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Evaluation of Medicines for Human Use

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**COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
(CHMP)**

**ENVIRONMENTAL RISK ASSESSMENTS FOR MEDICINAL
PRODUCTS CONTAINING, OR CONSISTING OF, GENETICALLY
MODIFIED ORGANISMS (GMOs) (Module 1.6.2)**

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1. SCOPE OF THIS CHAPTER

The application of the Centralised procedure to Marketing Authorisation (MA) applications for medicinal products consisting of or containing GMO(s) (GMO(s) as or in medicinal products) constitutes the scope of this Chapter. Proposals for using GMOs in clinical trials fall outside the scope.

Specifically, the guidance presented outlines both the procedural issues affecting applications for MA for these products and the information related to the Environmental Risk Assessment (ERA) which should be included in the applications.

2. LEGAL BASIS

2.1. EU environmental legislation

Directive 2001/18/EC¹ requires that an applicant for placing any GMO on the market as or in a product shall normally submit a Part C notification, including relevant administrative and scientific information, an ERA, a summary, and, if necessary, information on proposed monitoring and risk management strategies, to the designated Competent Authority (CA) of the member state in the territory of which the site intended for placing the GMO(s) on the market for the first time is located. In accordance with a procedure which allows the involvement of the designated GMO CA of each member state and of the European Commission, the notification is examined for compliance with the requirements of the Directive.

2.2. EU pharmaceutical legislation

European pharmaceutical legislation, in the form of Regulation (EC) 726/2004², requires that an applicant for an MA for a biotechnological medicinal product shall submit to the European Medicines Agency a dossier which includes all the necessary administrative, quality, non-clinical and clinical data for the medicinal product. These data are assessed in accordance with the Centralised procedure.

The active principles of several biotechnological medicinal products are proteins manufactured using recombinant micro- or macro-organisms or cell cultures. However, in most cases the recombinant systems are not themselves components of the finished medicinal product, and as a consequence these medicinal products neither consist of nor contain a GMO.

2.3. The EU environmental/pharmaceutical legislative interaction for GMOs

Exceptionally, human biotechnological medicinal products may consist of or, more likely, contain, a GMO. These products constitute a special regulatory case by virtue of their registration being governed by reciprocal provisions in the above-mentioned Directive 2001/18/EC (Article 12.2) and Regulation (EC) 726/2004 (Articles 6.2 and 6.3).

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.

² Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use, and establishing a European Medicines Agency.

These provisions require the environmental impact documentation, including the ERA, to be submitted as part of the medicinal product MA application, and to be assessed as part of the medicinal product Centralised procedure defined in the Regulation.

The ERA is required to be carried out in accordance with the principles set out in Annex II to Directive 2001/18/EC and its supplementing Commission Decision 2002/623/EC³, and on the basis of the type of information specified in Annexes III and IV to the Directive. This requirement of the Directive is stated to apply without prejudice to other relevant requirements as regards risk assessment, risk management, labelling, monitoring as appropriate, information to the public, and safeguard clauses provided by community legislation concerning medicinal products for human use (Article 12.2 of the Directive).

The general requirement of Directive 2001/18/EC for applicants to submit a notification, including a technical dossier, to the designated GMO CAs is waived in such cases. However, there is a requirement for the CHMP Rapporteur for the application to hold necessary consultations with these bodies and with the European Commission on the GMO-ERA aspects of the procedure.

3. DEFINITIONS

The definition of a GMO appears in Directive 2001/18/EC. In particular, an organism is defined as a biological entity capable of replication or of transmitting genetic material, and a GMO is defined as 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. These definitions are extensively expanded upon in the body of the Directive and in its Annex I.

In the context of the scope of this Chapter, effects on the environment should be understood to mean effects exerted on any living or non-living human or non-human inhabitant, component or compartment of the global ecosystem, with the exception of those effects exerted on the intended patient as a direct result of the administration of the product.

³ Commission Decision 2002/623/EC of 24 July 2002 establishing guidance notes supplementing Annex II to 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.

4. PROCEDURES FOR THE EVALUATION OF THE ERA AND ITS INTEGRATION INTO THE CENTRALISED PROCEDURE

4.1. Pre-submission activities

In view of the procedural and scientific complexities associated with the ERA evaluation, it is recommended that prospective applicants request pre-submission meetings with the EMEA six months to one year in advance of submission of the application.

