European Medicines Agency

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OVERVIEW OF COMMENTS RECEIVED ON DRAFT GUIDELINE ON THE SCIENTIFIC REQUIREMENTS FOR THE ENVIRONMENTAL RISK ASSESSMENT OF GENE THERAPY MEDICINAL PRODUCTS EMEA/CHMP/GTWP/125491/2006

Table 1: Organisations that commented on the draft Guideline as released for consultation

	Name of Organisation or individual	Country	No Comments
1	Schering-Plough Europe	Belgium	3
2	Amsterdam Molecular Therapeutics	The Netherlands	13
3	Biosafety Advisory Council	Belgium	9
4	Defra & ACRE	UK	19
5	National Competent Authority	The Netherlands	34
6	Merck Sharp & Dohme	Belgium	1
		Total	79

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Table 2:Discussion of comments

GENERAL COMMENTS - OVERVIEW
Overall, the wording in the guidance as it stands at the moment is imprecise for those who will need clear guidance, e.g. the document often refers to the patient when they are clearly out of the scope of the regulation (see also specific comments below). "subject/patient" is changed to "patient" "treated patient" is changed to "patient" Definition for environmental risk is changed: "intended person or patient" is replaced by "humans other than the patient" The changes regarding the specific comments are indicated elsewhere in the table However, if this document was read in the context of the previously published ERA guidance document (doc ref: EMEA/CHMP/BWP/473191/2006, which came into effect 1st July 2007) it does provide some helpful advice as to what should go into an ERA, but some areas could be further developed if readers are not aware of the earlier document (particularly those on post-market monitoring plans). Additional text has been included in step 5 on the application of management strategies: "Two types of monitoring… …monitoring methods e.g. pharmacovigilance." The "target patient" in the context of regulation (EC) 726/2004 can be either human or animal, as the regulation covers both human and veterinary medicinal products. Many veterinary gene therapies are being developed and the guidance as it stands has not specifically addressed the information that would be required in the ERA module for the marketing authorisation for veterinary products. This is an omission that could be addressed when revising the guidance. The methodology for an ERA for a medicinal product for human use is highly similar to the ERA methodology that can be applied for veterinary medicinal products. However, the focus of this guideline is on gene therapy medicinal products for human use.
In view of the heterogeneity of the GTMPs, it is difficult to define requirements for the ERA that are applicable to all products. For instance, the risk for unexpected events for a replication deficient AAV lacking viral genes will be completely different from that for a replication competent Adenovirus. Therefore the requirements for experimental preclinical and clinical data should be evaluated on a case by case basis, and it is important to stress this in the guideline. Included in main guideline text: "In view of the heterogeneity of GTMPs, it is difficult to define general requirements for the ERA that are applicable to all products and therefore the requirements for an ERA should be defined and evaluated on a case by case basis."
It is also important to consider that especially in the field of gene therapy, guidelines will also be read by (academic) scientists, rather than experts in regulatory affairs and/or toxicological development. As such, acronyms such as SPC and MA may not be clear to all readers if not written in full at first use. Acronyms have been fully written at first use. Additionally these acronyms are explained in the abbreviations list.
Step 2 requires the possible adverse effects to be listed and rated for risk. It could be considered to provide a comprehensive, categorised check list (e.g. with check boxes for not applicable, low to negligible, moderate, high) in an annex. A similar, short list is provided on pg 12 and could be extended for this purpose. Due to the heterogeneity of GTMPs it is difficult to design a generally applicable check list. Therefore this suggestion is not included.

