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NOTICE TO APPLICANTS
VETERINARY MEDICINAL PRODUCTS

VOLUME 6A

Procedures for marketing authorisation

CHAPTER 4

Centralised procedure

May 2006

This Chapter 4 "Centralised procedures" will be included in The Rules governing Medicinal Products in the European Community
The Notice to Applicants - Volume 6A – Veterinary medicinal products - Procedures for marketing authorisation

Commission européenne, B-1049 Bruxelles / Europese Commissie, B-1049 Brussel - Belgium. Telephone: (32-2) 299.11.11. Office: BREY 10/73. Telephone: direct line (32-2) 299.15.11. Fax: (32-2) 299.80.46.
Karin.Krauss@cec.eu.int

CHAPTER 4 Centralised Procedure

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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 veterinary medicinal products, for which there is a single application, 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 coordinating the existing scientific resources put at its disposal by the Competent Authorities of the Member States for the evaluation, supervision and pharmacovigilance of veterinary medicinal products. Within the EMEA, the Committee for Medicinal Products for Veterinary Use (CVMP) is responsible for preparing the Opinion of the EMEA on any question relating to the evaluation of veterinary medicinal products.

The Regulation confirms the need to protect public and animal health within the Community whilst at the same time allowing rapid access to the single market for certain new veterinary medicinal products referred to in 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 veterinary medicinal products should be based on objective scientific criteria of quality, safety and efficacy of the veterinary medicinal product concerned.

A marketing authorisation granted following the centralised procedure is valid for the entire Community market. A Community authorisation applies to all Member States, which means that the veterinary medicinal product may be put on the market in all Member States subject to restrictions for immunological veterinary medicinal products in accordance with Article 71 of Directive 2001/82/EC[1].

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

For veterinary medicinal products falling within the scope of the Annex, applicants are obliged to use the centralised procedure. For those falling within the scope of Article 3, applicants may, at their discretion, also use the centralised procedure.

The EFTA states, Iceland, Liechtenstein and Norway, have, through the European Economic Area (EEA) agreement, adopted a complete Community *acquis* on veterinary medicinal products, and

[1] As amended by Directive 2004/28/EC

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 the Community takes decisions on approval of veterinary medicinal products, Iceland, Liechtenstein and Norway will take corresponding decisions on the basis of the relevant acts[2].

1.1 Veterinary Medicinal products derived from biotechnology

Applicants for a marketing authorisation for a veterinary 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.

This requirement also applies to veterinary medicinal products, including those not derived from biotechnology, intended primarily for use as performance enhancers in order to promote the growth of treated animals or to increase yields from treated animals.

Any veterinary 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, irrespective of whether or not the constituent is an active substance of the veterinary medicinal product. This also applies where a recombinant DNA technology step is introduced in the manufacture of a proteinaceous constituent of a veterinary medicinal 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 and insertion,
- any veterinary 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 biotechnology process referred to in Point 1 of the Annex to the Regulation.

[2]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.

1.2 New Active Substances

Applications for veterinary medicinal products containing a new active substance[3] may use the centralised procedure in accordance with Article 3(2) of the Regulation where the substance was not authorised in the Community before 20 November 2005.

In addition, for the purpose of eligibility for evaluation via the Centralised Procedure, a fixed combination of active substances can be considered as a new active substance provided that this fixed combination has not previously been authorised as a veterinary medicinal product in the EU.

1.3 Other veterinary medicinal products – "optional scope"

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

- the veterinary medicinal product constitutes a significant therapeutic, scientific or technical innovation;
- the granting of an authorisation in accordance with the Regulation is in the interests of public or animal health.

Immunological veterinary medicinal products for the treatment of animal diseases that are subject to Community prophylactic measures may also be considered under the centralised procedure.

It has to be stressed that, once granted with a Community marketing authorisation based on Article 3(2) of the Regulation, a veterinary 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 (MAH) wishes to place on the market another veterinary 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 34 or 35 of Directive 2001/82/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 veterinary medicinal product with an active substance(s) already authorised via the Centralised Procedure, have 'automatic' access to the Centralised Procedure.

1.4 Generic and similar biological veterinary medicinal products

Generic applications of veterinary medicinal products authorised via the Centralised Procedure may be authorised via the EMEA. Alternatively they may be authorised by the Competent Authorities of the Member States through national, mutual recognition or decentralised procedures 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).

[3] New active substance (new chemical or biological active substance) as defined in Annex III to Chapter I of Volume 6A

Similar biological ("biosimilar") veterinary 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.

2. SCIENTIFIC ADVICE TO COMPANIES

According to Article 57(1)(n) of the Regulation, one of the tasks of the EMEA is "advising undertakings on the conduct of the various tests and trials necessary to demonstrate the quality, safety and efficacy of veterinary medicinal products".

Scientific advice may be requested for all veterinary medicinal products irrespective if they are eligible for the centralised procedure or not.

The CVMP has established a standing working party with the sole remit of providing scientific advice to companies. In addition, the CVMP may seek guidance on important questions of a general scientific or ethical nature.

2.1 Necessity for Scientific advice

Normally, advice is provided in the form of guidelines which are already published by the EMEA (http://www.emea.eu.int).