Applicants may also find it useful to apply for scientific advice or protocol assistance during the development of their medicinal products. For any scientific advice questions relating to the ERA, the necessary consultations will be held with the designated GMO CAs.

4.2. Presentation of the GMO/ERA data in the MA application dossier

The practical implementation of the application/assessment process begins with the presentation of the GMO environmental data in Module 1.6.2 of MA application dossiers submitted in the EU. It should be noted that this module section should be bound separately from the remainder of the dossier, and that there is no provision for a summary to be included in Module 2 of the dossier.

4.3. ERA consultation with bodies established under Directive 2001/18/EC

The CHMP Rapporteur for the application will include in the assessment team an appropriately qualified assessor for the Module 1.6.2 data. The options include an expert connected with a research institution, an expert connected with a Directive 2001/18/EC Article 4.4 CA, such as the lead consulted Directive 2001/18/EC CA mentioned in the next paragraph, or an MA application assessor from a medicinal product agency, who may possibly be also involved with the assessment of other parts of the dossier.

To expedite the progress of the consultation with those bodies established by the European Commission under Directive 2001/18/EC, and with the national GMO CAs designated by the member states for the purpose of implementing the Directive, the CHMP Rapporteur for the MA application may consider appointing one of the latter category to act as lead consulted CA. This lead consulted CA would act as the Rapporteur's contact point in the consultation, and would liaise as necessary with its fellow GMO CAs on the review/assessment of the Module 1.6.2 documentation forwarded to it by the Rapporteur.

4.4. Sharing the ERAs with CHMP working groups

The CHMP Biotechnology Working Party (BWP) has a major role in the assessment of the Module 3 (Quality) data for all biotechnological medicinal products. Since the GMO ERA data are expected to overlap to a substantial extent with the data presented in Module 3 of the MA application, and to influence the content of the final product information (Summary of Product Characteristics, labelling and Package Leaflet) for the medicinal product, it is considered important that the ERA assessment is shared with the BWP to ensure coherence with its consideration of the Module 3 data.

4.5. Centralised procedure steps integrating the evaluation of the ERA

Table 1 outlines a detailed paradigm for the necessary consultations with the GMO CAs and for ensuring coherence of the ERA assessment with the evaluation of the rest of the dossier.

Table 1. Details of the integration of the evaluation of the ERA into the Centralised procedure timetable for new product applications.

Step	Action
Before start of the procedure	<ul style="list-style-type: none">The Rapporteur selects the lead consulted Directive 2001/18/EC CA, and advises it of the pending procedure.
Day 1	<ul style="list-style-type: none">The EMEA informs the lead consulted CA and the Commission of the start of the procedure.
By day 10	<ul style="list-style-type: none">The applicant provides the requested copies of M1.6.2 to the GMO CAs.
By Day 70	<ul style="list-style-type: none">The lead consulted CA / ERA assessor sends its assessment report (AR) on M1.6.2 to all GMO CAs and to the Rapporteur.The Rapporteur compiles the Day 70 AR, including the assessment report on M1.6.2, and sends it to the EMEA and all CHMP members.
Day 70-120	<ul style="list-style-type: none">The EMEA schedules a BWP discussion on the Day 70 AR.If appropriate, the assessor for the M1.6.2 part of the dossier is invited to be present at the BWP discussion.
Day 100	<ul style="list-style-type: none">The CHMP members send comments on the Day 70 AR to the EMEA and other CHMP members.The GMO CAs send comments on the M1.6.2 part of the Day 70 AR to the lead consulted CA which forwards them to the Rapporteur.
Day 115	<ul style="list-style-type: none">The Rapporteur sends the draft LOQ and recommendations, taking into account any comments received from the lead consulted CA, to the EMEA and to all CHMP members.

Table 1. Details of the integration of the evaluation of the ERA into the Centralised procedure timetable for new product applications.