Little is asked in this guideline concerning the patients recruitment and management protocols which, in case of containing some misunderstanding or mistaken could generate Biosafety troubles. Where possible minor changes have been included in the text.
This Guideline (further referred to as 'the Guideline') is meant to offer guidance to risk assessors, for performing an environmental risk assessment (ERA) of a gene therapy medicinal product. The guidance in the Guideline is additional to the guidance that is already available in the CHMP guideline 'Environmental risk assessments for medicinal products containing, or consisting of, genetically modified organisms (GMOs) (Module 1.6.2)' (further referred to as 'Module 1.6.2'), that is part of the Common Technical Document. No change was introduced to the document based on this comment. The Guideline therefore has the same legal basis as Module 1.6.2; this could best be made clear in section 3, by either referring to Module 1.6.2, or by using the same texts. Text under legal base is changed so that it is similar to a previous guidance document describing the ERA for GMO's in general.
The scope of the document is restricted to gene therapy medicinal products. In our experience it is difficult to define the term 'gene therapy medicinal products' and different definitions are in use. If the scope is restricted to gene therapy medicinal products, a definition should be given that encompasses all products, and excludes all other medicinal products that consist of or contain GMOs. Not only is this a very difficult task, it would seem that there is also no reason to do this. The guidance for ERA that is provided in this Guideline applies to all medicinal products consisting of or containing GMOs. We would strongly advise you to broaden the scope of the document as such. If deemed expedient, the document could state that within these medicinal products it focuses on viral vectors used in gene therapy, as up to date we have most experience with these as medicinal products. In this rather loose connotation a further definition of 'gene therapy' would not be necessary. We welcome the initiatives and find the Guideline valuable to develop an effective, consistent, and efficient process for environmental risk assessment of gene therapy medicinal products. However, consistency in the ERA process across all medicinal products including medicinal products consisting of, or containing, genetically modified organisms (GMOs) and gene therapy medicinal products should be ensured. The scope is unchanged and is still on the ERA of GMO containing GTMPs. However reference is made in the document that the methodology of this ERA also applies to other GMO products.
In general, the document offers many useful comments and observations for performing an ERA. However, these comments are not always positioned at a logical place in the document, i.e. in the part of the document that deals with the step in the ERA where the comments are relevant. We will indicate this in our specific comments; we realize that it will take extensive redrafting to take care of these problems, still we are of the opinion that this effort is vital for the usefulness of the document. Changes are dealt with further on.
In general, this Guideline should be properly positioned in relation to Module 1.6.2. It is therefore necessary to make clear that this Guideline is complementary to Module 1.6.2, in offering further explanation and examples of how to conduct an ERA. Changes are dealt with further on.

GUIDELINE SECTION TITLE		
Line no.[1] + paragraph no.	**Comment and Rationale**	**Outcome**
	TITLE	
Title	The title mentions 'gene therapy medicinal products'. Rationale for change is given in the general comments	Change into 'medicinal products containing, or consisting of, genetically modified organisms (GMOs)'. Title is unchanged but it is indicated in guidance text that the ERA methodology also applies for non GTMP GMO's used as a medicinal product.
	TABLE OF CONTENT	
P2, table of content	It is perhaps interesting to insert a part containing the abbreviations list and their definition	This has been included.
	INTRODUCTION	
1. Introduction (page 2)	As explained in Article 12.2 of Directive 2001/18/EC, the ERA should be performed in agreement with the principles for an ERA as specified in the Annexes II and III of this Directive. This should be mentioned specifically in the introduction, so as to make the background of the ERA clear.	After 'Therefore an application for marketing authorisation of a medicinal product for human use must be accompanied by an environmental risk assessment (ERA)' add: ', performed inn accordance with the principles of Annex II of Directive 2001/18/EC'. Text has been added. In the last sentence, exchange 'identical' for: 'as specified in Annex III of 2001/18/EC'. Text has been changed.
PARA 1	It would be useful to provide a web- link to the previously published guidance on ERA for medicinal GMOs. (ref: EMEA/CHMP/BWP/473191/2006).	A reference to this guideline is included in the text on legal basis.
	SCOPE	
PARA 2	The draft guideline explains that the ERA concerns potential adverse effects on 'non-patients' clearly in the ***Scope*** (para 2). However, we suggest that this is given clearer prominence later in the document (see overall comments also).	In the scope it has been highlighted that effects on patients are important to consider while these might be indicative for possible effects on non-patients that are exposed to the medicinal product.

