are needed are coordinated by the EMEA.

5.6 Inspection fees

Detailed information on the inspection fees is available on the EMEA website (http://www.emea.eu.int/ – Human medicines, Inspections, Fees). In addition, for inspections outside the EU, travel costs are paid directly to the inspectorate by the applicant. One fee will be charged for each site inspected but additional fees may be charged for activities on the same site that require a separate inspection and also for each contract manufacturing site and contract testing laboratory that requires to be inspected in connection with an application.

6. PRE-OPINION INSPECTIONS: GCP AND GLP INSPECTIONS

6.1 GCP inspections during the assessment of the application

Inspections to evaluate compliance with Good Clinical Practice (GCP) are conducted by Member States' inspectorates on behalf of the European Community and are co-ordinated by the EMEA if they pertain to applications for a CHMP scientific opinion.

As laid down in Article 6 of the Regulation, the application documents must include a statement to the effect that clinical trials carried out outside the EU meet the ethical requirements of Directive 2001/20/EC[8]. This statement should be provided by the applicant in line with the NTA.

6.2 Operational Aspects

All new applications are examined to assess the need for GCP inspection(s). The EMEA Inspections Sector will liaise closely with the Product Team Leader, Rapporteur and Co-Rapporteur during the pre-submission phase and in the period during and immediately after validation to discuss the need to request GCP inspection(s). A need for inspection(s) may be identified at this stage, based on previous relevant experience of the Inspections Sector and the Member States' national inspectorates.

The assessment of the dossier may also identify a need for GCP inspection(s). Inspection(s) may be requested for adoption by CHMP at any stage of the assessment. In general GCP inspection issues are addressed in the consolidated List of Questions and, are therefore usually adopted at Day 120 (although the inspection may commence earlier once adopted by CHMP). This will allow these GCP inspection related issues to be addressed within the "clock stop" period.

The Reporting Inspector appointed is generally from the inspectorate of the Member State of the CHMP rapporteur (or the co-rapporteur).

The lead inspector for each site inspected will usually be from the inspectorate of the Member State where the site is located. In the case of third country inspections, the inspectors will usually be from the Rapporteur/Co-Rapporteur country inspectorates.

The applicant is requested to provide the information in the MAA in order to facilitate the review of the application and where needed preparation of GCP Inspections. This information should be provided in the individual Clinical Study Reports and their Appendices in line with the 'Note for Guidance on the Inclusion of Appendices to Clinical Study Reports in Marketing Authorisation Applications' (CPMP/EWP/2998/03), and the 'Note for Guidance on Structure and Content of Clinical Study Reports' (CPMP/ICH/137/95).

A list of inspection(s), already conducted or planned by other regulatory authorities, relating to the product and trial sites involved, should also be provided, preferably attached to the Application cover letter.

Each clinical study report should contain a statement indicating whether the study was performed in compliance with Good Clinical Practices (GCP), including the archiving of essential documents. A discussion on GCP compliance should also be included in the Clinical Overview.

[8] Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.

This information is required at the time of submission of all new applications and variations or extensions where new clinical data is presented.

Sites are expected to be inspection-ready and have relevant documentation, facilities and personnel readily available in the event that an inspection is requested. If an inspection is requested, the applicant will be required to provide the EMEA and inspectors with a written statement that the sites accept to be inspected and to make available all documents required, including medical records/source data at the investigator sites, for direct access by the inspectors. This commitment will be required prior to the departure of the inspection team on the inspection, in its absence the inspection may not be able to proceed. If data are not available for review by the inspectors they may not be acceptable (as they can not be verified with the source).

6.3 GLP inspections

The assessment of the non-clinical data in the application includes an evaluation of statements provided on GLP compliance, and the scientific content and if considered necessary by the assessor, an inspection request can be adopted at day 90 or day 120. The inspection will be carried out by the GLP monitoring authority of the member state in which the test facility is located. If the test facility is located in a third country, CHMP will nominate an authority to perform the inspection.

6.4 Inspection Fees

Please refer to section 5.6.

7. SCIENTIFIC EVALUATION OF AN APPLICATION BY THE COMMITTEE

The assessment will be performed according to EU/ICH guidelines; in absence of these, or otherwise justified, WHO guidelines apply. Deviation from EU/ICH or WHO guidelines needs to be justified by the applicant. The CHMP will decide on the appropriateness of such justifications. The same data requirements and evaluation standards will be adhered to as for EU medicines, 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. In the context of cooperation with WHO, observers from WHO and observers from authorities of developing countries (recommended by WHO) may attend CHMP plenary discussions on products under the CHMP scientific opinion procedure in cooperation with WHO, provided that they complete and sign the Public Declaration of Interests and Confidentiality Undertaking form. Experts and observers have no voting rights at the CHMP plenary.