Step	Action
Day 120	<ul style="list-style-type: none"> • LOQ is adopted by CHMP. • LOQ is sent to the applicant by EMEA. • The Rapporteur sends parts of LOQ and recommendations referring to M1.6.2 assessment (if any) to lead consulted CA for information. • The Rapporteur informs the lead consulted CA of the clock stop if any M1.6.2 issues are incorporated in the LOQ. • <i>If, on the other hand, there are no outstanding M1.6.2 issues, then the Rapporteur informs the lead consulted CA of the fact, and of the termination at this point of its involvement with the assessment process.</i>
Day 121	<ul style="list-style-type: none"> • If any M1.6.2 issues were incorporated in the LOQ, the EMEA informs the lead consulted CA of clock restart; the applicant shall send copies of their responses to M1.6.2 issues according to the requirements of the GMO CAs specified at the beginning of the procedure, in addition to those sent to the Rapporteur.
By day 150	<ul style="list-style-type: none"> • The lead consulted CA / ERA assessor sends its AR on the applicant's responses to M1.6.2 questions in the LOQ to all GMO CAs and to the Rapporteur. • The Rapporteur compiles the Day 150 AR, including the assessment report on answers to M1.6.2 related questions, to the EMEA and all CHMP members.
Day 150-180	<ul style="list-style-type: none"> • The EMEA schedules a BWP discussion on the Joint Day 150 AR. • If appropriate, the assessor for the M1.6.2 part of the dossier is invited to be present at the BWP discussion.
Day 170	<ul style="list-style-type: none"> • The CHMP members send comments on Joint Day 150 AR to EMEA and other CHMP members. • The GMO CAs send comments on the M1.6.2 part of the Day 150 AR to the lead consulted CA which forwards them to the Rapporteur.

Table 1. Details of the integration of the evaluation of the ERA into the Centralised procedure timetable for new product applications.

Step	Action
Day 180	<ul style="list-style-type: none">• The CHMP discusses the need for an oral explanation at the CHMP or Working Parties as appropriate. If so, a List of Outstanding Issues is adopted.• If there is to be an oral explanation involving the M1.6.2 data, the Rapporteur informs the lead consulted CA.• <i>If, on the other hand, there are no outstanding M1.6.2 issues, then the Rapporteur informs the lead consulted CA of the fact, and of the termination at this point of its involvement with the assessment process.</i>
Day 181	<ul style="list-style-type: none">• Oral explanation; if it involves the M1.6.2 data, the assessor of this aspect of the application may be invited to be present at the oral explanation.
Day 181-210	<ul style="list-style-type: none">• The Applicant includes any product literature particulars arising from the ERA and risk management in the relevant parts of the English product literature to be sent to EMEA and all CHMP members.
Day 210	<ul style="list-style-type: none">• Mentions of the M1.6.2 aspects of the application are included in the Opinion and CHMP AR to be adopted.
By day 300	<ul style="list-style-type: none">• The EMEA finalises the European Public Assessment Report (EPAR), including an account of the M1.6 assessment (after deletion of any confidential information).

5. INFORMATION REQUIREMENTS FOR MODULE 1.6.2, AND THE OBJECTIVES AND PRINCIPLES OF THE ENVIRONMENTAL RISK ASSESSMENT TO BE PERFORMED

5.1. Introduction

The fundamental dossier requirements for ERAs for GMOs proposed to be placed on the market as or in products are included in Directive 2001/18/EC and in Commission Decision 2002/623/EC. The guidance outlined in this section 5 is intended to be understood to complement these provisions in the particular case of the products being medicinal products.

The two legislative texts mentioned in the preceding paragraph include a number of definitions and explanations of terms applicable to ERAs for GMOs, including those for “hazard”, “risk”, “direct”, “indirect”, “immediate” and “delayed”. These definitions and descriptions apply equally to this Chapter.

For the present, GMOs as or in medicinal products are most likely to be viral or bacterial in nature. Intended routes of administration may be parenteral or non-parenteral, depending on the product. The fundamental objective of ERAs for all GMOs is to consider the possible effects of the GMO on human health and the environment. However, in the special case of GMOs as or in medicinal products, the target patient administered the medicinal product falls naturally outside the scope of “human health and the environment” for most or all direct effects of the GMO, while possibly falling within the scope for most indirect effects.

The routes by which GMO(s) which form components of medicinal product might be envisaged to come into contact with human beings other than the intended patient, or enter the environment, include:

- Dispersal of portions of product during normal handling and use.
- Accidental dissemination during handling and use.
- Disposal of unused product, waste product, and patient excreta.

