



COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE

(CHMP)

GUIDELINE ON ENVIRONMENTAL RISK ASSESSMENTS FOR MEDICINAL PRODUCTS CONSISTING OF, OR CONTAINING, GENETICALLY MODIFIED ORGANISMS (GMOs)

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ORGANISMS (GMOs)**

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EXECUTIVE SUMMARY

This guideline outlines the legislative framework governing the inclusion of Environmental Risk Assessment particulars in applications for Marketing Authorisation for medicinal products consisting of, or containing, a Genetically Modified Organism. The document also provides:

- An outline of the various special administrative and procedural details associated with the applications involved.
- A description of the environmental risk assessment methodology and scientific issues and data which applicants should address in the relevant parts of the application dossiers.

1. INTRODUCTION

Since the manner of use of medicinal products usually allows their constituents and/or their derivatives to enter the biosphere and interact with it, it is important to evaluate the potential impact on the environment of such products before granting a Marketing Authorisation (MA). The necessary general provisions requiring such evaluation appear in EU pharmaceutical sector legislation.

In the case of medicinal products consisting of, or more likely containing, a Genetically Modified Organism (GMO), the requirement for conducting an Environmental Risk Assessment (ERA) stems from provisions appearing in both pharmaceutical sector and environmental sector legislation. This guideline summarises the legal situation and explains how the legislative requirements should be implemented by regulators and complied with by applicants for MA for such products.

2. SCOPE

The application of the Centralised procedure to MA applications for medicinal products containing GMO(s) as or in medicinal products constitutes the scope of this guideline. Although applications for conducting clinical trials using such products fall outside the scope of the guideline, Section 4.2 of the document may prove useful to the design and conduct of such trials, especially if conducted with a view to submitting a future MA application for the product.

3. LEGAL BASIS

3.1 General legal considerations

This guideline should be read in conjunction with the introduction and general principles (4) and Part 1 of the Annex to Directive 2001/83/EC¹, as amended. The legal basis underlying the subject of the title of this guideline is described in the following sections. In the event of changes to this legal basis transpiring in the future, the guideline will, if necessary, be amended to take the new situation into account.

3.2 EU environmental legislation

Directive 2001/18/EC² 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 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

¹ Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use

² Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC

member state and of the European Commission, the notification is examined for compliance with the requirements of the Directive.

3.3 EU pharmaceutical legislation

European pharmaceutical legislation, in the form of Regulation (EC) 726/2004³, 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 these cases recombinant organisms are not themselves components of the finished medicinal product, and as a consequence these medicinal products neither consist of nor contain a GMO.

3.4 The EU environmental/pharmaceutical legislative interaction for GMOs

Exceptionally, human biotechnological medicinal products may 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).

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/EC⁴, 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 those bodies and with the European Commission on the GMO-ERA aspects of the procedure.

4. MAIN GUIDELINE TEXT

4.1 Procedures for the Evaluation of the ERA and its integration into the Centralised Procedure

4.1.1 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.

³ 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

⁴ 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 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC

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, necessary consultations will be held with the designated GMO CAs.

4.1.2 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 formal provision for a summary of Module 1.6.2 to be included in Module 2 of the dossier.

4.1.3 Appointment of assessor(s) for the Module 1.6.2 data

The CHMP (Co-)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 section 4.1.4 of this guideline, or an MA application assessor from a medicines agency, who may possibly be also involved with the assessment of other parts of the dossier.

The assessment report produced by the Module 1.6.2 assessor should comprise an introduction, a typical narrative assessment part, and a list of questions to be put to the applicant.

4.1.4 Consultation on the ERA with bodies established under Directive 2001/18/EC

To expedite the progress of the necessary consultations with those bodies established for the purpose of implementing Directive 2001/18/EC, the CHMP (Co-)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 (Co-)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.

4.1.5 Involvement of CHMP working parties in the ERA assessment

The data appearing in Module 1.6.2 of the application are likely to overlap with entries appearing in other parts of the dossier. Applicants should ensure that consistency prevails in all cases of such overlap, and that there is appropriate cross-referencing within the dossier.

It should also be kept in mind that official medicines and environmental regulatory texts may make use of different terminologies when describing the same or similar things.

The CHMP Biologicals Working Party (BWP) has a major role in the assessment of the Module 3 (Quality) data for biotechnological medicinal products. Since the Module 1.6.2 data are expected to overlap to a substantial extent with the data presented in Module 3 of the MA application, and could also influence the quality parts of the final product information (Summary of Product Characteristics, leaflet and labelling) 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.

Sharing of the ERA assessment with other working parties should also take place as necessary.

4.1.6 Centralised procedure steps integrating the evaluation of the ERA

The scheduling of the necessary consultations by the (Co-)Rapporteur with the GMO CAs needs to be harmonised with the accommodation of other demands of the Centralised procedure. The manner in which this integration is achieved is described in an EMEA Standard Operating Procedure.