7.1 Timetable for the evaluation

Once the application is validated and provided the rapporteur and co-rapporteur have confirmed preferably by electronic mail or by fax, that they have received the dossier (including any additional information requested during validation phase), the EMEA starts the procedure. If the rapporteur and the co-rapporteur have not received their copies of the dossier on the day where the dossier is validated by the EMEA, the start of the procedure will be delayed until the EMEA has received confirmation from the rapporteur and the co-rapporteur that they have received the dossiers.

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

Having taken into consideration the standard timetable agreed by CHMP for the evaluation of an application for a CHMP scientific opinion, a timetable is prepared by the EMEA in consultation with rapporteur and the co-rapporteur. This timetable is then proposed to CHMP for adoption.

The EMEA shall ensure that the CHMP scientific opinion is given within 210 days.

Standard timetable for the evaluation of an application for a CHMP scientific opinion

DAY	***ACTION***
1	Start of the procedure
80	Receipt of the Assessment Reports from rapporteur and co-rapporteur by CHMP members and EMEA. EMEA sends the rapporteur and co-rapporteur Assessment Reports 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 CHMP.
100	Rapporteur, co-rapporteur, other CHMP members and EMEA receive comments from CHMP members (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 / GCP inspection, if necessary (Inspection procedure starts).
121*	Submission of the responses, including revised SPC, 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, 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 the 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 CHMP. Where applicable, Inspection to be carried out.
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 an oral explanation by the applicant. If 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 SPC, labelling and package leaflet sent by applicant to the rapporteur and co-rapporteur, EMEA and other CHMP members.
By 210	Adoption of CHMP scientific opinion + CHMP Assessment Report.

After adoption of a CHMP scientific opinion, the preparation of the annexes to the CHMP scientific opinion and, in case of a positive CHMP scientific opinion, the preparation of the European Public Assessment Report on a scientific opinion in cooperation with WHO (EPAR) are carried out in accordance with the following timetable:

DAY	***ACTION***
By 240	The EMEA forwards the CHMP scientific opinion and its annexes to the applicant, WHO, the Commission, the Member States, Norway and Iceland.
By 300	Finalisation of EPAR in consultation with rapporteur, co-rapporteur, CHMP and applicant (the latter for confidentiality aspects).

7.2 Liaison between the applicant and the EMEA

For general information regarding the procedure, the applicant is advised to liaise with the project manager. 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 project manager of the outcome of their discussions.

7.3 Committee's request for additional information

The CHMP will consider the preliminary Assessment Reports from the rapporteur and co-rapporteur. From these and the comments of other CHMP members, 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 receive a positive CHMP scientific opinion provided satisfactory answers are given to the "other concerns" and the indications, other elements of the SPC or other conditions
- the provisional view of CHMP is that the product is likely to receive a negative CHMP scientific opinion since there are "major objections" which have been identified in the detailed List of Questions.

Alternatively, CHMP may consider the application to be approvable and is ready for adoption of an opinion, but remaining points, which could be resolved after a favourable CHMP scientific opinion, may be agreed upon by CHMP (see section 8.2).

The applicant would normally be expected to respond within the time frame agreed by CHMP, not exceeding 6 months from the date of receiving the 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 SPC or other conditions for a favourable CHMP scientific opinion. 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 (http://www.emea.eu.int/ – Human medicines, Application Procedures 'Pre-Submission Guidance').

7.4 Oral explanation

In addition to the written responses to the issues raised by CHMP, applicants may also avail themselves of an oral explanation to 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 explanation (clock-stop - usually not longer than 1 month).

Applicants may also be invited by CHMP for an oral 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 during such oral explanation.

The procedural guidance on Oral Explanations in relation to centralised applications is also applicable for applications for a CHMP scientific opinions in cooperation with WHO; further detailed information on the Oral Explanation procedure is available on the EMEA website (http://www.emea.eu.int/ – Human Medicines, Guidance documents, General Guidance 'Guidance to applicants on CHMP Oral Explanations in relation to centralised applications').

8. THE COMMITTEE'S SCIENTIFIC OPINION

On or before Day 210, CHMP adopts its scientific opinion in the light of the final recommendation of the rapporteur and co-rapporteur, the CHMP discussions and further evidence presented at the oral explanation. The rapporteur and the co-rapporteur, in co-ordination with the PTL, taking account of the full scientific debate within CHMP and the conclusions reached, prepares the final assessment report, which, once adopted by CHMP, becomes the CHMP scientific opinion assessment report and is appended to the CHMP scientific opinion.