Once released, the GMO, depending on its nature and on the nature of the receiving environment, may, in any combination:

- Spread.
- Undergo genetic or phenotypic change.
- Compete with existing species.
- Infect tissue.
- Remain latent.
- Reproduce.
- Transfer genetic material to other micro-organisms.
- Transfer genetic material to human beings, or animal or plant species.
- Degrade.

A special consideration for GMOs as or in medicinal products is that items of technical and scientific information presented in the ERA will overlap with items of information presented in other sections of Module 1, and in other Modules of the MA application dossier. Applicants are reminded to ensure full consistency of all data throughout the dossier, bearing

in mind that variability, reflecting different origins (medicinal product regulatory vs. environmental regulatory texts), may occasionally be encountered in the official terminology describing GMO attributes.

Quantitative estimates may find applicability to the evaluation of parameters cited in ERAs, though in practice qualitative estimates are more likely to apply, due to variability being an inherent property of the parameter being estimated, or due to the practical impossibility of making a quantitative estimate of the parameter. Commission Decision 2002/623/EC has standardised on a ranking system using the qualities “high”, “moderate”, “low”, and “negligible” for estimates of the consequences and their magnitudes, likelihoods, and risks of adverse effects occurring, and this system should form the basis of all relative estimates of GMO-containing medicinal product environmental effects also.

Applicants are reminded of the requirement to comply with Article 4.2 of Directive 2001/18/EC referring to genes expressing resistance to antibiotics in use for medical or veterinary treatment and their phasing out.

Article 6.2 of Regulation (EC) 726/2004 specifies the documents to be presented in M1.6.2 for a MA application for a medicinal product consisting of or containing GMO(s):

- A copy of any environmental CA’s written consent to the deliberate release into the environment of the GMOs for research and development purposes. Although already appearing in Module 1 (in the annex to the application form), this information should be repeated in Module 1.6.2.
- The technical and scientific information on the GMO specified in Annexes III and IV to Directive 2001/18/EC. As the Directive qualifies this point with a statement to the effect that not all listed points may be applicable to particular GMOs or GMO categories, the lists in these Annexes should be understood to be a compilation of points to consider which is subject to justified deletions and/or additions, depending on the nature of the medicinal product. The information also needs to take into account, *inter alia*, the diversity of sites of use of the GMO and the results of research and trials already completed on the GMO.
- The ERA dossier. The contents of this dossier should follow the order of headings and requirements specified within Annex II to Directive 2001/18/EC and expanded upon in Commission Decision 2002/623/EC. Complementary guidance, dedicated to the medicinal product situation, appears in sections 5.4 to 5.6 below.
- The results of any investigations performed for the purposes of research or development.

In addition it is recommended that the following should be included the contents of M1.6.2:

- Information on the proposed product information (including proposed conditions of use and handling) and on the packaging of the product. Although already appearing elsewhere in the MA application, this information should be repeated in Module 1.6.2 for the benefit of the lead consulted CA which will not receive the full MA application dossier.

- A plan for monitoring, in accordance with Council Decision 2002/811/EC⁴, during the period of use and beyond, of the product, or a justification for the omission of such a plan.
- A summary following the Summary Information Format set out in the Annex to Council Decision 2002/812/EC⁵.
- Bibliographical references.

5.2. Objective

Applicants are reminded that the objective of the ERA exercise is stated in Annex IIA of Directive 2001/18/EC, i.e. the objective of an ERA is, on a case by case basis, to identify and evaluate potential adverse effects of the GMO, either direct or indirect, immediate or delayed, on human health and the environment which the placing on the market of the GMO may exert; the ERA should be conducted with a view to evaluating if there is a need for risk management, and if so, the most appropriate methods to be used.

5.3. General principles

Applicants are reminded that the general principles which should be followed when performing an ERA are listed in Annex IIB of Directive 2001/18/EC, and include a comparison of the GMO with the non-GM organism, the application of a scientific case-by-case stepwise approach, and a consideration of the possibilities for cumulative long term effects.

5.4. Methodology

Characteristics of the GMO and releases

The Methodology section of Commission Decision 2002/623/EC begins with a statement that the ERA has to take into account the relevant technical and scientific details regarding characteristics of:

- The recipient or parental organism(s).
- The genetic modification(s), be it inclusion or deletion of genetic material, and relevant information on the vector and the donor.
- The GMO.
- The intended release or use including its scale.
- The potential receiving environment.
- The interaction between these.