The advice of the EMEA, within its Committees, on the conduct of tests and trials to demonstrate the quality, safety and efficacy of veterinary medicinal products may be requested. Advice will only be given in those circumstances where Pharmacopoeia monographs or guidelines (especially those adopted by the CVMP) and previous scientific advice do not already address the point of concern, or do not provide sufficient guidance. However, in case a company chooses to deviate in their development plan from guidance available, it is also possible to seek scientific advice from the EMEA, provided a justification for such a request is forwarded. Approval of study protocols will not be undertaken.

2.2 Scope of advice

Applicants seeking advice under Article 57(1)(n) of the Regulation must note that any advice given is not binding on the EMEA with regard to any future marketing authorisation application of the product concerned. However, the CVMP should provide argumentation during the evaluation of the application for marketing authorisation if questioning the design of studies performed following the provision of scientific advice.

Advice will be given in good faith, but circumstances may change, especially in the case of early advice or subsequent scientific developments. In some cases, e.g. as a result of scientific developments, an alternative approach to that advised may be appropriate. In this case companies can request a follow-up of the scientific advice. Where companies choose not to apply the advice, an explanation should be provided in the appropriate part of the dossier.

2.3 Procedure

Detailed guidance on the procedure may be obtained from the EMEA web site (http://www.emea.eu.int/pdfs/vet/sciadvice/085402en.pdf).

3. 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 Secretariat 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 use such an opportunity. 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 web-site – documents 'Pre-Submission Guidance').

3.1 Pre-submission

At least six 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 (SPC);
- a justification of the product's eligibility for evaluation under the centralised procedure;
- in the 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 of the number of strengths/pharmaceutical forms/pack sizes;
- if it is a product intended for food-producing animals a statement of whether maximum residue limits (MRLs) have been established for the pharmacologically active substance(s) (and excipients if pharmacologically active) included in the product and for the target species concerned by the application;
- the proposed legal basis of the application according to Articles 12(3), 13, 13a, 13b, 13c or 13d of Directive 2001/82/EC;
- in the case of generic or bio-similar applications, details of the proposed reference veterinary medicinal product used throughout the quality, safety and efficacy development programme (as appropriate);
- a statement on the appropriateness of the granting of a marketing authorisation under exceptional circumstances (in accordance with Article 39(7) of the Regulation), if appropriate;
- a statement of the intention to request an accelerated assessment procedure (in accordance with Article 39(8) of the Regulation), if appropriate;

- scientific advice received in the past in accordance with Article 57(1)(n) of the Regulation;
- proposed conditions or restrictions on supply and use of the veterinary medicinal product;
- if appropriate, their intention to present an Active Substance Master File for active substances prepared in accordance with the guidelines on the European Active Substance Master File Procedure
- proposed Invented Name
- details of compliance with the requirements of Directive 2001/18/EC of the European Parliament and of the Council on the deliberate release into the environment of genetically modified organisms, if relevant;
- the details of the proposed manufacturing and batch release sites for both the finished product and the active substance(s) (see point 5 on Pre-authorisation inspections);
- information on whether the veterinary medicinal product contains materials of animal origin or uses them in the manufacturing process;
- 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 regulatory issues or difficulties already identified which may require clarification or detailed consideration

Procedure regarding Maximum Residue Limits (MRLs)

A veterinary medicinal product intended for administration to food-producing animals and containing an existing pharmacologically active substance can only be authorised if any pharmacologically active substance contained within it is placed in Annexes I, II or III of Council Regulation (EEC) No 2377/90 or has been confirmed by the CVMP as not falling under the scope of these requirements.

For a veterinary medicinal product intended for administration to a food-producing species and which contains a pharmacologically active substance not included in Annexes I, II or III of Regulation (EEC) No. 2377/90 for the species concerned, the applicant is required to apply for the establishment of MRLs in accordance with that Regulation. In addition, documentation must be presented to prove that the substances used in the veterinary medicinal product are not pharmacologically active at the dose at which it is administered to the target animal via the veterinary medicinal product concerned.

In accordance with Article 12(1) of Directive 2001/82/EC, at least 6 months shall elapse between a valid application for the establishment of maximum residue limits and an application for a marketing authorisation. It is, however, recommended to submit an application for a marketing authorisation, only once an MRL for the active substance has been approved.

Admissibility to the Centralised Procedure

Upon receipt of the 'letter of intent' including the justification of the product's eligibility for evaluation via the centralised procedure, the EMEA will present to CVMP members whether the

product falls within the scope of the Annex or Art 3(2) of the Regulation, together with the justification and summary of product characteristics/product profile from the applicant.

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

If the CVMP 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 shall be appointed from amongst the members of the CVMP, alternates or co-opted members. Where appropriate, the Rapporteur can be supported by a Co-Rapporteur as agreed by the CVMP. The appointment of the Rapporteur and 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 available expertise in the EEA.

The role of the Rapporteur is to perform the scientific evaluation and to prepare an assessment report to the CVMP according to the timetable agreed for the evaluation procedure. The Co-Rapporteur shall prepare a critique of the Rapporteur's report.

The appointment process for Rapporteur/Co-Rapporteur is usually initiated at the CVMP 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 the Centralised Procedure.

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 CVMP meeting of the name of the Rapporteur and the Co-Rapporteur appointed by the CVMP, the dossier requirements of the different CVMP members and where to find information on the applicable fees.

