



EUROPEAN COMMISSION
ENTERPRISE DIRECTORATE-GENERAL

Single market : management & legislation for consumer goods
Pharmaceuticals : regulatory framework and market authorisations

Brussels,
F2/AW D(2001)

Final – Revision 0

NOTICE TO APPLICANTS

VOLUME 6B

Presentation and content of the dossier

Part II G and H:

Data related to the environmental risk assessment for products containing or consisting of genetically modified organisms (GMOs)

SEPTEMBER 2001

**These Guidance notes will be included in The Rules governing Medicinal Products
in the European Community**

**The Notice to Applicants Volume 6B Presentation and contents of the dossier for
marketing authorisation for veterinary medicinal products (page 130 and page 174)**

CHAPTER TO BE INCLUDED IN THE NEXT REVISION OF THE NOTICE TO APPLICANTS

VETERINARY MEDICINAL PRODUCTS CONTAINING OR CONSISTING OF GENETICALLY MODIFIED ORGANISMS

This Chapter contains three separate guidance documents relating to the environmental risk assessment which must accompany applications for marketing authorisation of veterinary medicinal products which contain or consist of Genetically Modified Organisms (GMOs)¹.

These guidelines should be read in conjunction with the current versions of the EMEA Standard Operating Procedures EMEA/CVMP/036/97 – REVISION and EMEA/CVMP/037/97 – REVISION.

Contents

- A. Guideline on the presentation of particulars concerning the environmental risk assessment for veterinary medicinal products which contain, or consist of, Genetically Modified Organisms
Page 2
- B. Guideline for the conduct of the environmental risk assessment for veterinary medicinal products which contain or consist of Genetically Modified Organisms
Page 15
- C. Guidance on the integration of the evaluation of the environmental risk assessment with the evaluation of the rest of the application for marketing authorisation for a medicinal product consisting of or containing live Genetically Modified Organisms
Page 25

¹ This guidance does not apply to products which are made using Genetically Modified Organisms but which, by virtue of the manufacturing method and with appropriate validation, do not contain or consist of GMOs

A. GUIDELINE ON THE PRESENTATION OF PARTICULARS CONCERNING THE ENVIRONMENTAL RISK ASSESSMENT FOR VETERINARY MEDICINAL PRODUCTS WHICH CONTAIN, OR CONSIST OF, GENETICALLY MODIFIED ORGANISMS.

1. INTRODUCTION

This text provides detailed guidance on the form in which the particulars relevant to the environmental risk assessment are to be presented by the Applicant as part of his/her application for authorisation to market a medicinal product for veterinary use which contains, or consists of, a genetically modified organism (GMO). It is important to distinguish carefully between products which contain substances simply derived from Genetically Modified Organisms, and those products which contain, or consist of, such organisms. While advanced methods of genetic modification such as recombinant DNA technology have been applied in several instances to micro-organisms for the purpose of producing drug substances from them, micro-organisms which have been genetically modified by such means and retain a capacity for replication, have only rarely themselves been developed for administration to animals for therapeutic or diagnostic purposes.

Council Directive 90/220/EEC² on the deliberate release into the environment of Genetically Modified Organisms requires that Applicants wishing to place on the market a product which contains, or consists of, a Genetically Modified Organism (GMOs) shall submit a notification for evaluation to an appropriate Competent Authority designated for carrying out the Directive's requirements. These provisions do not, however, apply to products containing, or consisting of GMOs covered by other Community legislation which provides for a specific environmental risk assessment similar to that laid down in the Directive. Where a notification is required by the Directive, it must include at least the following:

- specified information relating to the product and the release (Annex IIA of the Directive), including any relevant data arising from previous releases involving research and development, and an environmental risk assessment, and
- details of any proposed conditions for placing on the market of the product (Annex III of the Directive), including conditions related to use, handling, labelling and packaging where relevant.

The notification is evaluated according to defined procedures. Deliberate release may proceed only if the Applicant receives a formal consent, and is subject to any conditions specified in the consent.

However, where it is the case that the GMO constitutes, or more likely is contained in, a medicinal product, then, following from provisions appearing in Article 28 of Council Regulation (EEC) No.2309/93 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products:

- the above particulars shall accompany the application for authorisation to market a medicinal product;
- these particulars shall include in addition a copy of any previously obtained written consent or consents for deliberate release for research and development purposes:

² Council Directive 90/220/EEC will be repealed and replaced by Directive 2001/18/EC of the European Parliament and of the Council from 17 October 2002.

- as these requirements provide for a specific environmental risk assessment similar to that laid down in Council Directive 90/220/EEC, the provisions of the Directive relating to placing a medicinal product on the market no longer apply; (it should be noted that the provisions of the Directive relating to research and development or any purpose other than placing a medicinal product on the market continue to apply where relevant) and
- during the process of evaluating applications for marketing authorisations for such products, necessary consultations will be held by the Rapporteur with those bodies set up by the Community or the Member States in accordance with Council Directive 90/220/EEC.

2 DEFINITIONS

The definitions which appear in European Community law apply. The following extracts from these are intended for the purpose of introduction only.

Medicinal Product: any substance or combination of substances presented for preventing or treating disease in human beings or animals.

Immunological Veterinary Medicinal Product: a veterinary medicinal product administered to animals in order to produce active or passive immunity, or to diagnose the state of immunity.

Organism: any biological entity capable of replication: or of transferring genetic material.

Genetically Modified Organism (GMO): an organism in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination.

Deliberate Release: any intentional introduction into the environment of a GMO or a combination of GMOs without provision for containment such as physical barriers or a combination of physical barriers together with chemical and/or biological barriers used to limit their contact with the general population and the environment.

Environmental Risk Assessment: the evaluation of the risk to human health and the environment (which includes plants and animals) connected with the release of GMOs or products containing GMOs.

3. GENERAL CONSIDERATIONS

3.1 It is essential that the approach to the environmental risk assessment presented by the Applicant is similar to that laid down in Directive 90/220/EEC, including the relevant parts of Annexes IIA and III of the Directive. Headings in Annex IIA of the Directive have been omitted in this Note for Guidance in the cases in which it is considered that they are normally not applicable to medicinal products for veterinary use or to their placing on the market.