The Commission Decision adds, *inter alia*, that information from releases of similar organisms and of organisms with similar traits and their interactions with similar

⁴ Council Decision of 3 October 2002 establishing guidance notes supplementing Annex VII to Directive 2001/18/EC of the European Parliament and of the Council on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC.

⁵ Council Decision of 3 October 2002 establishing pursuant to Directive 2001/18/EC of the European Parliament and of the Council the summary information format relating to the placing on the market of genetically modified organisms as or in products.

environments can assist the ERA. In the case of GMOs as or in medicinal products, previous releases are likely to include the use of the product in clinical trials.

Steps in the ERA

The following six steps should be addressed as main topics in the ERA.

- Step 1. Identification of characteristics which may cause adverse effects.
- Step 2. Evaluation of the potential consequences of each adverse effect, if it occurs, and of the magnitude of each identified consequence.
- Step 3. Evaluation of the likelihood of the occurrence of each identified potential adverse effect.
- Step 4. Estimation of the risk posed by each identified characteristic of the GMO.
- Step 5. Application of management strategies for risks from the marketing of the GMO.
- Step 6. Determination of the overall risk of the GMO.

Step 1. Identification of characteristics which may cause adverse effects.

A list of characteristics of the GMO that may possibly result in adverse effects on human health or the environment (hazards of the GMO) should be compiled. At this stage in the methodology, it is important not to discount any potential adverse effect on the basis that it is unlikely to occur, as the likelihood element is dealt with in Step 3.

As a basis for identifying the hazards of the GMO, it is useful to consider what the most likely potential adverse effects might be. In the context of GMOs as or in medicinal products, these are likely to include human or animal disease, disease in plants, population dynamics changes, alteration to susceptibility to established pathogens, and compromisation of prophylactic or therapeutic medical, veterinary, or plant protection treatments.

A comparison of the characteristics of the GMO with those of the non-GM organism under corresponding conditions of the release is also likely to assist in identifying the potential adverse effects arising from the genetic modification in the GMO. Many microbiological, molecular biological, biological, physiological, pharmacological, and ADME (adsorption, distribution, metabolism, excretion) effects related to the GMO and the protein it expresses, especially those relevant to human and animal health and safety, will also be described in various modules of the MA dossier, while other effects will need to be identified and addressed uniquely for the ERA.

All hazards of the GMO, whether related or unrelated to the genetic modification, need to be considered. The former category (which is likely to predominate in most ERAs) should not be restricted to the nature of the expression of the inserted transgene(s) (or to the nature of the genetic recombination, in the case of GMOs which are not transgenic), but should also include those characteristics of the GMO which were introduced as a result of the technique of genetic modification. Particular attention need to be paid to statement in the Commission Decision that “Additional adverse effects, for example, pleiotropic effects, might have been generated as a result of the method used to create the transgenes, and of the location of the construction in the genome of the GMO where the transgenes were inserted. Where more than one transgene is transferred into a recipient or where a transgene is transferred into a GMO, the potential interaction of the different transgenes has to be taken into account considering potential epigenetic or regulatory effects.”

Adverse effects may occur directly or indirectly through mechanisms which may include the spread of the GMO(s) in the environment, the transfer of the inserted genetic material to similar or dissimilar organisms whether genetically modified or not, phenotypic and genetic instability, interactions with other organisms, or any other considerations arising.

It is important to consider whether attributes claimed for the GMO, such as “replication incompetent” or “non-viable” can be accepted as valid in an absolute sense, or whether they need to be qualified by a consideration of the limits of detection of the analytical techniques used to evaluate these attributes, or by stability considerations.

Step 1 should conclude with a neat summary in order to facilitate an orderly progression to Steps 2 and 3.

Step 2. Evaluation of the potential consequences of each adverse effect, if it occurs, and of the magnitude of each identified consequence

The consequences of each potential adverse effect need to be identified and evaluated for each ecological entity which could be affected (e.g. human beings, animal species, trophic levels, and ecosystems). One significant hazard may have more than one adverse effect, and the magnitude of each such effect may be different.

For input into Step 4, the magnitude of the each consequence of each adverse effect needs to be evaluated, together with an estimate of the uncertainty associated with each estimate of magnitude.

The Commission Decision states that the magnitude is the extent to which the consequences of any potential hazards of the GMO to be placed on the market are realised.