The (Co-) Rapporteur choose(s) amongst the experts included in the European experts list available at the EMEA, those who will form the assessment team. The names of such experts will be communicated to the applicant as part of the Day-70 Assessment Report.

The experts, on whom the CVMP 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 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/CVMP activities (meeting attendance, scientific evaluation, inspections, guidance development, etc) is available on the EMEA website.

Members of the CVMP and their expert are not permitted to have any direct financial or other interests in the pharmaceutical industry which could affect their impartiality. The EMEA has therefore established a procedure and policy on the handling of conflicts of interest 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/CVMP. In such case, applicants should be aware that potential re-appointment of (Co-) Rapporteur may become necessary due to other ongoing or planned assessments.

Procedure for multiple applications

In certain cases, companies may wish to obtain more than one marketing authorisation for the same veterinary 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, companies should inform both the EMEA and the Commission Services of their intentions and it is recommended to send this information 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 or animal health regarding the availability of veterinary medicines or for co-marketing reasons.

Applications for total or partial fee exemptions

Any request for total or partial fee exemptions, in particular for veterinary medicinal products intended for rare diseases or use in minor species for which no other products exist for a specific indication should be accompanied by the appropriate justification.

The request should provide evidence that:

- the product is eligible for evaluation under the centralised procedure;
- the product would qualify for total or partial fee exemption based on the considerations above.

The applicant is recommended to refer, whenever possible, to criteria established in other parts of the world and provide convincing details on the number of cases likely to be covered in the EU and other relevant data establishing the rarity of the disease as well as the benefits in terms of animal or human health.

Applicants who 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 or exemptions for scientific and administrative services, including scientific advice, inspections and (for veterinary medicines) establishment of maximum residue limits.

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 least 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 CVMP.

Name of Products evaluated via the Centralised Procedure

Applications for veterinary 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 31(1) of the Regulation).

Provided that the veterinary medicinal product is eligible for evaluation under the Centralised Procedure, the applicant is recommended to inform the EMEA of the proposed name(s) for their veterinary medicinal product, at the earliest 12 months and at the latest 4-6 months prior to the planned submission date of the dossier. The Invented name check will be performed by the EMEA in liaison with the national Competent Authorities, in order to determine if the name would raise any identifiable public health concern, for resolution at the following CVMP meeting.

Where the applicant chooses to use an invented name for veterinary medicinal products using the centralised procedure, details on the procedure to be followed and the criteria applied when reviewing invented names can be found in the "Guideline on the acceptability of invented names for veterinary medicinal products processed through the centralised procedure" and the "EMEA pre-submission guidance", which are published on the EMEA website.

Role of the Project Manager

A member of staff of the Veterinary Medicines Evaluation Unit of the EMEA will be officially appointed as an EMEA project manager and the applicant will be notified of the project manager's identity. The project manager will be responsible for:

- providing technical, scientific, legal and regulatory assistance to the Rapporteur and the Co-Rapporteur, the CVMP and the applicant;
- providing procedural guidance during the pre-submission phase;
- co-ordinating the validation of the application submitted and monitoring compliance with the timeframe provided for processing the application
- providing assistance to the applicant, Rapporteur and Co-rapporteur;
- verifying that documents are circulated in a timely manner;
- organising any meeting, as requested by the CVMP, the Rapporteur and the Co-rapporteur;
- preparing the scientific Opinion of the CVMP;
- co-ordinating, with the Rapporteur and Co-rapporteur, the preparation of the CVMP assessment report and its transformation into the subsequent European Public Assessment Report (EPAR) on the basis of the (Co-) Rapporteur's reports or critique;
- preparing and communicating relevant public information on the veterinary medicinal product
- ensuring the necessary follow-up to the CVMP Opinion (e.g. variations, post-marketing follow-up measures/specific obligations, pharmacovigilance), in consultation with the Rapporteur and where appropriate, the Co-Rapporteur;
- Co-ordinating the linguistic check of labelling to ensure consistency and high quality vis-à-vis the primary reference scientific text. In order to ensure standardisation of the headings and certain sections of the summary of product characteristics, labelling and package leaflet, 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/ – Veterinary Medicines - Application Procedures – 'Product Information Templates').

The project manager, in close co-operation with the Rapporteur and the Co-rapporteur, will also ensure that the applicant is kept informed on all issues relating to the application. The project

manager will serve as the liaison person between the EMEA, the Rapporteur, the Co-rapporteur and the applicant.

3.2 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 programme of the scheduled CVMP meetings in order to be able to identify optimal submission dates. Recommended submission dates for the application are published on the EMEA web-site ('Pre-Submission Guidance').

As soon as the applicant is aware that the original indicated submission date cannot be met he informs 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 therefore the Rapporteur and/or Co-Rapporteur may in exceptional cases request the appointment of a new Rapporteur and/or Co-Rapporteur.

The addresses for submission of the application are given in the EMEA SOP Submission of an Application for the Granting of a Community Marketing Authorisation.

3.3 Dossier to be submitted

Reference should also be made to the format proposed in Volume 6B of the Notice to Applicants.

The EMEA requires from the applicant:

- one full copy of the dossier, including the applicant's part of the Active Substance Master File, if any;
- two copies of Part I including the draft summary of product characteristics, labelling and package leaflet in English.