3.2 The particulars presented in accordance with this Note for Guidance will be in addition to the documentation already required in support of the claimed quality, safety and efficacy of the product. In the case of overlapping requirements the information should be repeated in full as necessary, though the data provided will in many cases be identical to data appearing in the remainder of the dossier. The Applicant will obviously need to take care to ensure consistency in the presentation of data. The various requirements affecting tests, trials, documentation etc, stated in the *Rules Governing Medicinal Products in The European Community*, as with the rest of the dossier, apply where relevant.

3.3 The particulars submitted in accordance with this Note for Guidance should form part of the dossier submitted in support of the application for marketing authorisation, and should therefore be bound, paginated and indexed as such.

3.4 Binding, pagination and indexation should be logical and thorough as stated elsewhere in the Notice to Applicants.

3.5 The particulars outlined in this Note for Guidance should be presented in a separate volume, which physically could stand alone and which could be handled separately from the remainder of the dossier if necessary.

3.6 The Applicant should indicate any information in Section II-H which he wishes to be treated as confidential, where this is allowed by Community law. The respective confidential and non-confidential parts should be appropriately marked, ideally on each page, and should be bound separately.

4. PRESENTATION OF DATA IN THE MAIN DOSSIER

The information presented in accordance with this Note for Guidance will form Part II-H of the dossier. The entries should be presented in six sections, Part II-H 1 to 6 as follows.

Part II-H: DATA RELATED TO THE ENVIRONMENTAL RISK ASSESSMENT FOR PRODUCTS CONTAINING OR CONSISTING OF GENETICALLY MODIFIED ORGANISMS (GMOs):

Part II-H-1.: Introduction.

This should include a brief product profile and a description of, and justification for, the proposed release.

Part II-H-2. A copy of the 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 90/220/EEC

Any written consent(s) to release obtained within the Community must be submitted. It would also be useful to submit any written consent(s) to release obtained outside the Community.

Part II-H-3. The complete technical dossier supplying the information requested in Annex IIA of Directive 90/220/EEC, including the results of investigations performed for the purposes of research and development.

The following points, which are extracts of Annex IIA of Directive 90/220/EEC, are those which are normally relevant to placing a veterinary medicinal product on the market. Headings in Annex IIA of the Directive which are considered to be normally not applicable to placing on the market, or not applicable to veterinary medicinal products, are omitted. The notes in italics indicate where overlap is likely or not likely to occur with entries already required in other sections of the dossier submitted in support of a marketing authorisation, the Part numbers referring to those of the Notice to Applicants for Veterinary Medicinal Products (where Part I is equivalent to Part V of Directive 81/852/EEC, as amended by Directive 92/18/EEC, Part II is equivalent to Part 6, Part III to Part 7 (and 9) and Part IV to Part 8).

The Applicant should add to the particulars listed below any additional items which are required by the nature or use of the GMO or the proposed release.

Similarly, not all the points included will apply in every case. It is to be expected, therefore, that individual applications will address only the particular subset of considerations, which are appropriate to individual situations.

The level of detail required in response to each subset of considerations is also likely to vary according to the nature and scale of the proposed release.

I. General Information.

A. Name and address of the notifier

The name and address of the Applicant should be stated, in the form in which it already appears in Part I of the dossier.

II. Information relating to the GMO.

A. Characteristic of the recipient or (when appropriate) parental organism.

The entries should address each organism (recipient and/or parental organism) as appropriate.

1. Scientific name;

Part IIC 2.1

2. Taxonomy;

Part IIC 2.1.

3. Other names (usual name, strain, name, etc.);

Part IIC 2.1.

4. Phenotypic and genotypic markers;

Part IIC 2.1

5. Degree of relation between donor and recipient or between parental organisms;

This information is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier.

6. Description of identification and detection techniques.

Part IIC, but Applicants should also note this requirement for the environment-specific entries which are not covered elsewhere in the dossier.

7. Sensitivity, reliability (in quantitative terms) and specificity of detection and identification techniques;

Already required for Part IIC, but Applicants should also note this requirement for the environment-specific entries which are not covered elsewhere in the dossier.

8. Description of the geographic distribution and of the natural habitat of the organism including information on symbionts and hosts;

This information is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier

9. Potential for genetic transfer and exchange with other organisms;

This information is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier.

10. Verification of the genetic stability of the organisms and factors affecting it;

This information is required (for the recipient parental organism) specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier.

11. Pathological, ecological and physiological traits:

(a) classification of hazard according to existing Community rules concerning the protection of human health and the environment;

This information is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier.

(b) Generation time in natural ecosystems, reproductive cycle;

This information is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier.

(c) Information on *survival*, including seasonability and the ability to form survival structures, e.g. spores;

This information is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier.

(d) Pathogenicity: infectivity, toxigenicity, virulence, allergenicity, carrier (vector) of pathogen, possible vectors, host range including non-target organism. Possible activation of latent viruses (proviruses). Ability to colonise other organisms;

This information is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier.

(e) Antibiotic resistance, and potential use of these antibiotics in humans and domestic organisms for prophylaxis and therapy;

This information is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier.

(f) Involvement in environmental processes: primary production, nutrient turnover, decomposition of organic matter, respiration etc.;

This information is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier.

12. Nature of indigenous vectors:

(a) Sequence;

Part IIC 2.1.

(b) Frequency of mobilisation;

Part IIC 2.1

(c) Specificity;

Part IIC 2.1.

(d) Presence of genes which confer resistance;

This information is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier.

13. History of previous genetic modifications.

Part IIC 2.1.

B. Characteristics of the vector:

1. Nature and source of the vector;

Part IIC 2.1.

2. Sequence of transposons, vectors and other non-coding genetic segments used to construct the GMO and to make the introduced vector and insert function in the GMO;

Part IIC 2.1.

3. Frequency of mobilisation of inserted vector and/or genetic transfer capabilities and methods of determination;

Part IIC 2.1.

4. Information on the degree to which the vector is limited to the DNA required to perform the intended function;

Part IIC 2.1.

