

# ENVIRONMENTAL RISK ASSESSMENT FOR HUMAN MEDICINAL PRODUCTS CONTAINING OR CONSISTING OF GMOS

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# ENVIRONMENTAL RISK ASSESSMENT FOR HUMAN MEDICINAL PRODUCTS CONTAINING OR CONSISTING OF GMOS

## I. INTRODUCTION

This guidance concerns the environmental risk assessment needed to comply with the requirements of Article 6(2) of Council Regulation 2309/93 on the authorisation of live medicinal products which contain or consist of genetically modified organisms (GMOs). The Regulation makes provision for an environmental risk assessment similar to that in Directive 90/220/EEC on the Deliberate Release into the Environment of Genetically Modified Organisms (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 IIA & III of the Directive. Under Council Regulation 2309/93 therefore, the environmental risk assessment should be a reasoned statement of the overall risk of damage to human health and to the environment from the proposed marketing of a medicinal product containing a GMO.

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

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

This guideline excludes 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

## II. SCOPE OF REGULATION

### **Types of products**

This guidance has been based largely on the considerations appropriate to what will probably be the most likely GMO medicinal products, namely live vaccines (bacterial and viral), viral vectors and modified somatic cells intended for use in gene therapy. Products such as complexed or naked nucleic acid fragments (including oligonucleotides), and nucleic acid fragments packaged in artificial liposomes arguably do not constitute genetically modified organisms within the meaning of Articles 2(1) and 2(2) of 90/220/EEC, and nor do products such as monoclonal antibodies or pharmaceuticals produced by GMOs. This assumes that the products are free of any contamination with living organisms.

### III. ENVIRONMENTAL RISK ASSESSMENT

#### **General considerations**

For medicinal products, it is appropriate first to consider the risks to human health and to address whether it is necessary to take certain management measures to control those risks. The potential risks to the environment should then be assessed on the basis that those management measures are in place.

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. It is important that the human risk assessment looks beyond the safety of the patient and considers the risks to those who handle or administer the product (such as medical and ancillary staff) as well as the health of the public in general. Risks to the public should encompass risks to the immediate relatives and contacts of the patient as well as to the general public. In such cases it will be necessary to consider the possible effects on healthy humans as well as to more vulnerable individuals (the young or old, immunocompromised or otherwise susceptible). For example, the increasing incidence of people who are receiving immuno-suppressants, 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. As with other branches of medicine, attention should be given to the fact that many treatments or gene therapies take place in hospitals which contain a higher proportion of ill people than the normal community.

Similar concerns may arise in apparently healthy people who might be especially susceptible to exposure to a GMO expressing a pharmacologically active product (e.g. a metabolic enzyme or a hormone). The assessment may either need to take into account the proportion of such people in the community or it should assume the consequences which would arise in the most vulnerable group of people.

#### **Sources of information**

The risk assessment is intended to be an overall statement reflecting the information which may be contained elsewhere in either the main marketing authorisation dossier or in the specific technical dossier which is prepared for Competent Authorities under 90/220 as part of the requirements of Article 6(2).

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

How much information is needed on 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 elsewhere in the dossier or in the text books or literature. But 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. In other words, if you are unable to categorically state that a particular modified virus does not replicate in any human cell type it would be better to assume, for the purposes of the assessment, that it might replicate in some cells than to obtain and test representatives of every cell or tissue type.

## IV. FRAMEWORK FOR RISK ASSESSMENT

The aim of any 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:

1. hazard identification;
2. assessment of consequences of the hazards;
3. assessment of the likelihood that the hazards will occur;
4. assessment of level of risk (by consideration of the severity of any adverse consequences and the likelihood that they will occur);
5. selection and assignment of appropriate control measures (risk management).

## ASSESSMENT OF RISKS TO HUMANS

### 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 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 other than the patient and should include the following:

#### **Pathogenicity or other adverse effects**

This is a major consideration for the types of medicinal products which will fall within the scope of the Future Systems procedure. It is anticipated that considerable detail on the pathogenicity of the parental organism and the GMO itself will all be considered in [see Part IIG.3.IIC]. 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 infections in immuno-compromised or other especially susceptible individuals should be identified.

The use of some vectors, especially in gene therapy, could potentially result in alteration of gene expression or the activation of cellular oncogenes and this possibility should be identified at this stage.

#### **Production of biologically active / toxic products**

Does the GMO contain genes encoding protein(s) with known or suspected pharmacological or physiological effect? Consideration should be given to possible effects other than those being sought in the construction. For example, some gene therapy products expressing an active protein

to treat a particular disease may have undesirable effects on healthy individuals who are accidentally exposed [example: vector expressing insulin or other hormone].

### **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.

### **Gene transfer**

Gene transfer may be considered a hazard if it could result in the spread of genes to other organism with potentially undesirable consequences (e.g. antibiotic resistance markers, other undesirable genes). In some senses it can be considered as a sub-section of genetic stability.