In addition, applicants are recommended to submit, in parallel to the EMEA, copies of the dossier to both the Rapporteur and the Co-Rapporteur otherwise there may be a delay in the start of the procedure due to the time lapse between validation by the EMEA and the confirmation from the Rapporteur and Co-Rapporteur that they have received the dossier.

Detailed requirements for submission of the application to EMEA and CVMP members are given on the EMEA website (http://www.emea.eu.int/ – Veterinary Medicines - Application procedures - 'Pre-Submission Guidance').

In those cases where an 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; those CVMP members requiring a full or at least Part II of the dossier should also receive a copy of the Active Substance Master File.

Applicants should provide with their application one English mock-up of the outer and inner packaging for each pharmaceutical form of the veterinary 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).

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 in the EEA for pharmacovigilance within the meaning of Article 48 of the Regulation and Article 12 (o) of Directive 2001/82/EC, together with a curriculum vitae and the address, 24h telephone and fax number;
- a detailed description of the pharmacovigilance system, and where appropriate, the risk management system that will be put in place (within the meaning of Article 12 (k) of Directive 2001/82/EC)
- 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 12 of Directive 2001/82/EC) including their address, 24h telephone and fax number.

In the case of a veterinary medicinal product containing or consisting of genetically modified organisms within the meaning of Article 2(1) and 2(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 II and III 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.

In addition the submission of complete copies using electronic storage media is encouraged. It is recommended to discuss details beforehand with the EMEA project manager. At a minimum, the applicant should submit an electronic (WORD) copy of the summary of product characteristics, labelling and package leaflet in English.

In principle, applicants may submit one full copy of the marketing authorisation application on a suitable PC-compatible medium, e.g. CD-ROM, together with 2 additional paper copies of Part I. 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 supplied is identical to that in any written submission. Applicants are advised to liaise with the EMEA Project Manager with regard to electronic submissions to CVMP members Manager (see also EMEA SOP Submission of an Application for the Granting of a Community Marketing Authorisation).

3.4 Validation by the EMEA Secretariat

The EMEA Secretariat will send the applicant an acknowledgement of receipt of the dossier.

During validation the EMEA project manager may consult the Rapporteur and Co-rapporteur, on the need for action relating to matters such as GMP inspection, samples for analysis, involvement of ad-hoc expert groups, liaison with environmental agencies 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 the validation of the dossier, it will contact the applicant requesting the supply of this data, information or clarification within a specific time limit. When supplying the EMEA Secretariat with this information, the applicant is advised to also send a copy of this information to the Rapporteur and the Co-rapporteur. In this case, the validation can only be completed after receipt and verification of the information submitted.

If the Rapporteur and Co-Rapporteur have not received their copies of the dossier and/or additional validation information on the day when the dossier is validated by the EMEA, the start of the procedure may be delayed until the next appropriate procedure starting date.

It is recommended that the applicants provide the EMEA with proof of delivery to the Rapporteur and Co-Rapporteur before the start of the procedure.

3.4.1 Positive outcome of the validation

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

The EMEA, CVMP 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 (see also EMEA Code of Conduct MB/15314/2004 on the EMEA web-site).

Consultation with the Authorities competent under Directive 2001/18/EC will be carried out in parallel to the evaluation by the Committee in accordance with SOP –V- 4012.

3.4.2 Negative outcome of the validation

Failure to provide the data, information or clarification requested or failure to adhere to the format required by the Notice to Applicants guidance will result in a negative validation of which applicant will be informed in writing.

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

The applicant will be required to initiate another procedure should a new complete dossier be submitted in the future to the EMEA.

3.4.3 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.

3.4.4 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 marketing authorisation for any product and for any of its presentations throughout its life cycle.

In the EMEA applications for marketing authorisation for a veterinary medicinal product are primarily identified by the name of the product and the active substance(s) it contains. However for administrative purposes, each application is also given a core-number composed of four sections: EMEA/V/C/..., where V stands for Veterinary, C for centralised procedure 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 and this number should be included in all future correspondence.

3.5 Need for samples and sample analysis

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

The CVMP may, however, request the testing of samples of the veterinary medicinal product and/or its ingredients during the assessment of the application in accordance with the provisions of Article 32 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 will carry out the required testing.

The results of the tests are reported to the Rapporteur, Co-rapporteur and the CVMP for consideration in finalising the CVMP Assessment Report.

The EMEA implements every year a post-authorisation sampling and testing programme, in accordance with Article 57.1 (r) of the Regulation, aimed at monitoring the quality of centrally authorised products. This programme is carried out in close collaboration between the Marketing Authorisation Holder, the (Co)Rapporteurs and institutional partners (OMCL, national authorities and inspections services). More information about this monitoring programme is available on the EMEA website (www.emea.eu.int – Inspections – Sampling and Testing).

4. PRE-AUTHORISATION INSPECTIONS (GOOD MANUFACTURING PRACTICE AND GOOD LABORATORY PRACTICE)

Inspection requests in connection with an application for a marketing authorisation must be adopted by the CVMP. It should be pointed out that pre-authorisation inspections, where requested by the CVMP, 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.