C. Characteristics of the modified organism:

1. Information related to the genetic modification;

(a) Methods used for the modification,

Part IIC 2.1.

(b) Methods used to construct and introduce the insert(s) into the recipient or to delete a sequence;

Part IIC 2.1.

(c) Description of the insert and/or vector construction;

Part IIC 2.1.

(d) Purity of the insert from any unknown sequence and information on the degree to which the inserted sequence is limited to the DNA required to perform the intended function;

Part IIC 2.1.

(e) Sequence, functional identity and location of the altered/inserted/deleted nucleic acid segments in question with particular reference to any known harmful sequence;

Part IIC 2.1.

2. Information on the final GMO.

(a) Description of genetic trait(s) or phenotypic characteristics and in particular any new traits and characteristics which may be expressed or no longer expressed;

Part IIC 2.1, but more data and detail may be required in so far as the data relate to the environmental risk assessment.

(b) Structure and amount of any vector and/or donor nucleic acid remaining in the final construction of the modified organism;

Part IIC 2.1.

(c) Stability of the organism in terms of genetic traits;

Part IIC 2.1.

(d) Rate and level of expression of the new genetic material. Method and sensitivity of measurement;

Also Part IIC2.1.

(e) Activity of the expressed proteins;

Part IIC 2.1.

(f) Description of identification and detection techniques including techniques for the identification and detection of the inserted sequence and the vector;

Part IIC 2.1.

(g) Sensitivity, reliability (in quantitative terms) and specificity of detection and identification techniques;

Part IIC 2.1.

(h) History of previous releases or uses of the GMO;

This information is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier. See also Part II-H-2.

3. Health considerations:

(i) Toxic or allergenic effects of the non-viable GMOs and/or their metabolic products;

Part III, especially Part IIIE.

(ii) Product hazards;

Part III, especially Part IIIC.8 and IIIE.

(iii) Comparison of the modified organism to the donor, recipient or (where appropriate) parental organism regarding pathogenicity;

This information is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier.

(iv) Capacity for colonisation;

This information is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier.

- (v) If the organism is pathogenic to humans who are immunocompetent;
- diseases caused and mechanism of pathogenicity including invasiveness and virulence;
 - communicability;
 - infective dose;
 - host range, possibility of alteration;
 - possibility of survival outside of human host;
 - presence of vectors or means of dissemination;
 - biological stability;
 - antibiotic-resistance patterns;
 - allergenicity;
 - availability of appropriate therapies.

The information specified under (v) is required specifically to fulfil the requirements of the environmental risk assessment and may not appear in Part III of the dossier in the detail which is required for the purposes of an environmental risk assessment.

III. Information Relating to the Conditions of Release and the Receiving Environment.

A Information on the release.

1. Description of the proposed deliberate release, including its purpose.
This is equivalent to the indications for use of the product and the information provided should be consistent with that stated in Parts IA, IB and IVA.1 of the dossier, in the Summary of Product Characteristics and on the labelling.
2. Method(s) to be used for the release.
This is equivalent to the indications for use of the product and the information provided should be consistent with that stated in Parts I and IV of the dossier in the Summary of Product Characteristics and on the labelling.
3. Information on, and results of, previous releases of the GMOs, especially at different scales and in different ecosystems.
Possibly addressed in Part IIID but this information is largely required to specifically fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier, for example the results of the release should include the consequences of any shedding of the virus.
4. Quantities of GMOs to be released.
Part IIA. The quantities of GMO to be administered per dose should be stated.

IV. Information Relating to the Interactions Between the GMOs and the Environment.

A. Characteristics affecting survival, multiplication and dissemination.

1. Biological features which affect survival, multiplication and dispersal;
Parts IIIA, IIIC 6.1, IIIC 6.2, IIIE.
2. Known or predicted environmental conditions which may affect survival, multiplication and dissemination (wind, water, soil, temperature, pH etc.);
This information is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier.
3. Sensitivity to specific agents.
This information is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier.

B. Interactions with the environment:

1. Predicted habitat of the GMOs;
Part IIIE.
2. Studies of the behaviour and characteristics of the GMOs and their ecological impact carried out in simulated natural environments, such as microcosms, growth rooms, greenhouses, animal houses etc. may also be of relevance to medicinal products;
This information is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier.
3. Genetic transfer capability:
 - (a) Post-release transfer of genetic material from GMOs into organisms in affected ecosystems;
Partly covered in Part IIIC 6.2 but this information is largely required to specifically fulfil the requirements of the environmental risk assessment and may not necessarily appear in detail elsewhere in the dossier.
 - (b) Post-release transfer of genetic material from indigenous organisms to the GMOs;
Partly covered in Part IIIC 6.2 but this information is largely required to specifically fulfil the requirements of the environmental risk assessment and may not necessarily appear in detail elsewhere in the dossier.
4. Likelihood of post-release selection leading to the expression of unexpected and/or undesirable traits in the modified organism;
This information is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier.

5. Measures employed to ensure and to verify genetic stability. Description of genetic traits which may prevent or minimise dispersal of genetic material. Methods to verify genetic stability.;

This entry should include detailed information specifically relevant to the environmental risk assessment and should if necessary be more extensive than that presented in Part IIC 2 of the dossier.

6. Known routes of biological dispersal or potential modes of interaction with the disseminating agent, including inhalation, ingestion, surface contact etc.;
- Part IIIA 1, IIIC 6.1, IIIC 6. 2, IIIE.*

7. Description of ecosystems to which the GMOs could be disseminated;
- Parts IIIA, IIIE.*

C. Potential environmental impact:

1. Potential for excessive population increase in the environment;
- Part IIIE.*

2. Competitive advantage of the GMOs in relation to the unmodified recipient or parental organism(s);
- Part IIIE.*

3. Identification and description of the target organisms;
- Parts IIIA 1, IIIC 6.1, IIIE.*

4. Anticipated mechanism and result of interaction between the released GMOs and the target organism;
- Part IIIE.*

5. Identification and description of non-target organisms which may be affected unwittingly;
- Parts IIIA 1, IIIC 6.1 and IIIE.*

6. Likelihood of post-release shifts in biological interactions or in host range;
- Part IIIE.*

7. Known or predicted effects on non-target organisms in the environment, impact on population levels of competitors, hosts, symbionts and pathogens;
- Part IIIE.*

8. Known or predicted involvement in biogeochemical processes;
- Part IIIE.*

9. Other potentially significant interactions with the environment;
- Part IIIE.*

V. Information on Monitoring, Control, Waste Treatment and Emergency Response Plans

A. Monitoring Techniques:

1. Methods for tracing the GMOs, and for monitoring their effects;
This information is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier.