Each consequence should be identified using terms with definite meanings, and the magnitude of each effect should be assigned a relative weighting on the standard high, moderate, low or negligible scale. The Commission Decision explains that “negligible” in this context means that no significant changes had been caused in any of the populations in the environment or in the ecosystem.

Consequences may arise directly (e.g. via infection of a family contact with virus shed from a target patient treated with a gene therapy product) or indirectly (e.g. via infection of an animal species by a novel organism originating from recombination of the GMO with a wild-type strain of the same species or genus), and the effects may be immediate (e.g. allergenicity) or delayed (e.g. oncogenicity).

The possibilities for cumulative long-term effects occurring should be evaluated carefully for each consequence.

Examples of considerations envisaged to be likely to be significant for the estimation of the magnitudes of adverse effect of GMOs as or in medicinal products include:

- Possibilities or lack of possibilities for limiting, treating or reversing the adverse effect, if it occurs. Examples might include the transience of infections in human beings or animals, the treatments available for unintended infection of an individual with shed GMO, or the agents available for inactivating spilled or discarded product.

- Dose-response relationships, which might be relevant to estimates of minimum effective doses or of classical toxicological effects.
- Effects on the population dynamics of wild species, especially endangered species.

Consequences for human health are generally considered serious, and many, such as lethality, infertility induction, teratogenicity and oncogenicity, will inevitably be rated as of high magnitude. All relevant categories of risk group, including vulnerable groups such as immunocompromised or elderly persons, should be addressed.

Step 2 should conclude with a neat summary in order to facilitate an orderly progression to Step 3.

Step 3. Evaluation of the likelihood of the occurrence of each identified potential adverse effect

Factors affecting the likelihood of potential adverse effects on human health and the environment occurring include:

- The nature of the GMO, including in particular the extent, if any, to which it is shed by the target patient, its reproduction rate and its capacity for transferring genetic material (both may be rapid in the wild in the case of replication-competent micro-organisms), its stability and persistence profile (for example, genetic stability, replication competence, potential for reversion to virulence, virion or cell viability in various environments and in various environmental conditions).
- The manner of the release into the receiving environment, including the number of GMOs proposed to be released with each use, and the frequency of usage.
- The characteristics of the receiving environment.

All expressions of likelihood need to be specified unambiguously in terms of exactly which hazard of the GMO they refer to.

For certain potential adverse effects, it may be possible to make quantitative estimates of likelihood, but for others the standard high, moderate, low, or negligible relative classification system should be used. It may also be possible to summarise likelihood in a way that covers all the ecological entities which could be affected.

As with magnitude, the level of uncertainty associated with each estimate of likelihood should be stated.

This step should conclude with a neat summary to facilitate an orderly progression to Step 4.

Step 4. Estimation of the risk posed by each identified characteristic of the GMO

An estimation of the risk to human health and the environment posed by each identified characteristic of the GMO which has the potential to cause adverse effects (each hazard of the GMO) should be presented.

Both Directive 2001/18/EC and Commission Decision 2002/623/EC state that the required risk estimate is obtained by combining the magnitude of the consequence of each identified potential adverse effect (Step 2 above) with the likelihood of its occurrence (Step 3). It should be noted that the Commission Decision states that it is necessary, whenever possible, to have

ERA results which are relative (compared with a similar non-GM organism, for example) even if they are qualitative. The combination may be presented for each hazard in the form of a table of the type illustrated in Table 2. Where justified in special circumstances, more sophisticated tables may be presented for particular hazards.

Table 2. Example of how magnitude and likelihood for a specific adverse effect may be combined to yield relative estimates of risk. Outcomes in square brackets are presented for illustrative purposes only and should not be regarded as definitive.

	Likelihood of occurrence of adverse effect			
	High	Moderate	Low	Negligible
Magnitude of adverse effect				
High	High	[High]	[Moderate]	[Negligible]
Moderate	[High]	[Moderate]	[Low]	[Negligible]
Low	[Moderate]	[Low]	[Low]	[Negligible]
Negligible	[Negligible]	[Negligible]	[Negligible]	Negligible

As the product of any magnitude x likelihood combination will depend on the details of the particular case under consideration, it is difficult to assign a standard quality (high, moderate, low or negligible) to the outcome of any particular combination. The Commission Decision illustrates this point by stating that, for example, a high magnitude of the consequence of an adverse effect may be combined with a negligible likelihood of it occurring, resulting in the whole range from high risk down to negligible risk.