4.1 Legal basis

According to Article 57(1)(i) of Regulation (EC) No. 726/2004 of the European Parliament and of the Council, the EMEA is responsible for the co-ordination of pre-authorisation Good Manufacturing Practice (GMP), 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 veterinary medicinal products is laid down in Article 33(2) of the Regulation EC) No. 726/2004.

GLP Inspections: Parts 3 and 7 of Annex I to Directive 2001/82/EC, require that safety and residue tests mentioned in the marketing authorisation applications 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.

4.2 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.

GLP inspections: they 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.

4.3 Inspection Team

The responsibility for performing GMP 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 manufactured or imported, controlled and released for sale within the European Economic Area (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).

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 CVMP 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.

4.4 Procedural Aspects

4.4.1- Timetable for Inspections

Inspection requests may be adopted by CVMP at any stage of the assessment. However, they are usually adopted by CVMP at Day 90 or at the latest by Day 120. For inspections 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) or discussed with the assessors.

Once an inspection request is adopted by the CVMP 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 be conducted within two months approximately from the date of adoption of the inspection request.

4.4.2- 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 submission of a Corrective action plan. The final report(s) is then sent to the EMEA inspection sector by day 180 as the latest, and circulated to the Rapporteur and Co-Rapporteur and CVMP. The Inspection Report should be available to EMEA by day 150 or 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.

4.4.3 Inspections 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).

5. SCIENTIFIC EVALUATION OF AN APPLICATION BY THE COMMITTEE

5.1 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, 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 Secretariat, the start of the procedure will be delayed until the Secretariat 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 member of the CVMP 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 CVMP has received the requested documentation.

Having taken into consideration the standard timetable agreed by the CVMP for the evaluation of a centralised application, a timetable is prepared by the EMEA Secretariat in consultation with the Rapporteur and the Co-rapporteur. The timetable is then notified to the CVMP.

The EMEA will ensure that the Opinion of the CVMP is given within 210 days.

TIMETABLE FOR THE EVALUATION OF A CENTRALISED APPLICATION

DAY	ACTION
1	Start of the procedure
70	Rapporteur's Assessment Report sent to the Co-rapporteur, CVMP members and EMEA Secretariat.
85	Co-rapporteur's critique of the Rapporteur's Assessment Report sent to Rapporteur, CVMP members and EMEA Secretariat. The Rapporteur's Assessment Report and the Co-Rapporteur's critique are sent to the applicant by the EMEA Secretariat (making it clear that they do not yet represent the position of the CVMP.)

100	Rapporteur, Co-rapporteur, other CVMP members and EMEA receive comments from Members of the CVMP. Between Day 70 and Day 100, a quality check on the English version of the Product Information[4]
115	Receipt of draft list of questions (including overall conclusions and overview of the scientific data) from Rapporteur and Co-Rapporteur by CVMP members and EMEA.
120	CVMP 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 CVMP of request for GMP inspection, if necessary (Inspection procedure starts).
121*	Submission of the responses, including revised summary of product characteristics, labelling and package leaflet text in English and restart of the clock.

* Target dates for the submission of the responses are published on the EMEA web-site – documents 'Pre-Submission Guidance').

After receipt of the responses, the Project Manager will prepare a revised timetable in consultation with Rapporteur and Co-Rapporteur for the evaluation of the responses. In general the following standard timetable will apply:

160	Joint response Assessment Report from Rapporteur and Co-Rapporteur received by CVMP members and EMEA. EMEA sends joint response 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 no yet represent the position of the CVMP. Where applicable, inspection to be carried out.
170	Deadline for comments from CVMP Members to be sent to Rapporteur and Co-Rapporteur, EMEA and other CVMP members.
180	CVMP discussion of the draft Opinion (summary of product characteristics, labelling and package leaflet) and decision taken 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 of the clock and oral explanation (if needed). The Project Manager sends updated summary of product characteristics and product literature in English to the applicant.
By 210	Adoption of CVMP Opinion + CVMP Assessment Report.
211	Transmission to applicant of CVMP Opinion + CVMP Assessment Report
215 at the latest	Applicant provides the EMEA with summary of product characteristics, Annex II, labelling, package leaflet and Annex A in all EU languages and Norwegian.
232	Applicant provides the EMEA with summary of product characteristics, Annex II, labelling, package leaflet and Annex A in all EU languages, taking account of comments received from Member States by Day 229.

[4] Detailed information on the Product Information Linguistic Review Process can be found at http://www.emea.eu.int/pdfs/human/regaffair/554202en.pdf

By 237	EMEA Transmission of Opinion and Annexes in all EU languages to the applicant, Commission and Members of the Standing Committee, Norway and Iceland.

Further details on the post-Opinion review of translations and forms to be used, are available on the EMEA website ((http://www.emea.eu.int/ – Veterinary Medicines - Application procedures - Product Information Templates – reference documents).

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

5.2 Accelerated Assessment

When a marketing authorisation application is submitted for a product which is of major interest, in particular from the viewpoint of animal health and from the viewpoint of therapeutic innovation, the applicant may request an accelerated assessment procedure in accordance with Article 39(8) of Regulation (EC) 726/2004.

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 2 months in advance of the marketing authorisation application.

