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NOTICE TO APPLICANTS VETERINARY MEDICINAL PRODUCTS

GUIDANCE ON ENVIRONMENTAL RISK ASSESSMENT FOR VETERINARY MEDICINAL PRODUCTS CONSISTING OF OR CONTAINING GENETICALLY MODIFIED ORGANISMS (GMOs) AS OR IN PRODUCTS

MARCH 2006

This updated guidance combines the three existing guidelines as recorded in Volume 6B "Annex I – Guidance for environmental risk assessment for GMOs" (p. 168-189) for clarity in addition to changes further to consultation of the competent authorities being responsible for Directive 2001/18/EC¹ on the deliberate release into the environment of genetically modified organisms. There are few changes to the existing guidance: the aim being to create easier-to-follow guidance but not to change any data requirements. This update includes reference to Regulation (EC) No. 726/2004.

This guidance will be included in The Rules governing Medicinal Products in the European Community - The Notice to Applicants Volume 6C Regulatory Guidelines

¹ Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EC

**GUIDANCE ON ENVIRONMENTAL RISK ASSESSMENT FOR VETERINARY
MEDICINAL PRODUCTS CONSISTING OF OR CONTAINING GENETICALLY
MODIFIED ORGANISMS (GMOs) as or in products**

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GUIDANCE ON ENVIRONMENTAL RISK ASSESSMENT FOR VETERINARY MEDICINAL PRODUCTS CONSISTING OF OR CONTAINING GENETICALLY MODIFIED ORGANISMS as or in products

INTRODUCTION

This Chapter contains guidance relating to the environmental risk assessment which must accompany applications for marketing authorisation of veterinary medicinal products which consist of or contain Genetically Modified Organisms (GMOs) within the meaning of Directive 2001/18/EC of the European Parliament and of the Council² (see Article 31(2) of Regulation (EC) no. 726/2004 of the European Parliament and of the Council.).

This guidance should be read in conjunction with the current version of the EMEA Standard Operating Procedure EMEA/V/SOP/4012 where information is provided 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 veterinary medicinal product consisting of or containing live Genetically Modified Organisms.

This guidance describes the format 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.

Directive 2001/18/EC of the European Parliament and of the Council³ 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 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 IIIA 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 II 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 31(2) of Regulation (EC) no. 726/2004

² 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

of the European Parliament and of the Council laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.

- 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:
- as these requirements provide for a specific environmental risk assessment in accordance with the principles laid down in Annex II to Directive 2001/18/EC , 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 Directive 2001/18/EC .

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, with the exception of human beings, 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 for which no specific containment measures are used to limit their contact with and to provide a high level of safety for the general population and the environment.

Risks relating to the use of the product (according to Directive 2001/82/EC): any risk relating to the quality, safety and efficacy of the veterinary medicinal product as regards animal and human health; any risk of undesirable effects on the environment.

Risk/benefit balance: An evaluation of the positive therapeutic effects of the veterinary medicinal product in relation to the risks defined above.

Environmental Risk Assessment: the evaluation of risks to human health and the environment (which includes plants and animals), whether direct or indirect, immediate or delayed, which the deliberate release or the placing on the market of GMOs may pose and carried out in accordance with the principles of Annex II of Directive 2001/8/EC.

3. GENERAL CONSIDERATIONS

3.1 It is essential that the approach to the environmental risk assessment presented by the Applicant is in accordance with that laid down in Directive 2001/18/EC, including the relevant parts of Annexes II and IIIA of the Directive. Headings in Annex IIIA 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 Union*, 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.

4. PRESENTATION OF DATA

The information presented in accordance with this Note for Guidance forms **Part II-H** of the dossier. The entries should be presented in five sections, Part II-H 1 to 5 as follows.

It is important to note that Part II-H of the dossier should be a stand-alone section of the dossier, bound in one or more separate volumes.

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 describing the characteristics of the vaccine and its components;
- a description of, and justification for, the proposed release &
- a copy of the proposed Summary of Product Characteristics

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 2001/18/EC

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 required under Annexes III A and IV of Directive 2001/18/EC, including the results of any investigations performed for the purposes of research and development.

The following points, which are extracts of Annex IIIA and Annex IV of Directive 2001/18/EC, are those which are normally relevant to placing a veterinary medicinal product on the market. 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.

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.