2: Specificity (to identify the GMOs, and to distinguish them from the donor, recipient or, where appropriate, the parental organisms), sensitivity and reliability of the monitoring techniques;
This information is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier.

3. Techniques for detecting transfer of the donated genetic material to other organisms.
This information is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier.

B. Control of the Release:

1. Methods and procedures to avoid and/or minimise the spread of the GMOs beyond the site of the release or the designated areas of use;
This information is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier, and is likely to be relevant in the case of vaccines disseminated as a baited formulation in an open environment.

C. Waste treatment:

1. Type of waste generated;
Parts IIIA 1, IIIC 6.2, IIIC 6.3.

2. Expected amount of waste;
This information is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier.

3. Possible risks;
Part IIIE.

4. Description of treatment envisaged;
Part IB, but this information is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier.

D. Emergency response plans:

1. Methods and procedures for controlling the GMOs in case of unexpected spread;

This information is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier, and is likely to be relevant in the case of vaccines disseminated as a baited formulation in an open environment.

2. Methods for decontamination of the areas, e.g. eradication of the GMOs.

This information is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier, and is likely to be relevant in the case of vaccines disseminated as a baited formulation in an open environment.

3. Plans for protecting human health and the environment in case of the occurrence of an undesirable effect.

Part IB, but this information is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier.

Part II-H-4. The complete technical dossier supplying the information requested in Annex m of Directive 90/220/EEC including the results of any investigations performed for the purposes of research and development.

A. The following information shall be provided:

1. Name of the product and names of the GMOs contained therein;

The information should be consistent with that provided in Part I of the dossier

2. Name of the manufacturer or distributor and their address in the Community;

The information should be consistent with that provided in Part I of the dossier

3. Specificity of the product, exact conditions of use including, when appropriate, the type of environment and/or the geographical areas(s) of the Community for which the product is suited;

4. Type of expected use: industry, skilled trades, consumer use by public at large etc.;

In the case of medicinal products for veterinary use, any veterinary or animal care personnel, institutions etc. specified for handling the product should be stated.

B. The following information shall be provided where relevant:

1. Measures to take in case of unintended release or misuse;
Proposed measures should also appear elsewhere in the dossier as appropriate, including the Summary of Product Characteristics, the labelling and the package insert.
2. Specific instructions or recommendations for storage and handling;
Proposed measures should also appear elsewhere in the dossier as appropriate, including the Summary of Product Characteristics, the labelling and the package insert.
3. Estimated production in and/or imports to the Community;
This information is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier.
4. Proposed packaging. This must be appropriate so as to avoid unintended release of the GMOs during storage, or at a later stage;
The information should be consistent with that provided in Parts I and II of the dossier.
5. Proposed labelling. This must include, at least in summarised form, the information referred to in A1, A2, A3, B1 and B2, above.
Proposed labelling and package insert particulars related to the environmental risk should also appear elsewhere in the dossier (i.e., Part I) as appropriate, should be consistent with the Summary of Product Characteristics and should comply with the requirements of Council Directive 81/852/EEC.

Part II-H-5. The environmental risk assessment resulting from the information provided under points II-H-1 to II-H-4 above.

The assessment of environmental risk should follow logically from the data presented in II-H-1 to II-H-4. Risks to human health, non-target animals, soil, water, air, individual ecosystems etc. should be addressed as appropriate. This section should be compiled in accordance with the Note for Guidance on the Conduct of the Environmental Risk Assessment for Veterinary Medicinal Products Containing or Consisting of GMOs .

Part II-H-6. Conclusion.

The Applicant should present his overall conclusions.

5. PRESENTATION OF PARTICULARS IN THE EXPERT REPORTS

Part II-H of the main documentation should be addressed in the Analytical (Chemical, Pharmaceutical and Biological or Microbiological) Expert Report and should include a critical evaluation, the opinion of the expert as to whether sufficient guarantees have been provided as to the suitability of the product for its proposed use, and an appendix containing a summary of all the important data. The entries should be compiled by the Expert in accordance with the general requirements for Expert Reports outlined in the Notice to Applicants. In particular, the Expert should be appropriately qualified.

B. GUIDELINE FOR THE CONDUCT OF THE ENVIRONMENTAL RISK ASSESSMENT FOR VETERINARY MEDICINAL PRODUCTS WHICH CONTAIN OR CONSIST OF GENETICALLY MODIFIED ORGANISMS

1. BACKGROUND AND INTRODUCTION

This guidance concerns the environmental risk assessment needed to comply with the requirements of Article 28(2) of Council Regulation 2309/93 on the licensing of veterinary medicinal products which contain or consist of Genetically Modified Organisms (GMOs). The Regulation makes provision for an environmental risk assessment similar to that in Directive 90/220/EEC on the Deliberate Release into the Environment of GMOs. In both this Directive and in the Regulation, the environmental risk assessment is derived from the technical dossier containing the information required under Annex II and III of the Directive. Under Council Regulation 2309/93 therefore, the environmental risk assessment should be a reasoned statement of the overall risk of damage to human health and to the environment from the proposed marketing of a veterinary medicinal product containing or consisting of a GMO.

There are no hard and fast rules for risk assessments. The following guidance outlines the generally accepted terminology for a risk assessment and includes some practical steps and a workable format to aid Applicants.

The level of detail to be considered in a risk assessment will depend on circumstances. It will be lower, for example, where it is immediately obvious that the hazards, and hence the consequent risks, are low or that the proposed control measures are clearly adequate to limit the contact of the product with humans and the environment.