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

The outcome of the assessment of the request by the CVMP, and the tentative timetable for an accelerated assessment procedure adopted by the CVMP will be attached to the letter confirming the positive outcome of the validation.

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

5.3 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.

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 CVMP 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.

5.4 Committee's request for additional information

The CVMP will consider the preliminary Assessment Reports from the Rapporteur and Co-Rapporteur. From these, and the comments of other members of the CVMP, the outstanding issues which the applicant should address will be identified. A consolidated list of questions will be sent to the applicant together with the CVMP recommendation and scientific discussion. The clock will be stopped at this point.

The CVMP 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 product is not approvable since major objections have been identified which preclude a recommendation for marketing authorisation at the present time. The details of these major objections are provided in the overall summary and list of questions document.

Alternatively, the CVMP may consider the application to be approvable and is ready for adoption of an Opinion, but remaining points, which could be resolved after granting of the marketing authorisation, may be agreed upon by the CVMP (see paragraph 7.2)

The applicant would normally be expected to respond within the timeframe agreed by the CVMP (e.g. 6 months) from the date of receiving the questions. This is felt to be an adequate time to prepare the answers to the requests for additional information. If the applicant is unable to respond in the time frame of 6 months then careful consideration should be given to withdrawing the application and resubmitting when the full information is available. The applicant is advised to consult with the Rapporteur, the Co-Rapporteur and the project manager if clarification is required on any of the questions. The applicant may also wish to consult the Rapporteur, Co-Rapporteur and the project manager regarding the strategy for the response and for revision of indications, other elements of the summary of product characteristics or other conditions for the marketing authorisation. Applicants should inform the EMEA/CVMP preferably one month in advance of the submission of the responses. Recommended dates for submission of the responses are published on the EMEA web-site.

5.5 Oral or written explanation

In addition to the written responses to the issues raised by the CVMP, applicants may also avail themselves of an oral explanation to the CVMP. The time limit set out in Article 31(3) of the Regulation will be suspended for the time allowed to the applicant to prepare an oral explanation (clock-stop – usually 1- 3 months).

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

Oral explanation

Oral explanations will be provided at the request of either the applicant or the CVMP. The CVMP 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 are strongly recommended to present a written request to the CVMP preferably one month before the anticipated date of the oral explanation and certainly prior to Day 180.

The CVMP 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 CVMP (usually at Day 180) and sent to the applicant.

The applicant would then liaise with the Rapporteur and the project manager 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 allow clarification of outstanding issues. Thus the applicant is advised to bear in mind the following:

- Oral explanations are conducted in English;
- For the presentation, slide projectors, overhead projectors and computerised systems are available at the EMEA. Applicants should consult in advance with the project manager on the facilities they would like to use;
- Any written explanation which the applicant wishes to present in order to support and elaborate on outstanding issues to be addressed during the oral explanation should be received by the EMEA project manager and CVMP members at least 14 days before the CVMP meeting;
- Copies of any audio/visual aid material, including paper copies of projector slides/overheads, must be sent to the CVMP Secretariat and project manager in advance or be brought to the meeting, for distribution prior to the oral explanation.

Applicants can appear before the CVMP, together with any experts they wish to accompany them. Depending on the issues to be discussed, it would normally be appropriate for between one and four persons per applicant to appear. More than four members of a delegation will be able to attend only in exceptional cases.

At least one week before the oral explanation, the applicant should provide the project manager with the definitive list of names and a brief *curriculum vitae* of the persons who will be attending the oral explanation.

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 CVMP, whether favourable or unfavourable to the case and whether there is any further or additional information to be given to the CVMP;
- The Chairman will invite the applicant representatives to make their presentation (usually not more than 30 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 CVMP to add supplementary questions or comments;

- At the conclusion of the oral explanation, the representatives of the applicant will be invited to leave and the CVMP will discuss and provide a preliminary recommendation on the acceptability of the application.
- The applicant will be informed of the trend of opinion at CVMP level at the end of the scientific discussion ahead of any formal vote to conclude the evaluation process.

5.6 Withdrawal of the application

Where an applicant decides to withdraw its application before an Opinion has been adopted by the CVMP or during the re-examination 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 this information being made publicly available.

6. THE COMMITTEE'S OPINION

The Project Manager, in co-ordination with the Rapporteur and Co-Rapporteur and taking account of the full scientific deliberation in the CVMP and the conclusions reached, prepare the final assessment report and the final summary of product characteristics, labelling and package leaflet, which, once adopted by the CVMP, becomes the CVMP assessment report and is appended to the CVMP Opinion.

On or before Day 210, the CVMP adopts its Opinion in the light of the final recommendation of the Rapporteur and Co-rapporteur and further evidence presented at the oral explanation.

The CVMP 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 a majority of the members. When divergent positions have been expressed, they will be referenced in the CVMP Opinion. Members expressing such divergent positions shall state clearly the grounds on which they are based. The divergent positions will be appended to the Opinion.