INFORMATION REQUIRED UNDER ANNEX IIIA OF DIRECTIVE 2001/18/EC

I. General Information.

A. Name and address of the notifier (company or institute)

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

B. Name, qualifications and experience of the responsible scientist(s)

C. Title of the project

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;
2. Taxonomy;
3. Other names (usual name, strain, name, etc.);
4. Phenotypic and genotypic markers;
5. Degree of relation between donor and recipient or between parental organisms;
6. Description of identification and detection techniques.
7. Sensitivity, reliability (in quantitative terms) and specificity of detection and identification techniques;
8. Description of the geographic distribution and of the natural habitat of the organism including information on symbionts and hosts;

9. Organisms with which transfer of genetic material is known to occur under natural conditions

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

11. Pathological, ecological and physiological traits:

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

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

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

(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;

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

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

12. Nature of indigenous vectors:

(a) Sequence;

(b) Frequency of mobilisation;

(c) Specificity;

(d) Presence of genes which confer resistance;

13. History of previous genetic modifications.

B. Characteristics of the vector:

1. Nature and source of the vector;

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;

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

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

C. Characteristics of the modified organism:

1. Information related to the genetic modification;

(a) Methods used for the modification,

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

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

(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;

(e) methods and criteria used for selection;

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

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;

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

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

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

(e) Activity of the expressed proteins;

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

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

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

3. Considerations for human health and animal health, as well as plant health.

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

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

(iii) Capacity for colonisation;

(iv) 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.

(v) other product hazards.

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.
2. foreseen dates of the release and time planning of the experiment including frequency and duration of releases,
3. preparation of the site previous to the release,
4. size of the site,
5. method(s) to be used for the release.
6. Quantities of GMOs to be released.
(The quantities of GMO to be administered per dose should be stated.
7. disturbance on the site (type and method of cultivation, mining, irrigation, or other activities),
8. worker protection measures taken during the release,
9. post-release treatment of the site,
10. techniques foreseen for elimination or inactivation of the GMOs at the end of the experiment,
11. Information on, and results of, previous releases of the GMOs, especially at different scales and in different ecosystems.

This information is largely required to specifically fulfil the requirements of the environmental risk assessment for example the results of the release should include the consequences of any shedding of the virus.

B) Information on the environment (both on the site and in the wider environment)

1. geographical location and grid reference of the site(s) (in case of notifications under part C the site(s) of release will be the foreseen areas of use of the product),
2. physical or biological proximity to humans and other significant biota,
3. proximity to significant biotopes, protected areas, or drinking water supplies,
4. climatic characteristics of the region(s) likely to be affected,
5. geographical, geological and pedological characteristics,
6. flora and fauna, including crops, livestock and migratory species,
7. description of target and non-target ecosystems likely to be affected,
8. a comparison of the natural habitat of the recipient organism with the proposed site(s) of release,

9. any known planned developments or changes in land use in the region which could influence the environmental impact of the release.

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;
2. Known or predicted environmental conditions which may affect survival, multiplication and dissemination (wind, water, soil, temperature, pH etc.);
3. Sensitivity to specific agents.

B. Interactions with the environment:

1. Predicted habitat of the GMOs;
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;
3. Genetic transfer capability:
 - (a) Post-release transfer of genetic material from GMOs into organisms in affected ecosystems;
 - (b) Post-release transfer of genetic material from indigenous organisms to the GMOs;
4. Likelihood of post-release selection leading to the expression of unexpected and/or undesirable traits in the modified organism;
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.;
7. Description of ecosystems to which the GMOs could be disseminated;
8. Potential for excessive population increase in the environment;
9. Competitive advantage of the GMOs in relation to the unmodified recipient or parental organism(s);
10. Identification and description of the target organisms if applicable;
11. Anticipated mechanism and result of interaction between the released GMOs and the target organism if applicable.;

12. Identification and description of non-target organisms which may be adversely affected by the release of the GMO, and the anticipated mechanism of any identified adverse reactions.
13. Likelihood of post-release shifts in biological interactions or in host range;
14. Known or predicted effects on non-target organisms in the environment, impact on population levels of competitors, hosts, symbionts and pathogens;
15. Known or predicted involvement in biogeochemical processes;
16. Other potential interactions with the environment.

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;
- 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;
3. Techniques for detecting transfer of the donated genetic material to other organisms.
4. Duration and frequency of monitoring

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;
2. Methods and procedures to protect the site from intrusion by unauthorised individuals,
3. Methods and procedures to prevent other organisms from entering the site.

C. Waste treatment:

1. Type of waste generated;
2. Expected amount of waste;
3. Description of treatment envisaged;

D. Emergency response plans:

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

This is likely to be particularly 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 is likely to be particularly relevant in the case of vaccines disseminated as a baited formulation in an open environment.