The CHMP scientific opinion assessment report shall contain the conclusions on the Quality, the Safety and Efficacy 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 scientific opinion, which may be positive or negative, is, wherever possible, reached by scientific consensus.

8.1 Favourable opinion

In the event of a positive CHMP scientific opinion, the following documents must be annexed and/or appended to the scientific opinion.

- An SPC in English as referred to in Article 11 of Directive 2001/83/EC[9], as amended;
- Conditions for manufacturing, batch release and supply;
- A draft labelling and package leaflet in English presented in accordance with Title V of Directive 2001/83/EC, as amended;
- The CHMP scientific opinion assessment report.

Should CHMP want to record any post-opinion follow-up, it will be included in the Assessment Report and referenced in an annexed letter of undertaking signed by the applicant.

8.2 Post-opinion follow-up

For all opinions of CHMP, it might be necessary to establish post-opinion follow-up in an agreed timeframe.

Unless otherwise requested by CHMP members, the data on the fulfilment of post-opinion follow-up should be sent by the Opinion Holder to the CHMP members and the EMEA. The data will be reviewed in accordance with the agreed timetable.

The Opinion Holders will be informed of the outcome of CHMP discussions by the EMEA.

Resulting variation applications

Opinion Holder should submit, within an agreed timeframe, any variation application resulting from the fulfilment of post-opinion follow-up.

Non-fulfilment of post-opinion follow-up

Opinion Holders must indicate realistic target dates for the submission of the post-opinion data in their letter of undertaking.

If no documentation is received in order to fulfil the post-opinion follow-up before the dead-line previously agreed by 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 post-opinion follow-up, CHMP can, after having consulted WHO, revise its opinion 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, as amended.

8.3 Unfavourable scientific opinions

The EMEA immediately informs the applicant and WHO when the opinion of CHMP is that the application does not satisfy the criteria for a positive CHMP scientific opinion set out in the Regulation.

The CHMP scientific assessment report stating the reasons for its negative conclusions shall be annexed to the opinion.

[9] Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use.

9. STEPS FOLLOWING THE CHMP SCIENTIFIC OPINION

9.1 Transmission of the CHMP scientific opinion and use of the opinion

The EMEA will prepare a "Summary of scientific opinion" in liaison with the applicant. Such Summaries will be published on the EMEA website after the adoption of the CHMP scientific 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, the EMEA will then forward the opinion (and the required annexes) together with the CHMP assessment report, within 15 days of its adoption to the applicant, WHO, the Commission, the Member States, Norway and Iceland.

The opinion and its annexes are sent either by electronic mail or by courier (if electronic mail is not available).

The current WHO Certification Scheme accommodates the issuing of Certificates of a Medicinal Product (CMPs) for products having received a positive CHMP scientific opinion in cooperation with WHO. As for centrally authorised products, the EMEA will issue these CMPs upon request from the Opinion Holder.

9.2 Request for re-examination

The applicant may notify the EMEA/CHMP of its intention to request a re-examination within 15 days of receipt of the opinion (after which if he does not request a re-examination, he shall be deemed to have agreed with the opinion and it becomes final opinion).

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

The CHMP may decide to appoint a new rapporteur and co-rapporteur (for whom applicants can express their preference), to co-ordinate the re-examination procedure, accompanied, if necessary, by additional experts. Within 60 days from the receipt of the grounds for the request for re-examination, CHMP will consider whether its opinion is to be revised. If considered necessary, an oral explanation can be held within this 60 days timeframe.

Once CHMP issues a final re-examined scientific opinion, it is forwarded (with the required annexes and the reasons for its conclusions) within 15 days of its adoption to the applicant, WHO, the Commission, the Member States, Norway and Iceland.

9.3 Public Assessment Report on the CHMP scientific opinion

In accordance with Article 13 of the Regulation, the EMEA shall make available the CHMP assessment report of the medicinal product and the reasons for the favourable CHMP scientific opinion, after deletion of any information of a commercially confidential nature.

This document is called the European Public Assessment Report on a scientific opinion in cooperation with WHO (EPAR). Updates to the CHMP scientific opinion will be reflected in the EPAR.

9.3.1 Operating approach to the preparation of the EPAR

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 CHMP formulates positive final opinions.

In accordance with Article 9.3 of the Regulation, applicants will receive the assessment report of CHMP. Applicants are then required to identify within a short period of time (for example within 15 days of adoption by CHMP) those issues which they consider to be commercially confidential. Such issues should be notified and justified by the applicant to the PTL.