### **Survival / dissemination**

The ability of the GMO to survive for long period in the environment (including indoors for examples in a treatment room, hospital ward or lavatory) may constitute a hazard if it could mean that there is a greater likelihood of contact with individuals, some of whom may be more susceptible to the other hazards manifested by the GMO. This may be further compounded if survival offers an increased possibility of wide spread dissemination either *via* aerosols, water or other routes, including any arthropod or animal vectors.

## **2. CONSEQUENCES OF A HAZARD OCCURRING**

This stage of the assessment should consider, for each identified hazard, what 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, permanent harmful consequences.

It is suggested that the consequence of each hazard is indicated qualitatively as “negligible”, “low”, “medium” or “severe”.

An adverse effect on a non-target population (for example medical staff or the general population) 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.

At this stage, it will also be necessary to consider whether everyone exposed to the GMO would suffer an adverse effect or whether the adverse effect would occur only in 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 (e.g. a one-in-a-million chance of vaccine associated encephalitis) or because a small proportion of the population are susceptible (e.g. one-in-a-million people are hyper-sensitive to a particular component of the GMO).

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 difference 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.

### **3. ASSESSMENT OF DEGREE OF EXPOSURE AND LIKELIHOOD OF 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 GMO in product**

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 workers (medical staff), relatives/contacts and the general public to the products should be borne in mind.

Given that medicinal products and their administration are more tightly controlled than other products, it is possible that exposure of humans other than the patient is virtually non-existent. The degree of exposure will have a bearing on the likelihood of a hazard occurring and some of the following considerations should be taken into account:

#### **Type of packaging & procedure before & after administration**

Most, if not all medicinal products containing GMOs will be securely packaged upon receipt and the packaging should allow any preparatory steps (e.g. reconstituting freeze-dried preparations) in a safe and aseptic manner. However, if there are any procedures foreseen for the product which may lead to medical staff being exposed to the GMO (during preparation, administration or waste disposal) these should be assessed. It will also be important to consider whether the product is designed to be self-administered by the patient (e.g. a nebulisers for gene therapy products) as this may increase the possibility of exposure by incorrect or accidental use.

#### **Route of administration (parenteral vs. oral vs. aerosol)**

For most of the products which fall within the scope of this Regulation, the product will be administered by either injection, orally or via nasal sprays. Injection is considered to cover cases where a small amount is administered via syringe as well as those cases, particularly in gene therapy, where larger amounts are perfused *via* an intravenous drip. It is to be expected that there is more opportunity for inadvertent exposure when the product is administered orally or nasally than via injection.

#### **Shedding of live vaccines (route, numbers, duration)**

Some medicinal products containing GMOs will consist of live GMOs intended as vaccines or gene therapy delivery systems. It has long been known that these vaccines may be shed into the

environment and that people in contact with the patient may be exposed. The degree of exposure will depend largely on the duration of the ‘infectious’ state, the mode of replication of the GMO and the site of replication in the body. For example, the replication and shedding of a live poliovirus is likely to be greater than vaccinia. Many products may well consist of attenuated or replication defective vaccines and the likelihood of exposure will be less than that associated with the wild type, parental, strain.

The overall degree of exposure should be indicated as detailed above. For example, a product based on a replication defective vaccinia virus administered sub-cutaneously and covered with a non-occlusive dressing may constitute a “low” level of exposure. In contrast, a vaccine based on attenuated poliovirus, administered orally and shed via faeces for some time, may constitute a “high” level of exposure. It should be noted that high exposure does not necessarily mean high risk and conversely that even “low” exposure, but with severe consequences, may lead to an unacceptable risk.

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

#### **4. 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 combination of the exposure/likelihood and consequence. It is inevitably always going to be difficult to “multiply” qualitative statements such as “high” and “low”, but the table below 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 of the 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 and would prompt some consideration of measures to control the risks to human health. It should be emphasised that unusual but serious harmful consequences affecting a small number of patients may be acceptable in a medicinal product intended to cure a life-threatening or debilitating acute illness but may not be acceptable if there is a similar, albeit unlikely, risk of the product affecting healthy humans.

A illustrative, not definitive, matrix which might be used in the assessment of risk is given in Annex 1.

#### **5. CONTROL OF RISK**

This stage of the risk assessment will require some consideration of the particular aspect of the assessment which lead to an unacceptable level of risk. For example, if it was 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 the 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, medical staff using the product will be subject to worker protection legislation such as the Biological Agents Directive (90/679/EEC as amended by 93/88/EEC), requiring among other things risk assessments and appropriate control measures.

In considering whether any additional controls should be adopted care should be taken in order not to invalidate other parts of the marketing authorisation application.

## ASSESSMENT OF RISKS TO THE ENVIRONMENT

Having decided on the controls that are appropriate (if any) in order to minimise the risks to humans, it is necessary to evaluate whether there could be any adverse effects on the environment resulting from the use of the product. In many cases, if the risks to humans are judged to be “effectively zero” or “low”, it is likely that the environmental risk will already be low because of the characteristics of the GMO and/or the intended control measures. However, it is important to consider the environmental hazards and risks although this **may** be a very simple exercise, if, for example, the GMO product is very unlikely to survive in the environment.

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.