2. SCOPE OF THE GUIDELINE (Types of products)

This guidance has been based largely on the considerations appropriate to what will probably be the most likely type of veterinary medicinal products containing or consisting of GMOs capable of replication or of transferring genetic material, namely: live viral, bacterial or parasitic vaccines, including vector vaccines.

3. ENVIRONMENTAL RISK ASSESSMENT

3.1 General considerations

For veterinary medicinal products it may be appropriate first to consider the risks to human health and to address whether it is necessary to take certain measures to control the risks arising from the administration and use of the product. The potential risks to the environment should then be assessed on the basis that those control measures are in place.

The main considerations for the risks to human health will be determined by whether or not the GMO is a zoonotic agent, or likely to be a zoonotic agent taking into account the characteristics of the parental organism, any organisms used as donors and the possibility of changes in host range, pathogenicity or tropism, as a result of the genetic modifications. The classification system for

pathogenicity of micro-organisms as set out in Council Directive 90/679/EEC, as amended, may provide a useful reference for these considerations.

To all intents and purposes, the human health part of the environmental risk assessment considers the risk to human health as if humans were a sub-set of the wider environment, or another non-target species. The human risk assessment must include consideration of the risk to those who handle or administer the product and or treated animals, risks to relatives and other contacts of these operators and risk to the general public. It will be necessary to consider the possible effects on healthy humans as well as to more vulnerable individuals (the young or old, immunocompromised, pregnant women or otherwise susceptible). For example, the increasing incidence of people who are receiving immunosuppressants, or have recently undergone chemotherapy, or who have developed AIDS may mean that there is a section of the population who are at greater risk and this needs to be taken into account at each stage of the risk assessment.

3.2 Sources of information

The risk assessment is intended to be an overall statement reflecting all the information contained in the dossier.

Although wherever possible the risk assessment should: be based on quantifiable outcomes, it is recognised that many of the judgements must necessarily be qualitative. Any statements or assertions in the assessment should, however, be supported by some evidence; quantitative where possible.

How much information is needed in any particular point will depend on its importance in the assessment and the extent to which it is generally accepted material. There is no need to spell out in great detail what is included elsewhere in the dossier or in textbooks or literature. However the logic of the argument should be clear and enough justification should be included on any unusual or particularly important points for the assessment to be testable. Note that it is always permissible to assume the worst and act accordingly if the cost of gathering the information (by experimentation or review) for a more precise assessment is disproportionate.

4. FRAMEWORK FOR RISK ASSESSMENT

The aim of the risk assessment is to identify hazards, to estimate the likelihood that the hazards will lead to actual harm and to take decisions regarding the appropriate control measures. The main elements of a risk assessment are therefore:

- (i) hazard identification;
- (ii) assessment of the likelihood that the hazard will occur;
- (iii) assessment of exposure to the hazard and the consequences of that exposure;
- (iv) assessment of the level of risk: (by consideration of the severity of any adverse consequences and the likelihood that they will occur);
- (v) selection and assignment of appropriate control measures (risk management).

4.1 Assessment of risk to humans

4.1.1. Hazard identification

In the context of this guidance, hazards are defined as those features of the GMO which have the potential to cause harm, either directly (such as infection) or through some form of possible event (such as the transfer of hazardous genes to and from other organisms). It is important to be exhaustive in the identification of possible hazards and not to discount at this stage any of the hazards given below

on the basis that they are unlikely to occur. The assessment of possible exposure and likelihood are separate stages of the assessment process.

This stage of the assessment should aim to identify all possible adverse effects on humans and should include the following:

4.1.1.a. Pathogenicity or other adverse effects

With respect to humans and animals, details of the pathogenicity of the parental organism and the GMO itself will have been considered during the safety studies on the product. When determining the hazards associated with the GMO, consideration should be given to the pathogenicity and virulence, any changes to the host range or tissue tropism and, if it is still potentially pathogenic, whether the GMO is susceptible to available therapies or is expected to exhibit altered interactions with host defence mechanisms. As well as the possibility of infection in healthy individuals, the possibility of infection in immunocompromised or other especially susceptible individuals should be identified.

4.1.1 b. Genetic instability (especially attenuating mutations)

Consider whether the GMO is stable over repeated generations and, in particular, whether any genetic instability could affect attenuating mutations or alter the behaviour of the GMO, particularly if it could result in a reversion to virulence. The type of attenuating mutation (point mutation or deletion) will be an important consideration in assessing the likelihood of the hazard occurring. Attention should be paid to those bacterial GMOs if potentially transferable vectors based on plasmids, bacteriophages or transposons have been used.

4.1.1.c. Gene transfer

Gene transfer may be considered a hazard under some circumstances, for example if it could result in the spread of genes to other organisms with potentially undesirable consequences. In some senses it can be considered as a subset of genetic stability.

4.1.1.d Survival /dissemination

The ability of the GMO to survive for long periods in the environment (for example in the litter of the poultry house or grazing pastures) may constitute a hazard under some circumstances, for example if it could mean that there is a greater likelihood of contact with individuals. This may be further compounded if survival offers an increased possibility of wide spread dissemination by water or other routes or by any arthropod or animal vectors.

4.1.2. Assessment of the degree of exposure and the likelihood of the hazard occurring

In order to determine the risk posed by the GMO it will be necessary to determine the likelihood of any of the above hazards occurring, i.e. whether people will be exposed to the hazard associated with a GMO and, if so, whether they would suffer an adverse effect.

4.1.2.a. Potential for exposure to the GMO in the product

At this stage, it will also be necessary to consider whether everyone exposed to the GMO would suffer an adverse effect or whether any adverse effect would occur in only a small proportion of exposed individuals. Infrequent adverse effects may be either due to a low probability of an effect occurring in any given individual or because a small proportion of the population is susceptible. The latter may

include immunocompromised individuals or those with a particular vaccination status or on an antibiotic regimen.