Upon receipt of the applicant's response on 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. The draft EPAR will then be circulated for adoption by CHMP at a subsequent meeting.

9.3.2 Availability of the EPAR

Once CHMP has agreed on the text, the EPAR will be sent to the applicant. The EPAR shall be made available at the EMEA web site after adoption by CHMP.

10. UPDATING THE CHMP SCIENTIFIC OPINION

The Opinion Holder is responsible to update the CHMP scientific opinion with post-opinion follow-up, variations and extension applications. The procedures and requirements in place for centrally authorised medicinal products (as provided for in Commission Regulation (EC) 1085/2003[10]) will also be applied, by analogy, to CHMP scientific opinions in cooperation with WHO as appropriate, with the exception of the EC Decision making phase; further detailed information on these procedures for centrally authorised medicinal products is available on the EMEA website (http://www.emea.eu.int/ – Human medicines, Application Procedures 'Post-Authorisation Guidance').

11. PHARMACOVIGILANCE

The Opinion Holder, by virtue of its contact person for pharmacovigilance (see section 4.3), should ensure that:

- a medicinal product, for which a positive opinion has been granted in accordance with this procedure, is entered in the EudraVigilance Medicinal Product Dictionary. Where several active substances are included in one medicinal product these should be individually identified. This reflects the requirements for identification of products regarding the reporting obligations related to pharmacovigilance as outlined below.
- all serious adverse reactions to a medicinal product, for which a positive opinion has been granted in accordance with this procedure, are recorded and reported promptly to the competent authorities of the countries where the product is marketed (according to their national pharmacovigilance reporting system) and to the EMEA electronically in full compliance with the ICH E2A, E2B(M), E2D, M1 (MedDRA) and M2 guidelines and standards.
- detailed records of all suspected adverse reactions are submitted, in the form of a periodic safety update report, to the EMEA immediately upon request or at least every six months after the first marketing authorisation granted by a competent authority during the first two years and

[10] Commission Regulation (EC) 1085/2003 of 3 June 2003 concerning the examination of variations to the terms of a marketing authorisation for medicinal products for human use and veterinary medicinal products falling within the scope of Council Regulation (EEC) No 2309/93.

once a year for the following two years. Thereafter, the reports shall be submitted at three-yearly intervals, or immediately upon request. These reports shall be accompanied by scientific evaluation, particularly of the benefit/risk balance of the medicinal product, to be reviewed by the rapporteur.

- any other information relevant to the evaluation of the risks and benefits of a medicinal product is submitted, particularly information concerning post-authorisation safety studies

If CHMP considers it appropriate to complement the normal pharmacovigilance reporting as outlined above by an active monitoring / risk management / risk minimisation programme, then the CHMP will recommend which measures should be put in place in collaboration with the Opinion Holder and the competent authority where the medicinal product is marketed.

CHMP can perform a benefit/risk review at any time. In some cases and taking into account the pharmacovigilance reporting received, CHMP can, after having consulted WHO, revise its opinion 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, as amended.

In accordance with Article 27 of the Regulation, the EMEA will collaborate with WHO and may exchange any information related to the pharmacovigilance of medicinal products evaluated under this procedure.

12. BATCH CONTROL, PRODUCT DEFECTS AND PRODUCT RECALLS

The Opinion Holder shall carry out tests on samples of each batch of the medicinal product before release on the market, according to the specifications and analytical methods approved by CHMP.

Where it considers it necessary in the interests of public health, CHMP may recommend that the Opinion Holder of live vaccines, immunological products and medicinal products derived from human blood or human plasma, submits samples from each batch of the bulk and/or the medicinal product before release on the market for testing by an EU Official Medicines Control Laboratory (OMCL)[11]. Where this recommendation is followed by the competent authority, a batch should not be placed on the market unless the OMCL has examined the batch in question and declared it to be conform the approved specifications by issuing a certificate of batch compliance (within 60 days of receipt of the samples).

The Opinion Holder should report to the competent authorities of the countries where the product is marketed and inform the EMEA about any defect in a medicinal product that could result in a recall or abnormal restriction in supply[12], together with the corrective actions proposed. Product recalls are the responsibility of the manufacturer and the competent authorities of the countries where the product is marketed.

In cases where the quality issues cannot be resolved by the corrective actions to ensure the protection of public health as proposed by the applicant, CHMP may revise its opinion.

[11] Within the meaning of Article 114 of Directive 2001/83/EC, as amended.

[12] Within the meaning of Article 13.1 of Commission Directive 2003/94/EC, of 8 October 2003, laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use.