[1] Where applicable

	LEGAL BASIS	
PARA 3	In the legal basis section, it should be explicit that under Directive 2001/18, *post-market environmental monitoring plans are a requirement, not an option*. If no such plan is submitted, a detailed justification for the omission is required. The previously published guidance (see comment under PARA 1 above) covered the subject of monitoring several times, whereas the current document covers this subject, with insufficient guidance, only very briefly towards the end of page 13 and again towards the end of page 14.	The text has been changed indicating the necessity of monitoring plans.
	MAIN GUIDELINE TEXT	
4. Main guideline text, page 3, paragraph 1	This paragraph tries to explain many aspects of the marketing authorisation procedure, including the ERA, but in doing so confuses the issue.	We propose to deal with issues one by one, and in particular in the following order. - Start with explaining that the ERA that is subject of this Guideline is part of the marketing authorisation procedure. This has been done in the previous section on legal basis; as this directly precedes this section, it is sufficiently clear. - The ERA is based on known facts *as well as theoretical assumptions* that are sufficiently underpinned. Text has been added: "An ERA is based on known facts, including those derived from specific testing of the GMO-containing GTMP, as well as on sufficiently underpinned theoretical assumptions, and the precautionary principle, which is described in the Communication from the Commission on the Precautionary Principle." - The conclusion of the ERA may be that there are risks that should be reduced by adequate risk management measures (step 5 in the ERA). One reason that measures may be indicated may be lack of scientific certainty; in that case the Precautionary Principle is applied. - The conclusions of the ERA are taken into account in the final benefit / risk evaluation, that is the basis for either granting or refusing marketing authorisation; the benefit / risk evaluation is not part of the ERA. A number of changes have been made to improve the flow of thoughts, more or less as explained above. Some changes are commented

		specifically: **'**Hazard identification identifies characteristics of the GMO linked to the genetic modification, which may result in adverse effects on human health or the environment. A comparison of the characteristics of the GMO with those of the non-modified organism, under corresponding conditions of the release or use, will assist in identifying any particular potential adverse effects arising from the genetic modification (familiarity principle). It is important not to discount any potential adverse effect on the basis that it is unlikely to occur'. 'Familiarity principle' has been added. 'The objective of an ERA is described in the text of Directive 2001/18/EC' has been deleted as redundant. 'This scenario could be based on the approach developed in the precautionary principle.' has been deleted, as the application of the precautionary principle only applies to the risk management stage, not to the risk assessment stage.
PARA 4	• The last sentence of the first para of the Main Guideline text section on page 3. The reference to clinical trial authorisation has the potential to confuse the reader, as this guidance document is for marketing authorisations, not clinical trial authorisations. The distinction should be made more clearly.	Text has been changed.
pg3, 1st paragraph of section 4, line 8	'preliminary ERA' is not defined. As such it is not clear what the requirement for a clinical trial authorisation is with respect to the ERA.	Preliminary ERA has been defined as an ERA performed for a clinical trial adequate for the development stage of the GMO-containing medicinal product.
P3§5	4. main guideline text……"however this document does not apply to that analysis." What does it mean?	Text has been changed.
	…", the ERA should be up to date and include information from clinical trials <u>if available</u>"… delete "if available"	"if available" has been deleted.
Methodology for the evaluation of the ERA,	'Evaluation' would appear to be the wrong term.	Change into 'Methodology of the ERA'. This change has been made.

page 4		
Page 4 of 15, Paragraph 3, Sentence 3, Lines 3 & 4	The sentence states that “New information becoming available after the marketing authorisation should be included in the monitoring plan.” All new information, however, may not be “relevant” or warrant inclusion in the monitoring plan. Additionally, a similar statement in Annex II of Directive 2001/18/EC clarifies that “If new information on the GMO and its effects on human health or the environment becomes available, the e.r.a. may need to be re-addressed in order to: =determine whether the risk has changed; = determine whether there is need for amending the risk management plan accordingly.” We suggest adding ‘Relevant’ to the beginning of the sentence.	… ***Relevant new ~~New~~*** information becoming available after the marketing authorisation should be included in the monitoring plan. The proposed change has been implemented.
Page 4 / 15 Paragraph 2 under section entitled **Experimental data contributing to the environmental risk assessment of a gene therapy product,** 2nd sentence	The sentence… “Assays used to demonstrate that the GMO is not infectious should have the same or better sensitivity as those used to detect the presence of the GMO.”…is contradictory to the statements on page 12 /15 under the *Testing methods* paragraph. While it is ideal for the assay (used to determine if the detected shed GMO is infectious or not) to have the same or better sensitivity than the PCR assay (that would be used to detect the GMO presence), the reality is that this is not likely. This reality is acknowledged in the *Testing methods* paragraph on page 12 and should also be reflected here, on page 4. We suggest adding ‘Ideally’ to the beginning of the sentence.	“***Ideally*****,** assays used to demonstrate that the GMO is not infectious should have the same or better sensitivity as those used to detect the presence of the GMO.” The proposed change has been implemented.
	• Second sentence of 3rd para on page 4. Reference to clinical trial authorisations should be removed.	Reference to clinical trial authorisation has been removed.
	• Last sentence of 5th para on page 4. “infectious” not a good term.	Infectious has been substituted by “capable of replication & dissemination/transmission.”
pg4, below header	GTMP – only acronym provided	This has been explained at first use.
P4, § 5	The definition of the term "infectious GMO" is necessary: for which kind	The term infectious has been substituted by “capable of replication &

