

TECHNICAL REPORT OF EFSA

Outcome of the public consultation on the draft Scientific Opinion of the Scientific Panel on Genetically Modified Organisms (GMO) on the Guidance on the risk assessment of genetically modified microorganisms and their food and feed products¹

European Food Safety Authority^{2, 3, 4}

European Food Safety Authority (EFSA), Parma, Italy

SUMMARY

On 20 October 2010, the Panel on Genetically Modified Organisms (GMO Panel) of the European Food Safety Authority (EFSA) endorsed a draft scientific opinion on the guidance on the risk assessment of genetically modified microorganisms (GMMs) and their food and feed products. This Scientific Report summarises the comments received through the public consultation and outlines how these were taken into account in the final scientific opinion.

EFSA received 268 comments on the draft guidance from 24 interested parties (consumer groups, non-governmental organisations, consultant associations, industry organisations and national assessment bodies). All the public comments received that were within the remit of the EFSA GMO Panel were assessed and the guidance on the risk assessment of genetically modified microorganisms and their food and feed products was revised taking these relevant comments into consideration. The EFSA GMO Panel addressed the general comments that were related to the structure and principles of this approach, as well as more technical comments related to specific issues.

The final guidance of the GMO Panel (EFSA Panel on Genetically Modified Organisms (GMO), 2011) provides updated guidance for the preparation and presentation of applications involving GMMs. EFSA has committed to publish a Technical Report on the outcome of the consultation on the guidance. This Technical Report summarises the relevant comments received through the consultation and outlines how these were taken into account in the final guidance.

¹ On request of EFSA, Question EFSA-Q-2010-01270, issued on 22 November 2010.

² The Guidance on the risk assessment of genetically modified microorganisms and their products intended for food and feed use is published on the EFSA Journal 2011;9(6):2193

³ Correspondence: GMO@efsa.europa.eu

⁴ Acknowledgement: EFSA wishes to thank the members of the Working Group on Updating the GMM Guidance Document for the preparation of this EFSA scientific output: Detlef Bartsch (member until 28 March 2011), Niels Bohse Hendriksen, John Heritage, Lieve Herman, Klaus-Dieter Jany, Sirpa Kärenlampi, Martinus Løvik, Annette Pöting, Christoph Tebbe, John Threlfall and Atte von Wright, and EFSA's staff members Jaime Aguilera and Ana Gomes for the support provided to this EFSA scientific output.

Suggested citation: European Food Safety Authority; Outcome of the public consultation on the draft Scientific Opinion of the Scientific Panel on Genetically Modified Organisms (GMO) on the Guidance on the risk assessment of genetically modified microorganisms and their food and feed products. Supporting Publications 2011:EN-165. [77 pp.]. Available online: <http://www.efsa.europa.eu>

TABLE OF CONTENTS

Summary	1
Table of contents	2
Background	3
Comments received	3
Screening and evaluation of comments received	3
1. General comments	3
2. Specific comments	4
Incorporation of the comments in the scientific opinion	5
CONCLUSION	6
REFERENCES	7
Appendix	8
Table of Public Comments	9

BACKGROUND

The European Food Safety Authority (EFSA) asked the Panel on Genetically Modified Organisms (GMO Panel) to establish a Working Group with the aim of updating the Guidance Document for the risk assessment of genetically modified microorganisms and their derived products intended for food and feed use (EFSA, 2006)⁵. To complete its mandate, the Working Group:

- i) reviewed the existing Guidance Document, and identified areas of improvement,
- ii) considered input received from the Member States and applicants on the existing Guidance Document and
- iii) discussed and developed improvements for those areas.

On 20 October 2010, the EFSA GMO Panel endorsed a draft scientific opinion on Guidance on the risk assessment of genetically modified microorganisms and their food and feed products, with the aim of launching it for a public consultation.

In line with EFSA's policy on openness and transparency and in order for EFSA to receive comments from the scientific community and stakeholders on its work, EFSA is engaged in public consultation on key issues. The work on the assessment of the safety of GMMs and their food and feed products is considered to be such an issue. Accordingly, the draft guidance was released for public consultation on EFSA's homepage⁶ for nine weeks (from 29 November 2010 until 31 January 2011). Stakeholders were informed and invited to submit comments.

EFSA has committed to publish a Technical Report on the outcome of the consultation on the draft guidance. This Technical Report summarises the relevant comments received through the consultation and outlines how these were taken into account in the final guidance.

COMMENTS RECEIVED

At the end of the public consultation period, EFSA had received 268 comments from 24 interested parties (consumer groups, non-governmental organisations, consultant associations, industry organisations and national assessment bodies). All comments received were scrutinised by the GMO Unit. Comments within the remit of EFSA were considered by the EFSA GMO Panel, in particular by its Working Group on Updating the GMM Guidance Document, when preparing the final guidance (EFSA Panel on Genetically Modified Organisms (GMO), 2011). The comments were subsequently compiled with reference to the contributor and the section of the draft guidance to which the comment referred (see Appendix). Comments submitted formally on behalf of an organisation appear with the name of the organisation.

SCREENING AND EVALUATION OF COMMENTS RECEIVED

1. General comments

In general, the comments were constructive and aimed to help improving the draft guidance. There was a general agreement that the updated guidance is clear and easy to follow, and more prescriptive than previously published guidance. The presence of a figure and a table specifying which requirements apply for different products was also acknowledged, and some commentators suggested to align them better with the main text.

⁵Mandate number M-2009-0114. Question number EFSA-Q-2009-00521.

⁶<http://www.efsa.europa.eu/en/consultationsclosed/call/gmo101129.htm>

Some comments related to the structure of the guidance, which is significantly different from previous guidance on GMMs. Some commentators criticised that the explanations of the different steps to conduct the risk assessment had not been gathered into a single chapter. The scope of the document and its legal framework were also criticised by some commentators. Comments referred to lack of clarity about the definition of the categories of different products involving GMMs and the extent to which each category is covered by the guidance. Some comments related to the coverage of synthetic biology. Other comments expressed difficulties in aligning the different sections of the guidance –in particular those in which the scientific information requirements are specified– with the information requirements stated in the current European legislations on GMOs. Some comments also reported that there was a lack of clarity concerning which of the different products would fall under which legislations.

Some comments questioned the adequacy of the principles for the risk assessment proposed in the draft guidance. Concerns were expressed about the use of the comparative approach for the risk assessment of GMMs, suggesting that in many cases an adequate comparator would be impossible to identify. Other comments pointed out that the comparative approach would not enable to identify unintended effects. The value of the Qualified Presumption of Safety (QPS) (refs EFSA, 2007 and update EFSA, 2010) status of the recipient strain for the risk assessment of GMMs was also questioned by some commentators. On the other hand, comments were received that welcomed its use and prompted to extend it to filamentous fungi.

There were also suggestions for editorial improvements and clarifications. Furthermore, a few proposals to correct or add new references to scientific publications were provided.

2. Specific comments

Major and/or repeated technical comments related to the specifics addressed in the different sections of the guidance are summarised as follows:

Scientific information requirements on recipient, donor and GMM

Some comments claimed that the amount of information required with respect to the recipient organism and the source of donor DNA has been weakened with respect to the existing Guidance. Conversely, other comments claimed that some of the requested information, particularly that on the donor species, was unnecessary for the risk assessment. With respect to the GMM, some commentators criticised the request to deposit it in a recognised culture collection. Moreover, they questioned the basis for the number of batches requested for the analysis of genetic stability.