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

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

6.1 Favourable opinion

In the event of an Opinion in favour of granting the relevant marketing authorisation the veterinary medicinal product concerned, the following documents shall be annexed and/or appended to the Opinion:

- A draft Summary of Product Characteristics as referred to in Article 14 of Directive 2001/82/EC;
- Manufacturing and/or importing conditions and proposed conditions of the marketing authorisation;
- Conditions or restrictions regarding supply and use;
- Any recommended conditions or restrictions with regard to the safe and effective use of the product;
- Where appropriate, statement of the maximum residue limits which may be accepted by the Community;
- Draft labelling and package leaflet presented in accordance with Title V of Directive 2001/82/EC;
- The CVMP assessment report;
- Where relevant, divergent positions of CVMP Members with signatures and their grounds for not supporting the Opinion.

Should the CVMP 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.

In the event of an Opinion in favour of granting the relevant authorisation to place the veterinary medicinal product concerned on the market, subject to the conditions provided for in Article 39(7) of the Regulation (i.e. under exceptional circumstances), the above-mentioned documents shall also be annexed to the Opinion.

The EMEA will prepare a 'Summary of Opinion' in liaison with the applicant. These Summaries will be published on the EMEA web-site as soon as possible after adoption of the CVMP Opinion – documents 'Opinions'.

6.2 Approval under Exceptional Circumstances

In accordance with Article 39 (7) of Regulation (EC) 726/2004, 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 Annex I to Directive 2001/82/EC. Continuation of the authorisation shall be linked to the annual reassessment of these conditions.

6.3 Specific obligations and follow-up measures

6.3.1 Specific obligations

When an Opinion is granted under exceptional circumstances, the marketing authorisation holder is obliged to submit post authorisation data to the Rapporteur, Co-Rapporteur, CVMP Members and the EMEA, within an agreed timeframe. These additional data, known as specific obligations, are set out in Annex II of the Opinion and are detailed in the letter of undertaking of the marketing authorisation holder as adopted at the time of the Opinion.

The specific obligations are to be reviewed at the intervals indicated and at the longest annually. The annual review includes a re-assessment of the benefit/risk profile.

A copy of the documentation relating to specific obligations should be sent by the marketing authorisation holder to the Chairman of the CVMP, all CVMP members and the EMEA. The documentation will be reviewed (usually by the Rapporteur) within the timescale which will be communicated to the applicant.

6.3.2 Follow-up measures

For all Opinions of the CVMP (whether or not under the exceptional circumstances of Article 39(7) of the Regulation), it might be necessary to establish follow-up measures.

These follow-up measures are set out in an annex to the CVMP Assessment report and are detailed in a Letter of Undertaking signed by the marketing authorisation holder as adopted at the time of the Opinion.

Unless otherwise requested by CVMP members, the marketing authorisation holder should send the data on the fulfilment of follow-up measures to the Rapporteur and EMEA Secretariat. The data will be reviewed (usually by the Rapporteur) within the timescale which will be communicated to the applicant.

The marketing authorisation holder will be informed of the outcome of CVMP discussions by the Secretariat.

6.3.3 Resulting variation applications

When considered appropriate, in view of the urgency of the matter (especially for safety issues), marketing authorisation holders may submit any variation application resulting from the fulfilment of the specific obligation or follow-up measure at the same time as the fulfilment of the Specific Obligation/Follow-up Measure concerned in order to minimise the processing and review time. The normal variation submission requirements and assessment procedures will apply (see Chapter 5 of Volume 6 of the Notice to Applicants). This also applies when a variation is submitted in order to fulfil a Specific Obligation/Follow-up Measure.

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

The 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 CVMP and after having received reminder letters from the EMEA, the matter will be put by the EMEA on the agenda of the following CVMP meeting.

In case of non-fulfilment of the specific obligations the CVMP will formulate an Opinion, on the basis of Article 39(7) of the Regulation, recommending the variation, suspension or withdrawal of the marketing authorisation.

In the case of non-fulfilment of follow-up measures, the CVMP will consider the possibility to recommend a variation, suspension or withdrawal of the marketing authorisation based on the re-assessment of the benefit/risk profile of the product in accordance with Article 30 of the Regulation and with Article 83 of Directive 2001/82/EC.

6.4 Unfavourable opinions

The EMEA immediately informs the applicant when the Opinion of the CVMP 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 CVMP assessment report stating the reasons for its negative conclusions;
- Where appropriate, divergent positions of CVMP Members with their grounds for not supporting the Opinion.

Information about unfavourable Opinions and refusals, including divergent positions if applicable, and the reasons for such Opinion shall be made publicly accessible even if the application has been withdrawn.

7. FOLLOW-UP TO THE CVMP OPINION

7.1 Translations of the CVMP opinion

Within 5 days after the CVMP 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.

7.2 Transmission of the CVMP opinion

The EMEA will send the adopted (English-language version) to the European Commission and to the applicant by Day 211.

If, within 15 days of receipt of the Opinion, the applicant does not provide the EMEA with written notice that he wishes to request a re-examination of the Opinion, the EMEA will forward the Opinion (and the required annexes) to the Commission, the Member States, Iceland, Liechtenstein and Norway and to the applicant together with the CVMP assessment report

The Opinion (and its annexes) shall be 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 of the Notice to Applicants starts once the Opinion with the Assessment Report has been received.

7.3 Re-examination

The applicant may notify the EMEA/CVMP of their request for 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 of receipt of the Opinion. If the applicant wishes to appear before the CVMP for an oral explanation, this should also be requested at this stage.