	of organisms, patients...	dissemination/transmission".
pg4, same section	Determination of shedding is hampered by limitations conferred by the instability of many GTMPs in unfavourable matrices such as urine. Stability issues will therefore have a major impact on the reliability of the outcomes. It should be taken into account that 'state-of-the-art' detection methods often may not be present at the site where the in life phase is performed, thus requiring storage conditions that may further deteriorate the quality of samples and therefore decrease the chance of detecting the GTMP.	The practical limitations of monitoring shedding is acknowledged in this section.
pg4, 5th paragraph	'Assays used to demonstrate that the GMO is not infectious should have the same or a better sensitivity as those used to detect the presence of the GMO.'. The definition of infectious is not completely clear in this respect. It would be appropriate to accurately define 'infectious', e.g. binding and entry of cells versus being able to enter cells resulting in expression of transgene, or one step further, being able to enter cells, multiply, and spread. The latter is creating the highest risk, and is therefore more important to assess than entry or transgene expression alone. Accurately define the word infectious in the context of this requirement:	The word infectious has been substituted by "capable of replication & dissemination/transmission".
pg4, 5th paragraph	'Assays used to demonstrate that the GMO is not infectious should have the same or a better sensitivity as those used to detect the presence of the GMO.' – Infectivity of shed GMO will be typically difficult to establish: 1) stability considerations: similar to the previous comment, stability in an unfavourable matrix is limited; 2) infectivity assays generally require a multiplicity of infection (MOI) that is well above 1 (e.g. ratios of 1000 viral particles to cells are not uncommon). Added to the fact that the matrix will need to be diluted to avoid killing the cells, the requirement regarding the sensitivity cannot be met. A more balanced statement is provided on pg 12 (last paragraph of section 'Step 3').	The wording has been changed to 'Therefore, assays used to demonstrate that the GMO is not capable of replication and dissemination or transmission should have the same or a better sensitivity as those used to detect the presence of the GMO.' A more balanced statement is provided in the section on step 3.
	Comments to Step 1, pp. 5 – 10	Major changes have been made in the document, mainly involving texts being moved in the document. Not all of these changes are mentioned here.
The nature of Step 1	The first step is 'hazard identification'. This is explained extensively in the title, which actually could better be the first paragraph of the text.	The title has been reduced to to 'Identification of characteristics of the GMO which may cause adverse effects'. The rest of the text in the title is used as an introductory test.

	We would advise to start this section with an introduction on the different aspects of hazard identification, that are will be treated later on in the text, e.g.: - The concept of hazard identification for an ERA - Direct and indirect effects (we will argue later on that it is dubious whether this should be a separate item) - Hazards associated with wild type parental organisms / viruses - Hazards arising from the transgene - Hazards arising from the GMO We propose that you make these the headings of the subsequent text. Many of the texts that are now in Step 1 in the Guidance can be used under these headings. The main purpose of our comment is to get a clearer structure of this part of the text. We will provide our comments according to this structure. First, however, we provide comments on the adoption of the Precautionary Principle, and the use of worst case scenarios, that does no belong in Step 1 of the ERA.	A worst case scenario is not included to determine the actual hazards but should be adopted in step 3 describing the evaluation of the likelihood. A new text explaining worst case scenarios has been added in the text describing step 3.
Adoption of the Precautionary Principle	An explanation of the role of the Precautionary Principle (PP) in risk assessment is quite important. This is however not the stage of risk assessment where the precautionary principle plays a role. We quote the Communication of the European Commission on this point: 'There is a controversy as to the role of scientific uncertainty in risk analysis, and notably as to whether it belongs under risk assessment or risk management. This controversy springs from confusion between a prudential approach and application of the precautionary principle. These two aspects are complementary but should not be confounded. The prudential approach is part of risk assessment policy which is determined before any risk assessment takes place and which is based on the elements described in 5.1.3; it is therefore an integral part of the scientific opinion delivered by the risk evaluators. On the other hand, application of the precautionary principle is part of risk management, when scientific uncertainty precludes a full assessment of the risk and when decision-makers consider that the chosen level of environmental protection or of human, animal and plant health may be in jeopardy.'	The application of the PP belongs to step 5 of the ERA, and should be treated in detail there. The heading mentioning the precautionary principle has been deleted. A paragraph on worst case scenarios has been added elsewhere. It could also be part of an explanatory text to 'Methodology of the ERA', where its role in the ERA could be explained, in particular in step 4 A paragraph on the use of the precautionary principle has been added. (in this step the conclusion can be drawn that the PP should be invoked) and in step 5 (where its procedures should be explained). The addition in step 4 takes care of this.
	• 4th para on page 5. Perhaps the chosen example of a "worst case scenario" is not appropriate as it is a real product currently	The reference has been removed.