4.1.7 Information to the public

All parties involved in the evaluation of an application submitted in accordance with Article 6 of Regulation (EC) 726/2004 are required to respect the confidentiality provision laid down in Article 76

of that Regulation. This includes the obligation to keep strictly confidential data in relation to the submission of the dossier, the name of the applicant and the product, all data contained in the dossier, and all assessment reports relating to the product. As stipulated in Article 12.2 of Directive 2001/18/EC, information to the public is to be provided in accordance with the provisions of the Community legislation concerning medicinal products for human and veterinary use. Therefore, none of the aforementioned information may be disclosed to any third party or the public during the evaluation of the application, and the information will only be made available to the public after the CHMP Opinion as part of the European Public Assessment Report (EPAR).

4.2 Information requirements for module 1.6.2, and the objectives and principles of the environmental risk assessment to be performed

4.2.1 Introduction to section 4.2

The fundamental dossier requirements for ERAs for GMOs proposed to be placed on the market as or in products are outlined in Directive 2001/18/EC and in Commission Decision 2002/623/EC. The guidance outlined in this section 4.2 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 guideline.

For the present, GMOs as or in medicinal products are most likely to be viral or bacterial in character. Intended routes of administration may be parenteral or non-parenteral, depending on the product.

The routes by which GMO(s) which form components of medicinal products 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 or waste medicinal product.
- Dispersal of GMO containing 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.

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.

For those aspects of the ERA for which quantitative data are not obtainable, it may be acceptable, and sufficient, to use qualitative data. For those aspects for which sufficient data, quantitative and/or qualitative, to allow an appraisal of the risk to the environment cannot be produced, a realistic theoretical worst-case scenario may be invoked. The approach used may be based on that developed within the scope of the precautionary principle, which is described in the year 2000 Commission Communication on that subject⁵.

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 that the following documents should be presented in applications for MA for medicinal products consisting of, or containing GMOs:

- A copy of any environmental CA’s written consent to the deliberate release into the environment of the GMOs for research and development purposes (i.e. any other purpose than placing on the market). Although already required to appear in Module 1 of the application dossier (in the annex to the application form), this information should be repeated in Module 1.6.2, in the interests of keeping this part of the dossier self-contained.
- 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 GMO and 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 appearing in 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 4.2.2 to 4.2.6 of this guideline.
- 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 Module 1.6.2:

- Copies of the proposed product information (Summary of Product Characteristics, leaflet and labelling, including proposed conditions of use and handling) and a description of the container/packaging arrangements for the product. Although already appearing elsewhere in the MA application, this information should be repeated in Module 1.6.2 in the interest of keeping this part of the module self-contained.
- A plan for monitoring, in accordance with Council Decision 2002/811/EC⁶, during the period of use and beyond, of the product, or a justification for the omission of such a plan.
- A copy of the Summary Notification Information Format (SNIF) set out in the Annex to Council Decision 2002/812/EC⁷.

⁵ Communication from the Commission on the precautionary principle, COM (2000) 1 final, dated 2.02.2000

⁶ Council Decision 2002/811/EC 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.

- Bibliographical references.

4.2.2 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.

4.2.3 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.

4.2.4 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 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 in sequence as the 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.

⁷ Council Decision 2002/812/EC 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.

Because Module 1.6.2 is intended to be a stand-alone document, it is recommended that the progression through the steps should be prefaced by a brief introductory section describing the nature of the GMO and of the medicinal product which it is contained in.

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, changes in population dynamics (meaning the factors that affect population changes in space and time, including the interactions between these factors), alteration of organism susceptibility to infection by established pathogens, and compromise of prophylactic or therapeutic medical, veterinary, or plant protection treatments. The analysis of each potential effect should be approached using an appropriate and justified methodology.

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. 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 application 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 the 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.

Claims made for replication incompetence or non-viability of the GMO need to be explained in full, with reference to, at least, the limits of detection of the analytical techniques used.

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.

Commission Decision 2002/623/EC 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 immuno-compromised 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 reproductive mechanism and rate and its capacity for transferring genetic material., 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

Since the product of any magnitude x likelihood combination will depend on the details of the particular case under consideration, it may be 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 at 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 event of accidents such as spillages, breakages, splashing on the skin or eyes of persons other than the target patient, and needle-stick injuries occurring. There should be a justification for the choice of cleaning/inactivating agents and procedures recommended to be used and applied in such cases, plus directions for safe cleaning or disposal of used cloths, mops, etc.
- 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 indentations 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, leaflet and labelling) 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).

4.2.5 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 principle, 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. Detection techniques employed need to be suitably validated.

4.2.6 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.

When submitting a variation to the terms of the MA, the marketing authorisation holder should consider any possible impact on the environmental risk assessment.

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

DEFINITIONS

GMO - 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 and the definitions of 'deliberate release' and 'environmental risk assessment' are extensively expanded upon in the body of the Directive and in its Annex I.

Effects on the environment - In the context of the scope of this guideline, effects on the environment should be understood to mean effects exerted on any inhabitant, component or compartment of the global ecosystem, including effects on human beings, with the exception of the effects on target patients as a direct result of the administration of the product to them, these latter effects being addressed in other parts of the application dossier.

REFERENCES

- Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use.
- Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC.

- 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.
- 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 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC.
- Communication from the Commission on the precautionary principle, COM (2000) 1 final, dated 2.02.2000.
- Council Decision 2002/811/EC 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.
- Council Decision 2002/812/EC 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.