It should also be noted that the Commission Decision requires the overall uncertainty for each identified risk to be described in the application, the discussion on this point possibly covering assumptions and extrapolations made at various levels in the ERA, different scientific assessments and viewpoints, the known limits of mitigation measures, and the limitations of conclusions that can be derived from the data.

Step 5. Application of management strategies for risks from the marketing of the GMO(s)

The most fundamental approach to minimising risks to human health and the environment is for potential hazards of GMOs to be taken into consideration during product design and development stages, so that, where possible, undesirable genetic elements are avoided and the associated risks reduced to negligible.

Where, despite efforts at removal during the development stages, GM-related risks to human health and the environment remain in the medicinal product proposed for marketing, a set of effective risk management strategies should be proposed for each product on a case-by-case basis. Realistic strategies are more likely to be directed at minimising or eliminating the likelihood of adverse effects occurring than minimising the consequences of their occurrence. Examples applicable in the medicinal product context include:

- Design aspects of the container, its closure, and any delivery system.
- Directions for proper transport and storage of the product.
- Directions to technical and healthcare personnel responsible for proper handling and administration of the product.
- Procedures to be applied in the case of accidents such as spillages, breakages, and needle-stick injuries; for spillages, appropriate inactivating agents such as sodium hypochlorite solutions should be identified.
- Containment and sanitisation measures which need to be applied on the occasion of the product being administered.
- Directions for the disposal of unused product or waste material.
- Directions for disposal of patient excreta.
- Precautions to be taken by the target patient.
- Precautions to be taken by regular or casual contacts of the target patient.

In the case of the last two indents above, realistic durations need to be proposed for the periods of applicability of the precautions.

Where a crisis scenario could be envisaged to possibly arise from the placing on the market of the GMO, an outline plan for dealing with such an eventuality should be presented.

All necessary directions and warnings concerning environmental risk management should appear in the product information (Summary of Product Characteristics, labelling and Package Leaflet) for the medicinal product.

Step 6. Determination of the overall risk of the GMO(s)

ERAs for GMOs are likely to need to address several characteristics of the GMO with potential for causing one or more adverse effect. For each identified characteristic, a concise summary of the preceding Steps 1-5 should be presented, ideally in the form of a table, and a reasoned determination of:

- The overall risk to human health and the environment of placing the GMO on the market.
- The overall uncertainties.

should follow and conclude this section. (It should be noted that an estimate of uncertainty is required for the estimate of the consequence of each identified hazard of the GMO becoming realised, and that this requirement for uncertainty estimates logically carries through the subsequent steps to the determination of the overall risk associated with the release of the GMO.)

5.5. Conclusions on the potential environmental impact from the placing on the market of the product

Taking into account:

- The points listed in Annex II D.1 of the Directive where relevant to medicinal products, including in particular the likelihood of the GMO becoming persistent and invasive in natural habitats under the conditions of the proposed release, any selective advantage

conferred on the GMO and the likelihood of this becoming realised under the conditions of use of the medicinal product, the potential for gene transfer to human beings (other than the target patient as a direct effect) or other animal or plant species, the potential immediate and/or delayed interactions between the GMO and non-target organisms, including pathogens, the possible immediate or delayed effects on human health, and the potential immediate or delayed effects on animal health, with consequences for the food chain resulting from consumption of the GMO or any product derived from it.

- The year 2000 Commission document on the precautionary principle⁶, and any succeeding documents of that ilk.

the overall risk presented in Step 6 above should be developed into a final conclusion on the environmental impact of the medicinal product, with an outline of any proposed post-marketing environmental monitoring plan for the GMO.

5.6. Review and adaptation of the ERA

The ERA and environmental risk management particulars for a GMO as or in a medicinal product should be kept under continuous review after the granting of an MA. This review should take into account any new information coming from such sources as research, other releases, and monitoring. Where a need for amendment to the terms of the MA is suggested by the evaluation of the new data, the necessary variation application should be submitted within the Centralised procedure.

Future regulatory developments including the appearance of new European guidance affecting ERAs for GMOs should also be taken into account as necessary.

⁶ Communication from the Commission on the precautionary principle, COM (2000) 1 final.