	going through the authorisation procedure.	
	• 4th para on page 5, the sentence beginning "If ganciclovir is administrated at …", and again further down the para. If this is referring to the patient, then this is out of scope of the ERA. If it is intended to mean "administered to another member of the public, by e.g., an accident", then it should probably say this. It needs to be made clear that the ERA is not concerned with the patient at all. Perhaps it would also be useful to point out to the reader that ganciclovir is not the GMO, but is used in conjunction with the GMO.	Section has been deleted.
pg5, section 4 (mid page)	The example provided here describes a number of steps required to assess the risk. A flow chart may greatly aid in illustrating which aspects need to be considered.	Description of the various steps has been edited which makes a flow chart no longer needed.
The use of worse case scenarios	In the hazard identification a worse case scenario may be used. Worse case scenarios are particularly useful if the actual incidence of a certain event is difficult to assess. Rather than spending effort on this assessment, it is fully acceptable in the ERA to suppose that the incidence is 1: it will occur, and to develop the ERA based on that supposition.	Explained in this way, the aspects of the worse case scenario that are highlighted typically belong to Step 3 of the ERA: evaluation of the likelihood of occurrence. The example that is provided focuses on these aspects. It would probably be more effective if it would be explained into much less detail, providing only the framework that is essential for the discussion. The section on worst case scenarios has been deleted here, and moved to step 3. Other examples could probably be constructed, where the worst case approach could apply to Step 1 of the ERA, e.g. maximizing an effect if no data are available as to the actual effect. It might therefore be a good idea to describe the use of worst case scenarios in the 'Methodology of the ERA'.
The concept of hazard identification for an ERA	The major point that should be made is that hazards are identified based on scenarios, i.e. causal chains of events that show how the application of the GMO as medicinal product could lead to adverse environmental effects. Adverse environmental effects are effects on man and other organisms in the environment that may occur when the GMO spreads into the environment.	This would require a new paragraph in the text. The term 'hazard identification' has been added.
	• 2nd para, page 7. It has been noticed that there appears to be an undeleted drafting note. The section on "safety strategies for retroviral vectors" (top of page 7). It has been poorly drafted (e.g. two different meanings for the phrase "packaging sequence") and this section is somewhat out of date (e.g. would	Section has been shortened.

	anyone consider using systems in which gag/pol/env are provided from one RNA; there is no mention of lentiviral vectors etc). This needs careful re-drafting.	
	• 2nd para, page 8. Sentence beginning "A GMO may contain exogenous genes".	The word exogenous has been replaced with "novel" genes.
	• 3rd para, page 8. The penultimate sentence of this para "…. complementation of missing genes in the *patient*.." The point to make here is exposure of the GMO, modified or otherwise, not to the patient, but to a member of the public or organisms in the environment.	Text has been redrafted.
	• 1st para, page 9. 1st sentence "In the event of exposure to humans"… It may be wise to stress the point again here that you mean "to humans, *other than the patient,* the availability…"	The wording "other than the patient" has been added.
P8, § 3	The last sentence of this paragraph could be completed by this: "The possible effects of a GMO with impaired immune evasion systems in individuals who may be or become immunosuppressed during the treatment should also be considered. This could indeed lead to undesirable effects of the administrated living GMO such as its proliferation or amplification."	Text has been changed.
P9 last § and the next § on P10	Both paragraphs are entitled "Recombination between related viruses". Indeed, comment on the recombination of adenovirus in the second paragraph is, to some extend, redundant with similar comments raised in the first paragraph. Therefore, for the sake of clarity, it is proposed to merge both paragraphs into a single one and rephrase them as proposed. **Recombination between related viruses**. Whilst the phenotype of the genetically modified virus is the primary consideration, some thought must also be given to the possibility that harmful sequences may be transferred as the result of a recombination event. Scenarios that need to be considered include the possibility that a disabled vector might recombine with the wild-type virus or with viral sequences present in the infected cell and revert to a replication-competent derivative of the GMO. For example, it has been shown that many healthy adults have adenoviral sequences present in their respiratory epithelium, which could putatively recombine with adenoviral vectors. In many viruses, such as adenovirus, it is reasonable to assume that the repair of the	Text has been changed.