### 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 potential receiving environment. Appropriate information about the recipient or parental organism and the donor(s), as well as information about the GMO itself, should be considered.

#### **Capacity to survive, establish and disseminate**

This is the key consideration: if an organism is not capable of surviving, say, because of multiple disablement, then no other hazards are likely to come into play. An organism is considered to survive if, in the period which it will be viable, it could have an impact on other organisms. The survival time should be estimated in the relevant environmental compartment(s), such as soil, air, fresh or sea water, sewage sludge etc. Wherever appropriate, standard methods for determining survival time should be applied if no data are available. If an organism is not likely to survive, either in the wider environment or outside the intended host species, the risk assessment can be completed at this stage since the risk of any damage to the environment would be 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.

### **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.

### **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.

### **Phenotypic and genotypic stability**

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

### **Pathogenicity to other organisms**

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

### **Potential for other effects (including non-target 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 transcapsidation, and the effects of recombination.

## **2. ASSESSMENT OF THE CONSEQUENCES**

It is likely that many medicinal products will be used under conditions that will mean that the hazards cannot actually be realised because the GMO does not reach the environment. However, it is necessary to consider whether it could reach the environment and if so, whether that environment would cause or allow the hazard to be realised for each of the hazards of the GMO identified. Thus, again the characteristics of the potential receiving environment need to be considered.

In particular, it is important to bear in mind that medicinal products intended as vaccines or gene therapy delivery systems may be shed into the environment.

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

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

### **3. 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. 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.

Particular characteristics of the local environment that could contribute to manifestation of the hazard should be identified and assessed. If the GMO is likely to enter the wider environment (i.e. if it is not to be contained within a building), climatic, and geographical and soil conditions, demographic considerations, the types of flora and fauna in the potential receiving environment are some of the important ones.

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 organisms. 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.

The mode of administration might have an impact on the likelihood that hazard(s) will be manifested. For example, per oral administration will often lead to faecal introduction of GMOs into the environment and thus is likely to lead to a higher likelihood than if the product is given per injection.

Likelihood should be expressed as "high", "medium", "low" or "negligible".

### **4. ASSESSMENT OF LEVEL OF RISK**

Having judged the magnitude of harm if the hazards 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 the equivalent section of 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.

## **5. SELECTION AND ASSIGNMENT OF APPROPRIATE CONTROL MEASURES (RISK MANAGEMENT)**

If the environmental risks are not as low as reasonably practicable, the process of risk assessment in relation to that hazard should be repeated to ascertain whether the application of additional management techniques could reduce the level of risk. Consideration might be given to dosages, to organism disablement or to alternative methods of administration of the product to patients. Administration per injection is likely to lead to a lower level of risk than, for example, per aerosol.

## **OVERALL ASSESSMENT OF RISK TO HUMANS AND THE ENVIRONMENT**

The overall risk associated with the proposed marketing of a medicinal product containing a GMO is estimated by combining the overall risk to human health and the overall risk to the environment, each of which takes into account the risks from each of the human health and environmental hazards identified.

**TABLE 1****Estimation of risk from consequence of hazard occurring, and likelihood or probability that the hazard will occur\***

CONSEQUENCE	LIKELIHOOD OF HAZARD OCCURRING			
	High	Moderate	Low	Negligible
Severe	High	High	Medium	Effectively zero
Medium	High	Medium	Medium/low	Effectively zero
Low	Medium/low	Low	Low	Effectively zero
Negligible	Effectively zero	Effectively zero	Effectively zero	Effectively zero

**SUGGESTED FORMAT FOR PRESENTATION OF CONCLUSIONS OF RISK ASSESSMENT**

- A.** Summary of overall risk of damage to the environment (including human health) from the proposed marketing of GMOs forming subject of a marketing authorisation application
- B.** Hazardous characteristics of GMO that could, in certain circumstances, lead to harm to humans:
  - 1) Pathogenicity or other adverse effects (e.g. allergenicity)
  - 2) Production of biologically active/toxic products
  - 3) Genetic instability (especially attenuating mutations)
  - 4) Gene transfer
  - 5) Survival/dissemination
- C.** Assessment of consequences of each hazard occurring
- D.** Assessment of degree of exposure and likelihood of each hazard occurring
- E.** Assessment of level of risk for each hazard
- F.** Assessment of overall risk of harm to humans (total risk after consideration of risk of each of hazards occurring): High, medium, low, effectively zero
- G.** Hazardous characteristics of GMO that could, in certain circumstances, lead to harm to the environment:
  - 1) Capacity to survive, establish and disseminate
  - 2) Potential for gene transfer
  - 3) Products of expression of introduced sequences

\* 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.

- 4) Phenotypic and genotypic stability
  - 5) Pathogenicity to other organisms
  - 6) Potential for other effects (including non-target effects)
- H.** Assessment of consequences of each hazard occurring
- I.** Assessment of likelihood or probability of each environmental hazard occurring
- J.** Assessment of risk for each hazard
- K.** Assessment of overall risk to the environment (total risk after consideration of risk of each of hazards occurring): High, medium, low, effectively zero
- L.** Assessment of overall risk to humans and the environment (from Points F and K)