One important component of this factor is whether the wider environment (including other humans) comes into contact with the GMO in the product under normal circumstances (i.e. are exposed to the GMO). The degree of exposure of operators will have a bearing on the likelihood of a hazard occurring. When considering the degree of exposure of operators and their relatives and contacts and the general public to the product, the following matters should be taken into account;

(i) Type of packaging and procedures before and after administration

Most, if not all, veterinary medicinal products containing GMOs will be securely packaged on receipt and the packaging should allow any initial preparatory steps (e.g. reconstituting freeze-dried preparations) to be undertaken in a safe and aseptic manner. However, the proposed method of preparation and administration will have a bearing on the degree of exposure of operators to the GMOs and needs to be considered. For example, single dose preparations for administration to a companion animal in the surgery is likely to result in less exposure than mass medication of farm animals. It may be appropriate to consider who is likely to administer the product (veterinary surgeon or farmer) and the likelihood of any necessary instructions for safe use of products being achievable. It will also be necessary to consider whether or not unused product can be readily disposed of in a reliably safe manner.

(ii) Route of administration (parenteral vs. oral vs. ocular vs. spray)

It may be expected that there is more opportunity for exposure of the operator to the product organisms when the product is administered by spray, orally or ocularly, than by injection but the risks of self injection must be borne in mind.

(iii) Shedding of live product organisms (route, numbers, duration)

The extent to which the product organisms multiply in the host, can be excreted and spread will have been studied as part of the safety studies. Many products may well consist of attenuated or replication defective organisms and the likelihood of exposure will be less than that associated with the wild type, parental strain.

The overall degree of exposure of humans such as animal attendants should be indicated. It should be noted that high exposure does not necessarily mean high risk and conversely, that even 'low' exposure, but with severe consequences, may lead to an unacceptable risk.

It is recommended that the possibility of exposure and likelihood of hazards occurring is qualitatively judged as either 'negligible', 'low', 'moderate' or 'high'.

4.1.3. Assessment of level of risk

Having identified any hazards and assessed the degree and likelihood of exposure and the consequences of that exposure it is necessary to evaluate the risk associated with each hazard. Risk is generally held to be the product of exposure likelihood and consequence. It is inevitably always going to be difficult to 'multiply' qualitative statements such as 'high' and 'low', but Table 1 should help this process. The risk matrix is not definitive and there will always be some scope for flexible, case by case evaluation. In many cases, it will be necessary to decide between one of two outcomes and, as in the earlier parts of the process, some justification for the choice should be provided. In addition, a range

of risks may be apparent if more than one hazard is being evaluated. There will, therefore, be a need to make an overall assessment of the risk taking all factors into consideration.

Once an overall assessment of the risk associated with each hazard has been produced, it will be necessary to evaluate the significance of the risk. It is generally considered that any risk other than 'effectively zero' or 'low' is unacceptable without some consideration of measures and proposals to control the risks to human health.

4.1.4. Consequences of a hazard occurring

This stage of the assessment should consider, for each identified hazard, what is the result of the hazard occurring i.e. what effect it may have on an exposed individual or population. It is anticipated that the range of consequences will fall between those that are negligible and self limiting and those that would be severe, either having an immediate and serious effect or possibly leading to long term, harmful consequences.

It is suggested that the consequences of each hazard be indicated qualitatively as 'negligible', 'low', 'medium' or 'severe'. An adverse effect may be either immediate or delayed. Immediate and relatively trivial effects such as seroconversion in casual contacts may be extremely easy to identify but may not be particularly important. However, longer term and less obvious effects, such as oncogenicity or toxicity, will clearly be difficult to assess but extremely important.

The assessment of the consequences of a hazard occurring will need to consider the effects on individuals as well as the overall community. For each hazard it may be necessary to split the considerations into the 'worst case' and the 'normal case'. During the overall assessment of the level of risk, such differences should then be weighed up in arriving at the final risk assessment. For example, the consequences to rare individuals may be judged to be 'serious'. However, because such individuals do not form a large part of the community (and therefore the likelihood of the hazard occurring is low), the risk associated with the particular hazard may be acceptable.

4.1.5. Control of risk

This stage of the risk assessment will require some consideration of the particular aspect of the assessment which leads to an unacceptable level of risk. For example, if it were caused by a lack of detailed knowledge on a particular hazard then it might be necessary to acquire further information, either by experimentation or from published literature. Alternatively, it could be that changes to the instructions for use or to any recommended precautions would reduce the level of exposure to staff or other people. In any case, personnel, such as those administering the product and those handling the animals at the time, will be subject to worker protection legislation such as the Biological Agents Directive (90/679/EEC as amended by 93/88/EEC), requiring, amongst other things, risk assessment and appropriate control measures.

4.2 Assessment of the risks to the environment

Having decided on the controls (if any) that are appropriate in order to minimise the risks to humans, it is necessary to evaluate whether there could be any adverse effect on the environment resulting from the use of the product. The characteristics of the GMO need to be considered, particularly its host range and pathogenicity. Account must be taken of the characteristics of the parental organism, any organisms used as donors and the possibility of changes to host range, pathogenicity or tropism as a result of the genetic modifications.

The objective of the environmental part of the risk assessment is to determine the probability of adverse consequences or 'harm' to the environment. Harm results if hazards are realised. The steps are, in principle, as for the human health part of the risk assessment, but the particular considerations are of course different.

4.2.1. Hazard identification

The starting point for risk assessment is to identify the characteristics of the GMO which are a hazard because they have the potential to cause harm in the receiving environment. Appropriate information about the recipient or parental organism and the donors, as well as information about the GMO itself, should be considered.

4.2.1.a. Capacity to transmit to non-target species

The specificity of the host range is very important for veterinary products. Any likely changes as a result of the genetic modification should be taken into account.

4.2.1.b. Shedding of live product organisms (route, numbers, duration)

The extent to which the product organisms multiply in the host, can be excreted and spread will have been studied as part of the safety studies. Many products may well consist of attenuated or replication defective organisms and the likelihood of exposure will be less than that associated with the wild type, parental strain. However, the potential for organisms passaged from animal to animal to become less attenuated must be taken into consideration.

4.2.1.c. Capacity to survive, establish and disseminate

This is also a key consideration if an organism is not capable of surviving, for example because of multiple disablement, as other hazards are then likely to be minimised. The risk assessment could be completed at this stage if the risks to the environment are low or effectively zero. However, if it is likely that the organism could survive for a sufficiently long period for it to cause harm, and possibly establish and disseminate in the environment, then not only this hazard but also other hazardous characteristics need to be considered.