3. Methods for disposal or sanitation of affected by the spread,
4. Methods for the isolation of the areas affected by the spread,
5. Plans for protecting human health and the environment in case of the occurrence of an undesirable effect.

OTHER RELEVANT INFORMATION REQUIRED (including information required under ANNEX IV OF DIRECTIVE 2001/18/EC)

- Proposed commercial name of the product and of the GMO contained therein and any specific identification, name or code used by the applicant to identify the GMO.
- Name and full address of the person established in the European Economic Area who is responsible for the placing on the market.
- Description of the geographical areas and types of environment where the product is intended to be used within the EEA, including, where possible, the estimated scale of use in each area.
- Intended categories of users of the product (veterinary surgeons only)
- Recommendations for measures to take in case of unintended release or misuse by the user
- Specific instructions recommendations for storage and handling.
- The draft Summary of Product Characteristics (SPC), labelling and package insert (Annex I, II, IIIA and IIIB in accordance with the English-language version of the current EMEA template.

Part II-H-4. The environmental risk assessment resulting from the information provided under points II-H-1 to II-H-3 above and in accordance with the principles of Annex II of Directive 2001/18/EC.

The assessment of environmental risk should follow logically from the data presented in II-H-1 to II-H-3. Risks to human health, non-target animals, soil, water, air, individual ecosystems etc. should be addressed as appropriate.

This guidance concerns the environmental risk assessment needed to comply with the requirements of Article 31(2) of Regulation (EC) no. 726/2004 of the European Parliament and of the Council for veterinary products which contain or consist of Genetically Modified Organisms (GMOs). The Regulation makes provision for an environmental risk assessment similar to that in Directive 2001/18/EC 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 Article 31(2) of Regulation (EC) no. 726/2004 of the European Parliament and of the Council 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.

According to Directive 2001/82/EC, the risk for undesirable effects on the environment is to be included in the overall risk benefit evaluation of the product.

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. Further information on environmental risk assessment may also be found in Commission Decision 2002/623/EC establishing guidance notes supplementing Annex II of Directive 2001/18/EC.

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.

Direct, Indirect, Immediate and Delayed Effects as defined in Annex II of Directive 2001/18/EC should be considered.

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.

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 Annex III to [Directive 2000/54/EC](#) of the European Parliament and of the Council 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.

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.

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).

SUGGESTED FORMAT FOR PRESENTATION OF THE CONCLUSIONS OF THE RISK ASSESSMENT

Applicants may find the following structure useful to record their risk assessment. Further details on aspects to be considered are given after the proposed format.

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

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

3.6 Selection and assignement of appropriate control measures (risk managment strategy)

4. Assessment of the overall risk

Assessment of the overall risk to humans and the environment and consideration of specific provisions seeking to limit it (from Points 2.5 and 3.5 above).

2. Assessment of risk to humans

2.1 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:

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.

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.

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.

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.

2.2 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.

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 ("high") 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'.

2.3 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.

2.4 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', 'moderate' or 'high'. 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.

2.5 Assessment of overall risk of harm to humans

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 Directive 2000/54/EC on the Protection of Workers from risks related to exposure to biological agents at work, requiring, amongst other things, risk assessment and appropriate control measures.

Suggestions seeking to limit the occurrence of an unacceptable risk should be discussed.

3. 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.

3.1 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.

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.

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.

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.

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.

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.

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.

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.

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.

3.2 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', 'moderate', 'low' or 'negligible'.

3.3 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.

3.4 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', 'moderate', '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.

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.

3.6 Selection and assignment of appropriate control measures (risk management strategy)

The most fundamental approach to minimising risks is for potential hazards of GMOs to be taken into consideration during product design and developmental stages.

A set of effective risk management strategies should be proposed for product on a case by case basis.

Suggestions seeking to limit the occurrence of an unacceptable risk should be discussed.

Table 1

ESTIMATION OF RISK

Consequence of hazard	Likelihood of Hazard			
	High	Moderate	Low	Negligible
Severe	High	High	Moderate	Negligible
Moderate	High	High	Moderate/Low	Negligible
Low	Moderate/Low	Low	Low	Negligible
Negligible	Negligible	Negligible	Negligible	Negligible

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.

Part II-H-5. Conclusion.

The Applicant should present his overall conclusions.

5. PRESENTATION OF PARTICULARS IN THE EXPERT REPORTS

Part II-H of the main documentation should also 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.

The Expert Report on Part II.H should also be included in the stand-alone Part II.H itself in addition to being provided in Part IC of the dossier.