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

The CVMP will appoint a new Rapporteur and where previously appointed (a) new Co-Rapporteur(s), to co-assess the grounds for the re-examination of the Opinion, accompanied, if necessary, by additional experts. 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 CVMP adopted the initial Opinion. The applicant may request that the CVMP consult a scientific advisory group in connection with the re-examination. The CVMP may agree to this request or may request the advice of additional expertise as appropriate.

Within 60 days from the receipt of the grounds for re-examination, the CVMP will consider whether its Opinion is to be revised. If considered necessary, an oral explanation can be held within this 60 day timeframe. No clock-stops apply to this procedure.

Once the CVMP 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 CVMP conclusions will be annexed to the final Opinion.

At the end of the re-examination procedure, the EMEA will publish a Summary of Opinion of the Committee's final Opinion. At the end of the re-examination procedure, the Summary of Opinion (SmOP) or the Questions and Answers document on the initial CVMP Opinion will be revised to reflect the outcome of the re-examination procedure, and will be published at the time of the CVMP Monthly Report. The EPAR/Refusal EPAR will be published once the Commission Decision has been issued.

7.4 European Public Assessment Report (EPAR)

In accordance with Article 38 of the Regulation, the EMEA shall publish the CVMP assessment report of on the veterinary 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.

Article 38(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.

7.4.1 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 project manager. The preparation of the EPAR is required in cases where the CVMP formulates positive final Opinions.

In accordance with Article 34(4) of the Regulation, applicants will receive the assessment report of the CVMP. Applicants are then required to confirm 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 Project Manager, 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 Project Manager 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 CVMP at a subsequent meeting for information.

7.4.2 Availability of the EPAR

As soon as the Commission Decision has been notified to the EMEA, the final EPAR will be sent to the applicant. The EPAR shall be made available as soon as possible after notification of the Commission Decision to grant the marketing authorisation.

7.5 Negative decision

Following a Commission Decision on the refusal to grant a marketing authorisation, which, in accordance with Article 37(2) of the Regulation, constitutes a prohibition to place on the market the veterinary medicinal product concerned throughout the Community, the EMEA shall make information about such refusal and the reason for it publicly accessible.

8. MARKETING OF THE VETERINARY MEDICINAL PRODUCT IN THE COMMUNITY

In accordance with Article 38(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 holder 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 be sent 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 may grant exemptions from these provisions on duly justified public health grounds.

9. POST-AUTHORISATION INSPECTIONS (GMP 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 44 of Regulation (EC) No 726/2004. The purpose of GMP re-inspections is to verify that manufacturers continue to comply with EU GMP and with the requirements of the marketing authorisation as accepted by the CVMP. 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 CVMP 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 (PhV) Inspections:

The legal basis is set out in Article 44 of Regulation (EC) No 726/2004 and in Article 80 of Directive 2001/82/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 CVMP 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 or follow up measures, variations, extensions or other information received post-authorisation (e.g. in relation to safety measures, risk management plan etc..) may trigger a GMP or PhV inspection request.

10. 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 notification of the administrative validation to the applicant and the fees will be payable within 45 days of the date of notification.

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

Within 30 days 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 person to whom the transfer is to be granted and to the Commission.

The Opinion would be unfavourable if the documents submitted in support of the application are incomplete or if it appears that the person to whom the transfer is to be granted is not established in the EEA, or cannot fulfil all the responsibilities as marketing authorisation holder for the veterinary medicinal product concerned.

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

The EMEA, by mutual agreement with the marketing authorisation holder and the person to whom the transfer is to be granted, will set the date by which the transfer will actually take place, i.e. the end of the transitional period during which there could be on the market products under the names of the new and old holder, after the Commission amends the Decision which granted the marketing authorisation. In all cases, and as documented by both parties in bullet point 4 above, the responsibilities of the marketing authorisation holder would be transferred to the new marketing authorisation holder as soon as the Commission amends the decision.

The EMEA will inform the Commission of this date, which marks the end of the transitional period and which may not exceed a period of 6 months from the date of the amendment to the Commission Decision as a result of the transfer.

11. RENEWAL OF MARKETING AUTHORISATION

According to Article 39 of the Regulation a marketing authorisation will be valid for five years and may be renewed after five-years on the basis of a re-evaluation by the Agency of the risk-benefit balance. For a veterinary medicinal product, which has been authorised by the Community, the application for renewal of the marketing authorisation should be submitted to the EMEA six months before the expiry of the marketing authorisation.

The application should be supported by a dossier containing the information required in accordance with the Guideline on the processing of renewals in the centralised procedure. The EMEA

will issue an invoice on the date of notification of the administrative validation to the applicant and fees will be payable within 45 days of the date of notification.

Once renewed, the marketing authorisation shall be valid for an unlimited period, unless the Commission, upon recommendation of the CVMP, decides on justified grounds relating to pharmacovigilance, to proceed with one additional five-year renewal. However, the CVMP may assess the risk-benefit balance of a veterinary medicinal product at any time the CVMP 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 Procedures", which is published in Volume 6C of the Notice to Applicants, as well on the EMEA website (http://www.emea.eu.int/ - Veterinary Medicines - Application Procedures).

Marketing Authorisations which have already been renewed under the system in force before the coming into force of Regulation 726/2004 should be renewed once more under the new system before the authorisation may gain unlimited validity.