4.2.1.d. Potential for gene transfer

Although most organisms have the ability to transfer genes, some do not. Consider, in particular, the extent to which the method of modification might increase the potential for transfer as, for example, in the case of non-integrating viral vectors.

4.2.1.e. Products of expression of inserted sequences

Identify all products of gene expression that could cause harm, bearing in mind that an inserted gene might code for a product that is toxic, or otherwise detrimental, to other organisms. Consider the extent to which those products could have an effect on other organisms.

4.2.1.f. Phenotypic and genotypic stability

Consider whether genes inserted into the GMO on extra-chromosomal elements might be transferred more readily and the extent to which genotypic instability might lead to phenotypic instability.

4.2.1.g. Pathogenicity to other organisms

The pathogenic properties of many organisms used as recipient or parental organisms are well documented and these should be identified, if appropriate. Consider whether a change in host range could occur as a result of the genetic modification which has been undertaken.

4.2.1.h. Potential for other effects

Consider whether the GMO might have the potential to exert other effects such as the transmission and replication of viruses in other organisms as a result of trans-capsidation and the effects of recombination.

4.2.2. Assessment of likelihood

The next step is to estimate the likelihood (probability and frequency) of hazard(s) being manifested. A key factor in determining this is the potential receiving environment. This includes the wider as well as the local environment in which the product is intended, or likely, to be used.

Particular characteristics of the local environment that could contribute to manifestation of the hazard should be identified and assessed. Climatic, geographical and soil conditions, demographic considerations, the types of flora and fauna in the potential receiving environment are some of the important ones.

Consideration should be given to any potential exposure of the living and non-living environment to the GMOs and the magnitude and duration of such exposure. When estimating probabilities and frequencies, consideration should include the number of organisms that might reach the environment since the probability that a hazard will be realised will often be influenced by the number of viable organisms in the environment due, for example, to excretion. For the hazard 'survival capacity', therefore, it is appropriate to assess the proportion of the GMOs that are likely to survive. In the case of the likelihood of gene transfer, the probable number of such events or the extent to which transfer will occur should be considered. If the GMO has pathogenic characteristics, assess the proportion of target organisms in the environment likely to be affected, including taking into consideration, the likelihood of the GMO to spread to, or reach, these organisms.

The mode of administration might have an impact on the likelihood that hazard(s) will be manifested. For example, spray or other forms of mass administration are more likely to lead to the introduction of the GMO into the environment than if given by injection. Likelihood should be expressed as 'high', 'medium', 'low' or 'negligible'.

4.2.3. Assessment of level of risk

Having judged the magnitude of harm if the hazard were to be realised, and the likelihood or frequency of such harm being caused, the level of risk is assessed by considering the combined effect of these two components.

This should be carried out for each of the hazards identified. The matrix in Table 1 used for the human health part of the risk assessment can be used again to come to an evaluation of the environmental risk for each environmental hazard.

4.2.4. Assessment of the consequence

For each hazard of the GMO identified, whenever it is possible or probable that the GMO in the product will reach the environment, it must be considered whether that environment would cause or allow the hazard to be realised. Thus again, the characteristics of the potential receiving environment need to be considered.

An assessment of the magnitude of harm is based on the assumption that the hazard will be realised. Inevitably there will be a degree of judgement in making the assessment, but the consequences should be described as 'severe', 'medium', 'low', or 'negligible'. A 'severe' consequence might be a major change in the numbers of one or more species leading to negative effects on the functioning of the ecosystem and/or other connected ecosystems. It is unlikely that the changes would be reversible. A 'low' consequence might be if any change in population densities is such that it has no negative effects on ecosystem function and no impact on endangered or beneficial species.

The above illustrations reflect the potential effect of the GMO on populations. In some cases, however, it may be more appropriate to consider the likely effects on individual organisms; for example endangered mammals. In most cases it should be possible to use the guidelines to assess in qualitative terms the degree of harm which a particular GMO might cause.

4.2.5.: Selection and assignment of appropriate control measures (risk management)

If the environmental risks are not as low as reasonably practicable, the process of risk assessment in relation to that hazard should be repeated to ascertain whether the application of additional management techniques could reduce the level of risk. Consideration might be given, for example, to limiting the proposed routes of administration to those likely to lead to a lower level of risk.

5. SUGGESTED FORMAT FOR PRESENTATION OF THE CONCLUSIONS OF THE RISK ASSESSMENT

Applicants may find the following structure useful to record their risk assessment.

1. Summary

Summary of the overall risk of damage to the environment (including human health) from the proposed marketing of the GMOs forming the subject of the application.

2. Assessment of risk to humans

- 2.1. Hazard identification: Hazardous characteristics of the GMO that could, in certain circumstances, lead to harm in humans:
 - a. Pathogenicity or other adverse effects
 - b. Genetic instability (especially attenuating mutations)
 - c. Gene transfer
 - d. Survival/dissemination
- 2.2. Assessment of the degree of exposure and the likelihood of each hazard occurring
- 2.3. Assessment of level of risk
- 2.4. Consequences of a hazard occurring

2.5. Assessment of the overall risk of harm to humans (the total risk after consideration of the risk of each of the hazards occurring): High, medium, low, effectively zero.

3. Assessment of the risk to the environment

3.1. Hazard identification. Hazardous characteristics of the GMO that could, in certain circumstances, lead to harm to the environment

- a. Capacity to transmit to non-target species
- b. Shedding of live product organisms (route, numbers, duration)
- c. Capacity to survive, establish and disseminate
- d. Potential for gene transfer
- e. Products of expression of inserted sequences
- f. Phenotypic and genotypic stability
- g. Pathogenicity to other organisms
- h. Potential for other effects

3.2. Assessment of likelihood

3.3. Assessment of level of risk

3.4. Assessment of the consequence

3.5. Assessment of the overall risk to the environment (the total risk after consideration of the risk of each of the hazards occurring): high, medium, low, effectively zero.

4. Assessment of the overall risk

Assessment of the overall risk to humans and the environment (from Points 2.5 and 3.5 above).