The possibility to omit certain information requirements when not applicable, providing instead a rationale for it, was indicated in other comments. In this sense, more guidance on when this information would not be relevant or applicable was requested.

Scientific information requirements on the product. Compositional and nutritional analyses

Some comments pointed to the need for more prescriptive information on the product, providing more detailed guidance on which type of information should be provided for each case. Other comments claimed that the information requested on physical and technological properties of products made with GMMs was unnecessary, given the scope of the guidance.

Toxicology

Some commentators suggested to extend the requirement to perform animal toxicological testing to all cases (GMMs and products), independently of the existence of other scientific evidence concerning their safety. In turn, other commentators suggested the provision of more guidance on which cases the animal feeding trials would be necessary.

Allergenicity

Some comments received questioned the need and adequacy of some of the techniques suggested by the guidance to study the potential allergenicity of GMMs and some of their products.

Environmental risk assessment

Some comments claimed that an environmental risk assessment (ERA) of products belonging to categories 1 and 2 should not be necessary when the production strain has been confirmed as Class I under the legislations on contained use.

Post-market environmental monitoring

The need for a post-market environmental monitoring for products belonging to Category 3 was criticised in some comments on grounds that they do not fall under the legislations on deliberate release of GMOs.

INCORPORATION OF THE COMMENTS IN THE GUIDANCE

The EFSA GMO Panel and, in particular, its Working Group on Updating the GMM Guidance Document, discussed the comments at several dedicated meetings. Many of the comments received were useful and of a high scientific value. These were considered adequate to enhance the scientific quality and clarity of the guidance. These comments were taken into account and the guidance was revised where appropriate.

First of all, and as a response to the suggestions expressed by some commentators, the text in the final guidance has been revised in such a way that the document is more focused in risk assessment aspects and the step-by-step-approach for conducting the risk assessment of GMMs and their products. The comparative approach is still considered as an adequate strategy for the risk assessment of GMMs and their products. In this way, guidance on the choice of an adequate comparator has been streamlined to take into account different circumstances that may occur, e.g. lack of previously unmodified recipient organism. The text also provides guidance for those cases in which no comparative approach is possible. The usefulness of the QPS for the risk assessment is retained, but QPS is not extended to filamentous fungi, as this issue is outside the mandate and remit of the GMO Panel.

The introduction of the guidance has been revised to clarify the different types of products covered, as requested in several comments. It is now clearly stated that the guidance is focused only on GMMs and their products intended for food and feed use. Other possible products, including those from synthetic biology, which is a concept not yet well defined, are not mature enough to enable specific considerations in the GMM guidance.

Another aspect which has been revised in response to several comments was the categorisation of the GMMs and their products covered by the guidance. This categorisation is built on scientific criteria, mainly associated to the extent of the ERA. The amount of scientific information to be provided for each category has been reviewed and Table 1 modified where needed to fully reflect the text. In addition, different legislations at EU level cover the range of products involving GMMs, depending on their nature and use. In order to improve clarity and offer better guidance, the final text now states the extent to which each product is covered, and which other guidance or legal guidelines, if any, are also applicable just after the categorisation is described. The guidance covers products under Regulation (EC) No 1829/2003 fully. Products falling under other legislation are covered partially, and it is specified which parts of the guidance should be followed for each case.

Some of the scientific information to be provided for the risk assessment of GMMs and their products has been reviewed in the light of different comments. The requirements concerning the possible presence of antibiotic resistance genes in the GMM have been modified to take into account the possibility that those genes are associated with mobile genetic elements. Additionally, the number of

batches required for certain studies such as genetic stability, or testing the presence of GMM cells or recombinant genes in the product, has been revised to take into account the characteristics of the product and the production process. Sampling strategies are still suggested, although, after the revision, the guidance indicates that different approaches may be considered, as long as their validity is properly justified. With respect to the request that the production strain is deposited in a recognised culture collection, the GMO Panel stresses the need to safeguard access to the GMM in case the assessment needs to be reviewed (e.g. as motivated by the outcome of any post-market monitoring or any adverse effect not detected during the pre-market risk assessment). Deposition of the strain in a recognised culture collection would enable risk assessors to have access to it. In this sense, it is noteworthy that no public access is requested: the deposition may be done under conditions of confidentiality.

With respect to the toxicological assessment of GMMs and their products, the information requirements for the newly expressed proteins have been revised. Furthermore, the necessity of animal feeding trials for the toxicological assessment has been reconsidered as suggested. Due to the wide variety of possible products, the requirements for toxicological testing should be considered on a case-by-case basis. It is recognised that there are cases for which animal feeding trials may be necessary (e.g. when there is no comparator available). The guidance has been modified to better express these considerations.

Regarding allergenicity, further guidance has been introduced on different possibilities to assess the potential allergenicity of the GMM and their products.

In the sections of the document dealing with ERA, clarifications have also been introduced to specify what kind of assessment is applied depending on the category of the product. It has been also clarified that an ERA made according to Directive 2001/18/EC should take due account of potential cumulative long-term effects associated with the interaction with other GMMs and the environment. In addition, the text has been revised to provide better guidance on the purposes of the post-market environmental monitoring, and in which cases a post-market environmental monitoring or a case-specific monitoring should be necessary.

CONCLUSION

All comments received through the public consultation were scrutinised by the GMO Unit and considered by the EFSA GMO Panel, in particular by its Working Group on Updating the GMM Guidance Document, when revising the draft guidance on the risk assessment of genetically modified microorganisms and their food and feed products.

The EFSA GMO Panel acknowledges the usefulness and quality of a large number of comments and would like to thank all commentators for their interest and input to its current and future work.

REFERENCES

- EFSA (European Food Safety Authority), 2006. Guidance document of the Scientific Panel on Genetically Modified Organisms for the risk assessment of genetically modified microorganisms and their derived products intended for food and feed use, *The EFSA Journal* 374, 1-115.
- EFSA Panel on Genetically Modified Organisms (GMO), 2011. Scientific Opinion on Guidance on the risk assessment of genetically modified microorganisms and their products intended for food and feed use. *EFSA Journal* 2011;9(6):2193, 77 pp.

APPENDIX

The text below is from the EFSA website of the public consultation:

Public consultation on: "Guidance on the risk assessment of genetically modified microorganisms and their food and feed products"

Deadline: 31 January 2011

EFSA's Panel on Genetically Modified Organisms (GMO) has launched an open consultation on a Guidance on the risk assessment of genetically modified microorganisms and their food and feed products. This document provides updated guidance for the preparation and presentation of applications involving genetically modified microorganisms (GMMs). The Guidance covers GMMs for food and feed use: food and feed containing or consisting of GMMs, food and feed produced from or containing food ingredients or feed materials produced from GMMs, as well as substances such as additives, vitamins and enzymes produced with GMMs. In particular, it provides detailed guidance to assist in the preparation and presentation of applications to market GMMs and their products for food and/or feed use, according to Regulation (EC) No 1829/2003.

This Guidance updates and supersedes the current Guidance Document for the risk assessment of GMMs and their derived products intended for food and feed, adopted by the EFSA GMO Panel in 2006.