	disabling mutation would result in the loss of genetic inserts that are positioned at the site of the disabling mutation. Inserted sequences should be so positioned wherever possible. The decision to insert genes at another site should be fully justified in the risk assessment. However, this may not be the case in larger viruses such as herpes or poxviruses. In addition other viruses and viral sequences may be able to complement disabled vectors. For example, human papillomavirus (HPV) and Epstein-Barr virus proteins have been shown to complement E1A mutant adenoviruses in trans. Therefore in the environmental risk assessment the presence of other viral sequences should be considered.	
pg9/10	Section 'Recombination between related viruses' is present twice, but the content is partially different.	Text has been changed.
pg10, top paragraph	'However, this may not ……poxviruses' – it is not clear to which sentence the 'however' refers to.	Text has been changed.
Direct and indirect effects	What exactly are 'direct' effects and 'indirect' effects is difficult to define. Directive 2001/18/EC makes a difference between direct effects and those effects that require a causal chain of events, but it can be argued that any effect, also a direct one, relies on a causal chain of events. It is not useful to try and make a definition here.	The important point here is that hazard identification should take into account 'direct' effects of the GMO itself, and effects that require some other factor, e.g. complementation by or recombination with another virus, extension of tissue or host specificity, and that could be called 'indirect' for that reason. We think that this argumentation does not merit a high profile; it could very well be part of the 'concept of hazard identification'. The new paragraph has no heading; its first sentence reads 'The ERA also needs to consider direct and indirect, immediate and delayed effects of the final GMO.' The paragraph starting 'An example of an indirect effect' has been linked to the previous paragraph.
Hazards associated with wild type parental organisms / viruses	The text covers the main points of importance. As it is based on casuistry, it will be hard for the reader to get a comprehensive picture of the factors that are important for an ERA. A listing of the factors would be more instructive.	A listing of traits that should / could be considered here can be derived from the text; the examples could be used then to further clarify the list. The text has been shortened and changed accordingly.
Safety strategies for retroviral	The subject of 'safety strategies' as it is presented here belongs more to risk management, for a particular case. What is important in general is the fact that in many cases the viral vector will be replication deficient. On page 13 there is also a paragraph on replication deficiency. It is not	Text has been redrafted.

vectors Site of insertion of the transgene (page 7)	easy to find an appropriate place for these considerations, but they should figure early in the document, probably in the section on 'methodology of the ERA' (page 4). The considerations under 'Site of insertion of the transgene' can also be taken into account in this discussion. Make a general section on replication defective viral vectors; take into considerations way in which a replication defective vector could start replicating again: by recombination, or by complementation by wild type virus / genes (like in production cell lines).	
Hazards arising directly from the inserted gene/element	It should be made clear that this is the crux of the ERA. The hazards posed by the application of the GMO stem from the considerations of the transgene, and are put into perspective by the considerations on the vector, that the document has been talking about until now.	This section has been redrafted.
Hazards arising from the final GMO: alteration of existing pathogenic traits	From here on the typography of the document is unclear: this should be a main heading, with the subsequent headings being sub-headings. The next main heading is 'Transfer of harmful genes' Again, we would prefer a clearly structured text, stating the main points to be considered, and that is less dependent on casuistry.	The structure has been modified.
Transfer of harmful gene sequences	We think that this is not a hazard like the others. It is the basis of whether there are any environmental hazards. If no transfer of sequences to organisms in the environment can occur, the other hazards do not have to be taken into consideration in an ERA. This could best be explained in the 'methodology of the ERA' section. Put this discussion, or at least mention its rationales, in the general section on 'methodology of the ERA'. A more developed argumentation as we see it is: - Transfer of sequences is a first consideration in the ERA: if there is no transfer, that finishes the ERA However, it will be hard to totally exclude transfer. Therefore the other	This suggestion has been included in the redrafted version of the guideline.