Table 1

ESTIMATION OF RISK

Consequence of hazard	Likelihood of Hazard			
	High	Moderate	Low	Negligible
Severe	High	High	Medium	Effectively Zero
Medium	High	High	Medium/Low	Effectively Zero
Low	Medium/Low	Low	Low	Effectively Zero
Negligible	Effectively Zero	Effectively Zero	Effectively Zero	Effectively Zero

This matrix is not intended to be definitive, but illustrative of the way in which an estimate of risk might be obtained from the consequence and likelihood that a hazard will be realised. Different components may be differently weighted, however, depending on the knowledge and experience of the GMO and operation involved.

C. GUIDANCE ON THE INTEGRATION OF THE EVALUATION OF THE ENVIRONMENTAL RISK ASSESSMENT WITH THE EVALUATION OF THE REST OF THE APPLICATION FOR MARKETING AUTHORISATION FOR A MEDICINAL PRODUCT CONSISTING OF OR CONTAINING LIVE GENETICALLY MODIFIED ORGANISMS

1. INTRODUCTION

The particulars and documents required in support of an application for a marketing authorisation for such a medicinal product will include an environmental risk assessment and related information, in accordance with Article 28.2 of Council Regulation (EEC) No. 2309/93.

The authorisation procedure, which is laid down in the Regulation, is mandatory for such medicinal products containing live GMOs, since they fall within the scope of Part A of the Annex.

The key principles in the evaluation procedure of a medicinal product containing a live GMO are as follows:

2. APPLICATION DOSSIER

The application is submitted to the EMEA in accordance with the current version of the Standard Operating Procedure (SOP) on the SUBMISSION OF AN APPLICATION FOR THE GRANTING OF A COMMUNITY MARKETING AUTHORISATION.

In the case of a medicinal product consisting of, or containing, a live GMO, the dossier will include (Article 28.2 of the Council Regulation (EEC) No. 2309/93):

- a copy of written consents issued by the competent authorities to the deliberate release of GMOs for research and development purposes
- the results of any investigations performed for the purposes of research and development
- the complete technical dossier supplying the information as set out in Annexes IIA and III of Council Directive 90/220/EEC,
- the environmental risk assessment resulting from this information.

3. PRESUBMISSION

An Applicant may seek advice from the Agency within its Committees on the conduct of the various tests and trials necessary to demonstrate the quality, safety and efficacy of medicinal products. Usually the Committee concerned will appoint one of its members to co-ordinate the advice to be given. Advice may also be sought on the fulfilment of the requirements of Article 28.2 of Council Regulation N° (EEC) 2309/93. Applicants may seek advice on applications prior to submission. *See appropriate section in the Notice to Applicants on advising Applicants on the conduct of various tests and trials necessary to demonstrate the quality, safety and efficacy of: medicinal products. (Article 51 of the Regulation).*

See also SOPs EMEA/CVMP/036/97- REVISION and EMEA/CVMP/036/97- REVISION

4. EVALUATION

During the evaluation the Rapporteur shall hold the necessary consultations in a timely manner with the bodies set up in accordance with Council Directive 90/220/EEC. The conclusions and results of any consultation will be included in the Rapporteur's assessment report, including requests for clarification or further information.

The CVMP will give its opinion within 210 days of the receipt of a valid application. The opinion shall respect the environmental safety requirements resulting from the risk assessment on the basis of Council Directive 90/220/EEC to ensure that appropriate measures are taken to avoid the adverse effects on human health and the environment which might arise from the deliberate release or placing on the market of a medicinal product containing live GMOs.

In order to provide its Opinion, the CVMP shall carry out the evaluation according to the following timetable:

Day 1

Once the application has been validated, the EMEA Secretariat will send a copy of the timetable to the CVMP Chairman and Members, the Applicant and the Competent Authorities under Council Directive 90/220/EEC. These Competent Authorities will be given the opportunity to request Part II.H of the application dossier from the Applicant. This request will be channelled via the EMEA Secretariat and a deadline for requests of copies will be set in order to facilitate the copying of large volumes of documentation by the Applicant.

Day 1 – 70

The risk assessment submitted with the application will be considered in conjunction with the assessment of quality, safety and efficacy according to the requirements laid down in the Annex to Council Directive 81/852/EEC, as amended, and will be assessed by the Rapporteur, Co-Rapporteur or their Experts. Copies of the Rapporteur's assessment on *this part* of the application will be sent to the Competent Authorities under Council Directive 90/220/EEC by the Secretariat (on Day 70).

Day 70 –90

The Competent Authorities under Council Directive 90/220/EEC will be asked to provide any questions they may have on the dossier or assessment by Day 90 to the Rapporteur or such person designated by the Rapporteur, with a copy of any questions to the EMEA Secretariat.

Day 90 – 119

The Rapporteur, or such person designated by the Rapporteur, will decide on the inclusion, or not, of any questions from the Competent Authorities under Council Directive 90/220/EEC in the draft CVMP List of Questions. The questions submitted by these Competent Authorities will be tabled and discussed at the Rapporteur's meeting to be held on Day 119.

Day 120

Once the CVMP List of Questions has been adopted, the EMEA Secretariat will extract from the List of Questions those questions raised on Part II.H of the application. This extract will be forwarded to the Competent Authorities under Council Directive 90/220/EEC by the Secretariat.

Day 150

The section of the joint Rapporteur/Co-Rapporteur assessment report on the Applicant's answers to questions on Part II.H of the dossier will be forwarded to the Competent Authorities under Council Directive 90/220/EEC by the Secretariat.

Day 180

Should the clock be stopped and the Applicant invited to attend an oral explanation, the Competent Authorities under Council Directive 90/220/EEC will be informed of any issues on Part II.H of the dossier that are to be further clarified.

The outcome of the oral explanation will be communicated to the Competent Authorities under Council Directive 90/220/EEC where this is appropriate.

Day 210

The final conclusion, however, remains with the Committee, which, having assessed the quality, safety and efficacy data provided by the Applicant in support of the product, shall discuss the risk versus the benefit of the use of the product and shall recommend or not the granting of a Community Marketing Authorisation.