	considerations also need to be taken into account in order to establish the level of potential harm. If the potential harm is high, this could constitute an appreciable risk together with even a very low chance of transfer.	
	Comments to Step 2, page 10	
Title	Keep the title short: 'Evaluation of the consequences … occurs'. The remainder of the title can be the first paragraph.	Title has been shortened.
Evaluation of potential consequences, page 10	This evaluation should focus on the hazards identified in step 1. The considerations mentioned here in bullets may be relevant in some cases, but do not help in general to evaluate the hazards A short elaboration on the first sentence, stating that the adverse effects found in step 1 have to be taken into consideration here, probably suffices here. In the practice of performing an ERA, steps 1 and 2 as they are formally discriminated, are one and the same.	A sentence has been incorporated indicating that the evaluation of the potential consequences should focus on the hazards that have been identified in step 1 of the ERA.
	Comments to Step 3, page 10 - 12	
Title	Shorten title, similar to steps 1 and 2.	Title has been shortened.
Production strategies, page 11	These considerations belong to the section that we proposed to make, on replication competence.	These considerations have been included in the redrafted section on Hazards associated with the parental / recipient wildtype virus.
Consideration of the ability for infection in vivo	These considerations belong to the section on transfer of sequences.	These considerations have been moved.
Probability that rare events will occur, page 11	It appears to us that this section is not about rare events, but rather about events for which it is not straightforward to determine a frequency of occurrence. In fact, this is the case for most issues in GMO risk assessment. It is also the case for rates of mutation and recombination. Parts of this discussion have relevance to other steps, to the ERA in general and to the application of the PP.	Parts of this discussion have been included in sections with more general considerations.
Testing methods (page 12)	The subject of testing methods, i.e. the merits and problems of different testing methods and how to interpret test results, is very important in general, and should be more visible in the document, e.g. in the 'methodology of the ERA'.	An example of problems with testing methods has been included in a section on testing for shedding.

	• 1st para, page 11, last sentence. "if the *ERA* is still incomplete…". Should this read "If the *data are* still incomplete.." ?	Text has been changed.
	• 4th para, page 11, 1st sentence. "…its ability to spread within the host or within a community." Perhaps should replace the word "host" with "*patient, and therefore* within a community".	Text has been changed.
	Comments to Step 4, page 12-13	
Title	Shorten title, similar to steps 1 - 3.	Title has been shortened.
	Comments to Step 5, page 13	
Title	Shorten title, similar to steps 1 - 4.	Title has been shortened.
	In our experience it is important to stress that only those measures that have relevance to environmental safety should be mentioned here. There is a tendency to simply copy the measures that are important for patient care; these do not necessarily apply to environmental safety.	Such a statement would be confusing and has not been incorporated.
Emergency plan, SOPs, waste treatment, post market monitoring, page 14	These subjects belong in a general section. They are not a sub-paragraph of 'demonstrating replicating incompetence'.	The paragraph on demonstrating replication incompetence has been removed therefore also the suggestion that they are part of a paragraph on demonstrating replication incompetence is no longer present
	• Page 13 & 14. Guidance on post market monitoring is not sufficient. See previous comments on this subject also. The differences between the 2 types of post market monitoring under the deliberate release legislation for the marketing of GMOs should also be clearly explained.	An explanation has been included.
Pg 13, item IV	Control measures to minimize aerosols Please give examples of these, to clarify this statement.	Clarification has been included.
pg13 bottom	The first two paragraphs of 'Demonstrating replication incompetence' contain overlapping information.	Text has been redrafted.
	Comments to Step 6, page 14	

Title	Shorten title, similar to steps 1 - 5.	Title has been shortened
Determination of overall risk	More guidance is needed here; reference could be made to Module 1.6.2.	
P14, § 3	A paragraph containing the precise parameters (protocols...) of recruitment of patients could be included into the ERA dossier in order to evaluate their health status (immune status…) and to consider the risk to have a mistake or an unexpected event which could be followed by injurious consequences for the patients and/or the environment. The SOPs for handling accidental spillage and waste should also be provided.	Recruitment of patients is mainly of interest for clinical trials. No change to the text has been made.
P14, definitions	The definition of a GMO, in the context of this kind of dossier, is necessary.	The context of a GMO has not been additionally defined.
	DEFINITIONS	