Interested parties are invited to submit written comments by 24 January 2011. Please use exclusively the electronic template provided with the documents to submit comments and refer to the line and page numbers. Please note that comments submitted by e-mail or by post cannot be taken into account and that a submission will not be considered if it is:

- submitted after the deadline set out in the call
- presented in any form other than what is provided for in the instructions and template
- not related to the contents of the document
- contains complaints against institutions, personal accusations, irrelevant or offensive statements or material
- is related to policy or risk management aspects, which is out of the scope of EFSA's activity.

EFSA will assess all comments from interested parties which are submitted in line with the criteria above. The comments will be further considered by the relevant EFSA Panel and taken into consideration if found to be relevant.

Publication date: 29 November 2010

TABLE OF PUBLIC COMMENTS

Table of Member States and stakeholders comments received during the public consultation on the draft Scientific Opinion of the Scientific Panel on Genetically Modified Organisms (GMO) on the Guidance on the risk assessment of genetically modified microorganisms and their food and feed products

	ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT
1	United States of America, Food and Drug Administration	USA	Abstract	The U.S. Food and Drug Administration (FDA) would like thank the European Food Safety Authority (EFSA) for the opportunity to offer comments as part of EFSA's public consultation on "Guidance on the risk assessment of genetically modified microorganisms and their food and feed products." It is clear that a great deal of time and consideration have gone into the development of this updated guidance document. The FDA offers the following comments.
2	Federal Agency for Nature Conservation	DEU	Abstract	<p>The entry mask does not provide for the possibility to make some general comments. Therefore we take the liberty to place some general comments under Abstract and Summary.</p> <p>General Comments part I (See Summary for part II)</p> <p>The draft is not in compliance with major principles of the environmental risk assessment of Directive 2001/18/EC, such as integrated assessment of the GMO, protection of the environment and precautionary principle (See general comments on part II). Instead, the risk assessment of the draft heavily relies on the comparison of the GMO to a non-modified organism and misses a comprehensive concept of a bottom up assessment of food/feed safety and environmental aspects. The sole consideration of the differences between a GMM and its comparator leads to a mainly product-based assessment and thus departs from the principles of the environmental risk assessment as presented in the Directive 2001/18/EC that emphasizes the protection of the environment and the precautionary principle and stipulates an integrated assessment of the GMO. Also, the draft does not contain a coherent concept for the identification of unintended effects (See general comments on part II).</p> <p>It is appreciated that a broad documentation for the e.r.a. of GMMs of the 3rd and 4th category is required; nevertheless the draft focuses heavily on food and feed safety assessment. Altogether the importance of considering the environmental impact of GMMs should be further strengthened.</p> <p>The draft does not meet several of the specific provisions of Directive 2001/18/EC Annex IIIA for e.r.a. and moves some of them into PMEM (See general comments on III.B and specific comments on Chapters 1.2.1, 1.3.1, 1.3.2, 1.4.5, 1.4.8, and 3). The PMEM should be more focussed on the specific requirements of placing on the market of GMM.</p> <p>There is no reference to Directive 2001/18/EC (e.g. recital 22, Article 4, 2. or Annex II) when antibiotic resistance marker genes are addressed in the draft. Furthermore, several specifications concerning antibiotic resistance genes were not adapted from the present guideline to the draft, namely that (i) antibiotic resistances not normally associated with the GMM genus or species should be highlighted, that (ii) micro-organisms in which antibiotic resistance is conferred by an inactivating mechanism encoded by a gene that is located on a mobile genetic element and targeting an agent(s) in clinical or veterinary use should not be used in the recipient and that (iii) the level of gene expression and the potential for the induction of gene expression should be evaluated when antibiotic resistances of particular concern are observed. These essential requirements need to be readopted in the present draft and the controversial use of antibiotic resistance marker genes should be discussed with the view of giving guidance for the recommended phasing out antibiotic resistance genes "which may have adverse effects on human health and the environment" (Article 4, General Obligations, para 2, second sentence, Directive 2001/18/EC).</p>
3	Belgian Biosafety Advisory	BEL	Abstract	Editorial comments:

ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT
Council			<p>General editorial comment: The wording "Directive 2001/18/EC" should be used throughout the text instead of "Directive 2001/18" (e.g. line 252, line 266, footnote 7; line 295) or "Directive 2001/18/ECC" in line 277, 279.</p> <p>Line 770. Typing error. ...other than the ones mentioned.....</p> <p>Line.772: EFSA, 2003a is not in the Reference list.</p> <p>Line.988: ... with allergens that are already known . Omit space between "known" and the "full stop".</p> <p>Line 901. Typing error. ... this (delete "in") should often, in practice...</p> <p>Line.991: "... to induce allergy in man or animals." May be replaced by "... to induce allergy in humans or animals."</p> <p>Line 1044. Typing error. the protein expressed by the newly introduced gene protein should...</p> <p>Line 1403. Printing error. difficult to predict. ((full stop))The applicant...</p> <p>Line 1539: Typing error : "food and feed" and not "food and fed"</p> <p>Line 1724-1729: References may be presented in a chronological order.</p> <p>Line 1798: Typing error : "Microorganism" and not "Micro Organism"</p> <p>Line 1826. Printing error. transferring genetic material genes ("genes" should be deleted)</p>
4 Belgian Biosafety Advisory Council	BEL	Abstract	<p>Line 2 - Title : The previous version of the Guidance focused on GMM and derived products intended for food and feed use. The new title is more general but also ambiguous as it could be interpreted in such a way that the new guidance covers all uses of GMMs (and not only food and feed uses).</p> <p>The same ambiguity comes from the reference which is made to Regulation (EC) 1107/2009 and Directive 98/8/EC on pages 8 and 9.</p> <p>As a consequence, a certain confusion about the exact scope of the Guidance remains. We are of the opinion that the title and the introductory paragraphs should be written in such a way that it is clear that the guidance only applies to food and feed applications.</p>
5 Federation of European Specialty Food Ingredients Industries	BEL	Summary	<p>The Federation of European Specialty Food Ingredients Industries (ELC) would like to indicate that it supports the comments its member association, the Association of Manufacturers and Formulators of Enzyme Products (Amfep), made on the draft Guidance.</p> <p>Best Regards, Caroline Rey (ELC)</p>
6 Federal Agency for Nature Conservation	DEU	Summary	<p>The entry mask does not provide for the possibility to make some general comments. Therefore we take the liberty to place some general comments under Abstract and Summary.</p>

ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT	
			<p>General Comments part II (See Abstract for part I)</p> <p>The scope is not well and incomprehensively defined since the cases for which the draft applies are dispersed over several Chapters (I. Scope of the document, I. Legal background, III.B.2 Information relating to the product).</p> <p>The risk assessment strategy should be explained in total in Chapter II and not be divided throughout the guideline to allow for better understanding. (See general comments on Chapter II). The handling of uncertainties is not properly discussed (See general comment on Chapter III.B.) and the risk assessment is not well and not specifically linked to the several legal references presented voluminously in Chapter I. Legal background. (See comments on Chapter I Legal Background and general comments on Chapter II).</p> <p>To improve the guidance the draft should indicate more often what kind of information (description, data, report or experimental evidence) is required and – in case of experimental data – specify the details and conditions. (See general comment on III.B.2.2, 2.4.6, comment on Table 1 and others).</p> <p>Many footnotes refer to legal documents which are better listed under references at the end of the document.</p>	
7	DSM	NLD	Summary	DSM finds the new guidance document more operational than its previous version, and well adapted to scientific progress.
8	on behalf of the Association of Veterinary Consultants	ESP	Summary	Summary: Lines 22-57. The updated guidance is clear, precise, easy to follow, prescriptive & includes key examples, hence a practical tool for anyone working in regulatory affairs.
9	Ajinomoto Eurolysine S.A.S.	GAB	Summary	<p>General comment</p> <p>The updated Guidance on the risk assessment of GMMs and their derived food and feed products prepared by the GMO Panel of EFSA, which takes into account a) scientific progress and b) the experience gained by EFSA in the evaluation of many dossiers involving GMMs since the 1st version in 2006, is highly appreciated. Compared to the 1st version of 2006 it is more operational and provides useful clarifications and better guidance on several points.</p>
10	Genencor, A Danisco Division	NLD	Summary	Genencor, A Danisco Division, agrees with the comments submitted by AMFEP, the Association of Manufacturers and Formulators of Enzyme Products.
11	Novozymes A/S	DNK	Summary	Novozymes A/S agrees with the comments submitted here by AMFEP.
12	FEFANA	BEL	Summary	Line 22: (general comment) We find the new guidance document more operational than its previous version, and well adapted to scientific progress.
13	AMFEP	BEL	Summary	(general comment) Amfep finds the new guidance document more operational than its previous version, and well adapted to scientific progress.
14	DSM	NLD	Background as provided by the EFSA GMO Panel	(line 134) Indeed, not all GMM / products fall under the scope of Regulation 1829/2003. A notable exemption from this scope is products obtained with GMMs fermented in contained use.
15	DSM	NLD	Background as provided by the EFSA GMO Panel	(line 129) Enzymes should be mentioned alongside additives, vitamins and flavourings.

ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT
16	DSM	NLD	Background as provided by the EFSA GMO Panel (general comment) A number of enzyme-producing GMMs have been evaluated in the recent past in e.g. France and Denmark according to requirements similar to those of the previous EFSA guidance. It should be specified that all evaluations performed for food enzyme GMMs by the French or Danish competent authorities exempt the applicant from providing possible additional data pursuant to the new guidance.
17	Ajinomoto Eurolysine S.A.S.	GAB	Background as provided by the EFSA GMO Panel Lines 134 to 136 Through this statement, it appears that the GMO Panel underlines that the approach it has developed for the risk assessment of GMMs and their food and feed derived products is science-based and independent of the legal categorisation which may apply to a group of products. Indeed, many food and feed products produced using, more precisely 'produced with' a GMMs in containment do not fall within the scope of Regulation (EC) No 1829/2003, as described in recital 16 of Regulation (EC) No 1829/2003 and in the 'report from the Commission to the Council and European Parliament on the implementation of Regulation (EC) No 1829/2003 (COM (2006) 626 final of 25.10.2006), section 10, p. 23.
18	Genencor, A Danisco Division	NLD	Background as provided by the EFSA GMO Panel Genencor, A Danisco Division, agrees with the comments submitted by AMFEP, the Association of Manufacturers and Formulators of Enzyme Products.
19	Novozymes A/S	DNK	Background as provided by the EFSA GMO Panel Novozymes A/S agrees with the comments submitted here by AMFEP.
20	FEFANA	BEL	Background as provided by the EFSA GMO Panel (line 134) Indeed, not all GMM / products fall under the scope of Regulation 1829/2003. A notable exemption from this scope is products obtained with GMMs fermented in contained use.
21	Food Standards Agency	GBR	I. INTRODUCTION UK expert Committee (ACNFP) Comment 1 (Introduction) In general the Committee found that the EFSA guidance is very thorough, well written, and easy to follow.
22	Novo Nordisk A/S	DNK	I. INTRODUCTION General We have noted that the guideline has been totally rephrased and that the paragraphs have been renumbered. We shall urge EFSA to deal with existing applications without claiming rephrasing or renumbering of the text in the existing applications. Claims of rearrangement and renumbering of existing material will cause large and unnecessary delays of the ongoing approval processes.
23	Ministry of Agriculture	ARG	I. INTRODUCTION CHAPTER I - Lines 163-167. On the scope: Suggest to consider the possibility to include bacteriophages, which can be used in food processing.
24	AMFEP	BEL	Background as provided by the EFSA GMO Panel (general comment) A number of enzyme-producing GMMs have been evaluated in the recent past in e.g. France and Denmark according to requirements similar to those of the previous EFSA guidance. It should be specified that all evaluations performed for food enzyme GMMs by the French or Danish competent authorities exempt the applicant from providing possible additional data pursuant to the new guidance. (line 129) Enzymes should be mentioned alongside additives, vitamins and flavourings. (line 134) Indeed, not all GMM / products fall under the scope of Regulation 1829/2003. A notable exemption from this scope is products obtained with GMMs fermented in contained use.

ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT	
25	Testbiotech	DEU	Scope of the document	<p>synthetic genes</p> <p>Line 174 We agree with the statement "Guidance on the risk assessment of microorganisms generated by Synthetic Biology requires a separate document which takes into account the unique features of such organisms." However, in</p> <p>Line 574 the Guidance refers to synthetic DNA that might be used in Genetically Modified Organisms. What is missing is a clear distinction between Synthetic Biology and those organisms that are assessed under the planned Guidance.</p>
26	Federal Agency for Nature Conservation	DEU	Scope of the document	<p>It should be clearly stated in this chapter whether the draft provides or provides not i) guidance for food feed and environmental aspects, ii) guidance for applications for market or for experimental release of GMMs as well and iii) guidance for deliberate release and for contained use as well.</p> <p>Line 168-176 This para presents an opinion about Synthetic Biology which has not left the state of fundamental research yet. Please clarify here that applications of Synthetic Biology are not covered by this draft document by simply adding it to the list in line 164-167. The remaining text in this para is dispensable.</p>
27	The Netherlands Commission on Genetic Modification (COGEM)	NLD	Scope of the document	<p>The GMMs covered in the guidance document include the domains of the Archaea, Bacteria and Eukarya (line 163). In the document Eukarya includes 'filamentous fungi, yeasts, protozoa, and microalgae' (line 163-164). From a biological and taxonomical point of view, the description of the organisms used is not precise. The term 'protozoa' is outdated and microalgae are not a well-defined group of organisms. Algae are present in various eukaryotic lineages. COGEM is of the opinion that EFSA should adhere to the latest taxonomic classification and should use terms that are taxonomically correct.</p>
28	Ministry of Rural Development	HUN	Scope of the document	<p>Line 168-176 Organisms created by synthetic biology have no history of safe use. Therefore the release of these into the environment or into the food/feed chain would be irresponsible. These organisms should only be kept under strictly contained conditions, mainly for research purposes.</p>
29	DSM	NLD	Scope of the document	<p>(lines 168-176) It is stated that synthetic biology will require separate guidelines, but no precise definition of synthetic biology is provided. Insertion of individual synthetic genes – even with unknown donor – does however not seem to fall under EFSA's definition of synthetic biology. Amfep proposes to modify the chapter on synthetic biology so that it only contains the first sentence (lines 168-170) followed by a sentence stating that separate guidance for synthetic biology GMM will be developed in a future update of the present document following the developments in the field of synthetic biology.</p>
30	Belgian Biosafety Advisory Council	BEL	Scope of the document	<p>In line 165, it is stated that the guidance does not cover the use of tissue cultures of plant or animal cells. What is the reasoning behind the exclusion of tissue cultures? We consider that for many aspects, the risk assessment of tissue cultures is similar to the risk assessment of other GMMs.</p> <p>Lines 168-176: - It is indeed important to keep in mind the current developments in the field of "synthetic biology", minimal genomes /cells, but also developments in nanobiotechnology.</p>
31	Belgian Biosafety Advisory Council	BEL	Scope of the document	<p>Line 162: Although the difference between "produced from GMMs" and "produced with GMMs" is explained in footnote 4 (and can also be found in the preamble of Regulation EC 1829/2003), we are of the opinion that section I of the guidance should better explain this difference and the fact that the scope of the guidance goes beyond applications submitted under Regulation (EC) 1829/2003.</p>

ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT	
			Such an explanation should also serve as a mean to clarify the status of GMMs of category 1 (Figure 1 and in Table 1), in particular as regards why information relating to the description of the product and to considerations of the GM product for human health is not required for this category.	
32	Genencor, A Danisco Division	NLD	Scope of the document	Genencor, A Danisco Division, agrees with the comments submitted by AMFEP, the Association of Manufacturers and Formulators of Enzyme Products.
33	Novozymes A/S	DNK	Scope of the document	Novozymes A/S agrees with the comments submitted here by AMFEP.
34	FEFANA	BEL	Scope of the document	Lines 168-176: It is stated that synthetic biology will require separate guidelines, but no precise definition of synthetic biology is provided. Insertion of individual synthetic genes – even with unknown donor does however not seem to fall under EFSA's definition of synthetic biology. We propose to modify the chapter on synthetic biology such that it only contains the first sentence (lines 168-170) followed by a sentence stating that separate guidance for synthetic biology GMM will be developed in a future update of the present document following the developments of the field of synthetic biology.
35	AMFEP	BEL	Scope of the document	(lines 168-176) It is stated that synthetic biology will require separate guidelines, but no precise definition of synthetic biology is provided. Insertion of individual synthetic genes – even with unknown donor – does however not seem to fall under EFSA's definition of synthetic biology. Amfep proposes to modify the chapter on synthetic biology so that it only contains the first sentence (lines 168-170) followed by a sentence stating that separate guidance for synthetic biology GMM will be developed in a future update of the present document following the developments in the field of synthetic biology.
36	Austrian Agency for Health and Food Safety	AUT	Legal background	line 288-292: Additives for use in animal nutrition (Regulation (EC) No 1831/2003): Please include the phrase “and therefore also fall within the scope of this guidance document” (as it was stated in the old guidance document). Suggestion: In addition, feed additives containing, consisting of, or produced from GMOs also fall within the scope of Regulation (EC) No 1829/2003 and have to be subject to an application under this Regulation and therefore also fall within the scope of this guidance document.
37	Federation of European Specialty Food Ingredients Industries	BEL	Legal background	The Federation of European Specialty Food Ingredients Industries (ELC) would like to comment on the sentence in lines 284 - 286. This sentence comes from recitals of the Food Improvement Agents Package whereas the corresponding articles leave less room for misinterpretation as to, when applicable, the sequence of authorisation. That is why we would suggest the following amendment, which aims to mention the specific article of regulation 1829/2003: "A food additive, a food enzyme, or flavouring or a source material which falls within the scope of Regulation (EC) No 1829/2003 should also be authorised in accordance with (that) the Article 5 of this Regulation". Best Regards, Caroline Rey (ELC)
38	Federal Agency for Nature Conservation	DEU	Legal background	This chapter is very voluminous although the reason for it remains unclear. If it is intended to provide a comprehensive overview about the legal background the various paras should be arranged in a chronicle order starting with the oldest one.

ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT
			<p>Line 178-180 It says here that the legal documents of the EU are the primary source of advice. However, the draft does not always and not consistently refer to these primary sources; in particular principles and strategies for R.A. of GMM in Chapter II are not deduced from the legal background and therefore insufficiently linked.</p> <p>Line 234-238 The legal background consists of several EU legal documents (Directives, Regulations and Decisions). However, the EFSA guidance document mentioned in line 234-238 is not a legal document. Either these lines should be deleted or an accompanying explanation is required here.</p> <p>Line 239-245 This para draws a sloping picture of the relationship between Directive 2001/18/EC and Regulation (EC) 1829/2003. It isn't just "necessary for the environmental risk assessment to comply with the requirements referred to in Directive 2001/18/EC", but the requirements for environmental risk assessment are actually laid down in Annex II of Directive 2001/18/EC and further specified in Commission Decision 2002/623/EC. Recital 9 of Regulation (EC) 1829/2003 is relevant for the interplay and should be referenced, saying that the new authorisation procedures for genetically modified food and feed should include the new principles introduced in Directive 2001/18/EC.</p> <p>Line 246-270 This para is relevant and welcome, but much too long and laborious.</p> <p>Line 271-279 The message of this para is relevant, but should be put in a few words under scope of the document, e.g. this document provides guidance for the intended release of GMMs, but not for their contained use, with a footnote referring to the Directive for contained use. If however, it is deemed required to discuss the matter of containment in this context, it should be done right in the text rather than in a footnote (see footnote 20).</p> <p>Line 280-287 This para should be rephrased to better clarify its relevance for the present draft. Central to this is to describe, which kind of food additives, food enzymes, or flavourings fall within the scope of Regulation (EC) No 1829/2003.</p>
39	DSM	NLD	<p>Legal background</p> <p>The sentence in lines 284-286 seems to imply that additives, enzymes and flavourings produced by GMMs would systematically fall under the scope of Regulation 1829/2003. In reality a food additive, food enzyme or food flavouring produced by a GMM in contained use do not fall under the scope of 1829/2003.</p> <p>(lines 289-292) We suggest to add a sentence at the end of this paragraph: "Feed additives produced by GMMs in contained use do not fall within the scope of Regulation (EC) 1829/2003".</p>
40	DSM	NLD	<p>Legal background</p> <p>(line 280) This title should read "Food improvement agents package".</p>
41	DSM	NLD	<p>Legal background</p> <p>The sentences in lines 276-279 should read: "Neither GMMs fermented under contained use nor their products fall under the scope of Regulation (EC) No 1829/2003 and Directive 2001/18/EC. However, products from GMMs fermented in contained use seem to be subject to the present guidance (categories 1 & 2). Additionally, GMMs, including those developed by self-cloning, which are released, are also subject to this guidance." Justification: as stated in the guidance, line 134, products obtained with the help of GMMs fermented in contained use are exempted from the scope of Regulation 1829/2003. Similarly, substances used as processing aids are exempted from the scope of Regulation 1829/2003.</p>

	ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT
42	Ajinomoto Eurolysine S.A.S.	FRA	Legal background	<p>1) General comment</p> <p>Although it is specified in footnote 11 that only EFSA views are reflected, the explanations provided as well on the legislative texts which may involve evaluation by EFSA GMO Panel according to the Guidance document proposed as on the articulation between different pieces of legislation is highly appreciated.</p> <p>2) Lines 271 to 279</p> <p>The views expressed on the interplay between Regulation (EC) No 1829/2003 and Directive 2001/18/EC (lines 239 to 245) and also of the interplay between Directive 2009/41/EC (contained use of GMMs) and both Directive 2001/18/EC and Regulation (EC) No 1829/2003 (lines 271 to 279) are welcome.</p> <p>In particular, EFSA indicates that :</p> <ul style="list-style-type: none"> - line 272: "The contained use of genetically modified microorganisms is regulated by Directive 2009/41/EC. ...", and - lines: 276-277: "GMMs kept under contained use do not fall under the scope of Regulation (EC) No 1829/2003 and Directive 2001/18/EC" <p>However, EFSA also indicates (lines 277-279 underline added) that " When GMMs, including those developed by self cloning, and their derived food or feed are released, they fall under the scope of Regulation (EC) No 1829/2003 and Directive 2001/18/EC and therefore are subject to this guidance."</p> <p>In the case of self-cloning, it could be appropriate to remind - because this technique has been the topic of many debates and a source of confusion, as EFSA is likely aware – the logic supporting EFSA position. Indeed this technique is not part of those listed in Annex I B to Directive 2001/18/EC (in connection with article 3 (1) yielding organisms to be excluded from (the scope) of this Directive. The Annex I B list is a limitative/exhaustive list. This technique is also not part of those listed in Annex I A, Part 2 (also a limitative/exhaustive list in connection to Article 2 (2) (b)) which are not considered to result in genetic modification.</p> <p>Therefore, a contrario, self-cloning may be part of those techniques considered as resulting in genetic modification and yielding organisms in the scope of Directive 2001/18/EC (and of Regulation 1829/2003), as provided by article 2 (2) (a) of this Directive : "genetic modification occurs at least through the use of the techniques listed in Annex I A, part 1. The list in Annex IA, part 1, contrary to the two previous lists is non limitative.</p> <p>EFSA should also be aware that Directives 2009/41/EC (formerly 90/219/EEC) and 2001/18/EC (formerly 90/220/EEC) were not always transcribed in the same way in the national legislation of the different EU Member States. In certain countries self cloning was excluded from the scope of as well contained use of GMMs as of dissemination of GMOs.</p> <p>In several countries outside the EU, the definition of self-cloning may differ from the EU one provided in Directive 2009/41/EC. Moreover, in some third countries, self-cloning is not considered to yield a GMO, even for dissemination in the environment. This may be a source of confusion for operators, especially producers located in third countries.</p> <p>3) Lines 277 to 279</p> <p>The sentence in lines 277 to 279 may be understood differently depending on whether considered from a scientific (risk assessment) point of view or from a legal (risk management) point of view.</p> <p>In this place of the document it has to be understood according to the risk assessment point of view, i.e., as indicated by EFSA in lines 135 –</p>

	ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT
				<p>136, "irrespective of whether or not they fall in the scope of Regulation (EC) No 1829/2003.</p> <p>For the legal position of food and feed products 'produced with' a GMM, please see previous comment made in regard of lines 134 to 136.</p>
43	Genencor, A Danisco Division	NLD	Legal background	Genencor, A Danisco Division, agrees with the comments submitted by AMFEP, the Association of Manufacturers and Formulators of Enzyme Products.
44	Novozymes A/S	DNK	Legal background	Novozymes A/S agrees with the comments submitted here by AMFEP.
45	FEFANA	BEL	Legal background	<p>Lines 199 to 203 deals with GMO and the differentiation of feed sources of GMO, then the description immediately changes to GMM impacts. Again, the different understanding of GMO (generally plants) and GMM (micro-organisms in fermentation processes) should be precised to have consistency even for the further risk assessment since there is normally the major difference that GMO plants will be alive when released and possible GMMs are inactivated.</p> <p>The sentences in lines 276-279 should read: "Neither GMMs fermented under contained use nor their products fall under the scope of Regulation (EC) No 1829/2003 and Directive 2001/18/EC. However, products from GMMs fermented in contained use are subject to the present guidance. Additionally, GMMs, including those developed by self-cloning, which are released, are also subject to this guidance." Justification: as stated in the guidance, line 134, products from GMMs fermented in contained use are exempted from the scope of Regulation 1829/2003. Similarly, processing aids are exempted from the scope of Regulation 1829/2003. But e.g. food enzymes produced from GMMs in contained use and used as processing aid are covered by the guidance.</p> <p>Line 280: This title should read "Food improvement agents package".</p> <p>Lines 289-292: We suggest to add a sentence at the end of this paragraph: "Feed additives produced by GMMs in contained use do not fall within the scope of Regulation (EC) 1829/2003 but should also be evaluated in accordance with the present guidance document."</p>
46	AMFEP	BEL	Legal background	<p>The sentences in lines 276-279 should read: "Neither GMMs fermented under contained use nor their products fall under the scope of Regulation (EC) No 1829/2003 and Directive 2001/18/EC. However, products from GMMs fermented in contained use seem to be subject to the present guidance (categories 1 & 2). Additionally, GMMs, including those developed by self-cloning, which are released, are also subject to this guidance." Justification: as stated in the guidance, line 134, products obtained with the help of GMMs fermented in contained use are exempted from the scope of Regulation 1829/2003. Similarly, processing aids are exempted from the scope of Regulation 1829/2003.</p> <p>(line 280) This title should read "Food improvement agents package".</p> <p>The sentence in lines 284-286 seems to imply that additives, enzymes and flavourings produced by GMMs would systematically fall under the scope of Regulation 1829/2003. In reality a food additive, food enzyme or food flavouring produced by a GMM in contained use do not fall under the scope of 1829/2003.</p> <p>(lines 289-292) We suggest to add a sentence at the end of this paragraph: "Feed additives produced by GMMs in contained use do not fall within the scope of Regulation (EC) 1829/2003".</p>
47	Austrian Agency for Health and Food Safety	AUT	II. PRINCIPLES AND STRATEGIES FOR RISK ASSESSMENT OF GENETICALLY	We appreciate the effort of EFSA to update the guidance document on genetically modified microorganisms. This updated document provides on several occasions clear guidance what kind of and to which extent information is required to achieve a scientifically sound - up to date - risk assessment of GMMs. This is of substantial benefit for the applicant as well as for the involved risk assessors.

	ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT
			MODIFIED MICROORGANISMS	<p>However, there are several sections in this updated guidance document, where reasonable requirements, which had been compulsory in the old version of the document, have now been omitted or substantially relieved. This approach may be appropriate in some instances but for the overwhelming majority of the noted cases we are of the opinion that these requirements are vital parts for the risk assessment of GMMs helping to provide the necessary amount of data for a sufficient precise exclusion of adverse effects on human and animal health and the environment. Therefore we strongly recommend to revert to the old wording of the guidance document at the indicated positions in the text of the updated guidance document.</p> <p>Concerning the risk assessment of potentially involved antibiotic resistance genes – a pivotal part of the risk assessment of GMMs – we had to realize that the corresponding section was substantially shortened and partially replaced by referencing to a technical guidance document prepared by the EFSA FEEDAP Panel. This FEEDAP Panel guidance is missing vital information making it ineligible as proper basis for the risk assessment for antibiotic resistance genes because it is focusing mainly on the phenotypical determination of resistance and completely excludes any phenomenon mediated by the transfer and uptake of free DNA in natural habitats (no reference included to natural genetic transformation). We strongly recommend the EFSA GMO Panel to review this document for appropriateness as reference for providing enough information for a sufficiently reliable risk assessment of antibiotic determinants.</p>
48	Federal Agency for Nature Conservation	DEU	II. PRINCIPLES AND STRATEGIES FOR RISK ASSESSMENT OF GENETICALLY MODIFIED MICROORGANISMS	<p>General Comments to Chapter II, part I (for part II see comments under DEFINITIONS IN RISK ANALYSIS)</p> <p>The risk assessment strategy should be fully explained in Chapter II and should not be divided throughout the guideline (Chapter II (definitions in risk analysis, categorisation of the GMMs and derived products for risk assessment purposes, comparative approach, intended and unintended effects) and Chapter III (hazard identification and characterisation, choosing of comparators (1.4.1), exposure assessment/characterisation, risk characterisation). This would greatly enhance the understanding of the risk assessment process and would collect all requirements (for example on the choosing of an appropriate comparator) in one place.</p> <p>The wording should be synchronized with the EFSA guidance document on the environmental risk assessment of genetically modified plants (EFSA Journal 2010; 8(11):1879) (Hazard identification = problem formulation, exposure assessment = exposure characterisation) and should be used consistently throughout the guideline.</p> <p>The handling of GMMs without an available comparator should be discussed exhaustively and the description of a bottom up assessment of food/feed safety and environmental aspects of these micro-organisms should be included. A comparison of the GMM to non-modified organism under corresponding conditions should only assist in identifying potential adverse effects of the GMO but must not be the only way to detect these effects.</p> <p>The comparative approach should be explained in more detail and should include a guideline on the selection of appropriate comparators. The handling of unintended effects and uncertainties should be described in more detail and in relevant chapters (e.g. see comments to line 919). In line 388-389, it is mentioned that unintended effects are addressed in the safety and nutritional assessment of the product without referencing to the corresponding parts of the guideline and without explaining what the general strategy is concerning unintended effects.</p> <p>We agree with EFSA that accumulation of data on different levels (data on molecular characterisation, compositional analysis, phenotypic characteristics etc.) enables the detection of unintended effects. But contrary to EFSA, we are of the opinion that unintended effects can only be excluded to the greatest possible extent when all data on every level are taken together. Data on only one level cannot exclude the occurrence of unintended effects and must not make further examinations unnecessary. It can only give indications on what should be especially considered on another level as the individual levels only represent a small part of the complex interaction between the micro-organism and the environment.</p>
49	Federal Office of	DEU	II. PRINCIPLES AND	Line 295:

	ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT
	Consumer Protection and Food Safety (BVL)		STRATEGIES FOR RISK ASSESSMENT OF GENETICALLY MODIFIED MICROORGANISMS	Add "environmental" after „Principles for“. Annex II of Directive 2001/18/EC describes specifically the principles for the environmental risk assessment.
50	Food Standards Agency	GBR	Definitions in risk analysis	UK expert Committee (ACNFP) Comment 2 (Section II: Definitions in risk analysis) Given the emerging understanding of the importance of epigenetics in controlling the genome, and the likelihood that GM may influence epigenetic status, it is surprising that there is no mention of epigenetics in the opinion. The opinion includes a definition of unintended effects (lines 381 - 386) but this does not mention epigenetic changes which can influence expression and can also have much wider implications. Unintended effects should include explicit reference to "epigenetic modification such as DNA methylation and histone modification".
51	Federal Agency for Nature Conservation	DEU	Definitions in risk analysis	General Comments to Chapter II, part II (for part I see comments under II. PRINCIPLES AND STRATEGIES FOR RISK ASSESSMENT OF GENETICALLY MODIFIED MICROORGANISMS) Apart from three general references (lines 295, 296 and 299) the elaborations in this chapter are not specifically referenced and linked to the legal documents mentioned in chapter I legal background. The definitions on risk analysis (line 297-328) are adapted from Article 3 of Regulation (EC) 178 /2002 (general food law). There is a reference in line 295-296 to the principles for environmental risk assessment (here called just risk assessment) of Directive 2001/18/EC, Annex II, but important e.r.a. principles are not adapted and incorporated in the draft. According to Annex II the objective of an e.r.a. is, on a case by case basis, to identify and evaluate potential adverse effects of the GMO, either direct and indirect, immediate or delayed, on human health and the environment which the deliberate release or the placing on the market of GMOs may have. However, the draft does shift this task completely to the post-market environmental monitoring (line 1417-1420). Just the same applies to cumulative long-term effects which are only mentioned in para 1452-1454 in chapter F.1. about PMEM of GM products and which are especially relevant for GMMs of category 3 and 4 (see general comment to B.3). Also, there is no reference to the precautionary principle throughout the whole draft, although it is central to Annex II. For all the above mentioned reasons the draft is not in compliance with the Directive 2011/18/ EC. Information on principles and strategies for R.A. of GMMs is dispersed in the present draft in the chapter legal background and in chapter II. Substantial revision is required to comprehensively present the legal background and deduce requirements and guidance from it. Line 312-320 This draft is about risk assessment. The lengthy definitions of risk management and risk communication are not relevant here and should be deleted.
52	Belgian Biosafety Advisory Council	BEL	Definitions in risk analysis	Line 311 : We suggest to add the following new sentence at the end : "The characterisation of the risk will possibly lead to the proposal of risk management measures or strategies, against which an evaluation of the overall risk of the GMO(s) will be made".
53	Ministry of Rural Development	HUN	Categorisation of the GMMs and derived products for risk assessment purposes	line:350-352 Change sentence „Depending of the Category and scope of the product, its characterisation (specification) and safety assessment will be undertaken according to relevant legislation (See Chapter I) for which different Guidance Documents or Guidelines apply (See page 23, Section 2).“ To: independent of the Category and scope of the product, its characterisation (specification), because of intended, and most importantly

	ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT
				<p>unintended changes, full assessment will be undertaken according to relevant legislation.</p> <p>Please re-write line 354-367 accordingly.</p>
54	DSM	NLD	Categorisation of the GMMs and derived products for risk assessment purposes	<p>(line 334-335) We suggest to replace by "represent examples at one end of this spectrum and Microbial Food Culture like probiotics or dairy starters at the other extreme."</p> <p>We suggest rewording for the sentence in lines 341-342: "with GMMs in which both the GMMs and residual recombinant DNA from these GMMs have been removed"</p>
55	Ajinomoto Eurolysine S.A.S.	FRA	Categorisation of the GMMs and derived products for risk assessment purposes	<p>Lines 345 – 347</p> <p>For category 3 defined as "products produced from GMMs in which GMMs capable of replication or of transferring newly introduced genes are not present, but in which newly introduced genes are still present (e.g. heat-inactivated starter cultures)" it seems it could merit some clarification or additional precisions.</p> <p>Compared to categories 1 and 2, recombinant DNA (i.e. DNA corresponding to the newly introduced genes) is still present, i.e. quantifiable, in the final product.</p> <p>However, what seems the important point is:</p> <ul style="list-style-type: none"> - whether this DNA is of a size below full-length coding sequences or of a gene (without any biological function and not transferable) - or this DNA corresponds to full-length coding sequences with a potential to transfer. <p>Therefore, it seems two types of products could be distinguished in 'category 3'.</p> <ul style="list-style-type: none"> - Type 1: the inactivation treatment(s) implemented during the manufacturing process of the product– and as part of the contained use of the producer microorganism – result(s) not only in the absence of viable cells of the microorganism but also in the degradation of its DNA, with sizes of DNA fragments below full-length coding sequences, or even below the size of small genes. These fragments which are not functional will not transfer, even in very special conditions. This is the situation usually sought by applicants e.g. for biomasses intended to be used as feed materials. In this case, the products should not be submitted to the ERA described in Section III, B, 3.2 lines 1136 to 1179. A risk evaluation, as described for category 2 should suffice. - Type 2: the inactivation treatment(s) or other treatment implemented during the manufacturing process of the product result(s) in the absence of viable cells of the microorganism, but the DNA degradation is only partial and DNA fragments corresponding to full-length coding sequences (or size higher than a gene) will/may remain in the product. In this case there would be a risk of gene transfer and it seems these products should rather be part of category 4.
56	Belgian Biosafety Advisory Council	BEL	Categorisation of the GMMs and derived products for risk assessment purposes	<p>Lines 329-352 and other places in the document: - The 4 categories are rather generally presented and many more examples can be mentioned:</p> <ul style="list-style-type: none"> - Category 1 : only amino acids and vitamins are mentioned as bio-products, mostly derived from fermentation processes; this category also includes : organic acids as food preservatives (acetic, lactic, propionic...) or acidifier (lactic, acetic, malic, citric, gluconic, tartaric...); bacteriocins (nisin, pediocin...); antioxidants (ascorbic acid or vitamin C, alfa-tocoferol or vitamin E...); essential fatty acids (PUFA's: EPA, GLA,

ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT
			<p>DHA...); thickening agents (xanthan, gellan, dextran, pullulan, curdlan, bacterial cellulose...); flavouring compounds (MSG, nucleotides, 4-decalactone, l-menthol...); biopigments (beta-carotene, riboflavin, astaxanthin, monascin...); low caloric sweeteners (xylitol, mannitol, erythritol, fructose, neosugar, aspartame...).</p> <p>- Category 2 & 3 : line 341 .. "most enzyme preparation": it all depends on purity of the preparation, whether GMM's and genes are removed or not.</p> <p>line 343 .. "cell extracts": it all depends on how these are prepared: heat treatment, high pressure, osmotic lysis, enzymatic treatment... and extent of further downstream processing ?</p> <p>- Category 4 : replication ???, referring to e.g. live starter cultures for fermented foods & drinks... (see remark below under line 345)</p> <p>Lines 338-352, p 12: The categorisation of the GMMs in 4 categories refers to "newly introduced genes" only. The wording should be revised in order to include also GMMs obtained by deletion.</p> <p>Line 345 and other places in the text: : In several places in the document, the term "replication" is used (see e.g. lines 345, 348, 807, 1136, 1180, p.43 Figure 1, p.46-47 Table 1...). We guess this wording refers to the EU definition of a "micro-organism". Nevertheless "replication" is a scientific term in "Microbiology" exclusively used to refer to viral/phage multiplication. Given to the fact that the scope of the document is limited to prokaryota (bacteria and archaea) and micro-eukaryota, therefore specifically excluding viruses (see lines 163-167, 1844), we are of the opinion that the term "replication" should be replaced all over the text by "cell growth/cell multiplication".</p>
57	Genencor, A Danisco Division	NLD	<p>Categorisation of the GMMs and derived products for risk assessment purposes</p> <p>Genencor, A Danisco Division, agrees with the comments submitted by AMFEP, the Association of Manufacturers and Formulators of Enzyme Products.</p>
58	Novozymes A/S	DNK	<p>Categorisation of the GMMs and derived products for risk assessment purposes</p> <p>Novozymes A/S agrees with the comments submitted here by AMFEP.</p>
59	FEFANA	BEL	<p>Categorisation of the GMMs and derived products for risk assessment purposes</p> <p>Lines 334-335: We suggest to replace by "represent examples at one end of this spectrum and Microbial Food Culture like probiotics or dairy starters at the other extreme."</p> <p>Suggested rewording for the sentence in lines 341-342: "with GMMs in which both the GMMs and residual recombinant DNA from these GMMs have been removed".</p>
60	AMFEP	BEL	<p>Categorisation of the GMMs and derived products for risk assessment purposes</p> <p>(line 334-335) We suggest to replace by "represent examples at one end of this spectrum and Microbial Food Culture like probiotics or dairy starters at the other extreme."</p> <p>We suggest rewording for the sentence in lines 341-342: "with GMMs in which both the GMMs and residual recombinant DNA from these GMMs have been removed".</p>
61	Federal Agency for Nature Conservation	DEU	<p>Comparative approach</p> <p>See General Comments to Chapter II for more comments on the comparative approach.</p> <p>It should be explained why the comparative approach is chosen as the risk assessment strategy. It is unembodied that this strategy has several deficits and therefore may not be the first choice.</p> <p>Line 357-359</p>

ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT
			<p>Other than what is claimed here, the Scientific Committee recommends implementation of the QPS system for micro-organisms intentionally added to the food chain only, but not to the feed chain as well (EFSA 2007, p. 15). In terms of the feed chain other environmental aspects have to be considered and – because of the amounts entering the environment - most probably given more weight. Therefore, and in compliance with the recommendation of the Scientific Committee the environmental risk assessment of GMM used for feed shall not rely on the application of the QPS system.</p> <p>Line 366-367 It is stated that if the parental has a QPS status, the risk assessment can focus on the changes introduced during the development of the GMM. If the risk assessment focuses on introduced changes only unintended effects are not considered. Therefore the QPS status plus the introduced changes can serve as a basis but additionally unintended changes have to be taken into account as well.</p>
62	Ministry of Rural Development	HUN Comparative approach	<p>Line:367-377 Change sentence „The safety assessment of the GMM may then focus on those differences, together with those introduced during the development of the final GMM.</p> <p>To:</p> <p>The safety assessment of the GMM shall still be carried out and may specifically then focus on those differences introduced during the development of the final GMM.</p>
63	Ministry of Rural Development	HUN Comparative approach	<p>Line 354-367 QPS, as its name states is presumed to be safe, but it is no guarantee of safety. Therefore every should be fully safety assessed.</p> <p>Because of intended and mainly the unintended and unexpected alterations in the genome of GMM, all GMM should be fully safety assessed.</p> <p>In the context of this Guidance Document, the QPS status cannot be used as a justification for the safety of the parental microorganism. If the parent has a QPS status, full risk assessment should be carried out.</p>
64	DSM	NLD Comparative approach	<p>(lines 353-377) The document discusses QPS and the significance of QPS. It is mentioned that previous assessments on a host strain in the same pedigree can be used for the risk assessment and that the applicant then must focus on the differences. It is proposed to take the next step along this line of thinking and recognize the "safe strain lineage" concept as developed by Pariza and Johnson (Evaluating the Safety of Microbial Enzyme Preparations Used in Food Processing: Update for a New Century. Regulatory Toxicology and Pharmacology 33, 173–186 (2001)), and Pariza and Cook (Determining the safety of enzymes used in animal feed. Regulatory Toxicology and Pharmacology 56 (2010) 332–342).</p>
65	on behalf of the Association of Veterinary Consultants	ESP Comparative approach	<p>Comparative approach: Lines 353-377. The comparative approach has scope for reduced toxicity testing, especially of Category 2 GMMs with QPS status or history of safe use (e.g. most GMO feed & food enzymes are derived from parental strains with an established history of safe use). The AVC therefore recommend & encourage the use of in vitro safety testing (e.g. on toxins, virulence factors, relevant transferrable resistance, antimicrobial production, strain genetic stability). In vitro safety testing for such cases should replace in vivo toxicology testing in laboratory & other animal species. To this end, the AVC suggest that EFSA GMO consider & include relevant references (Pariza & Johnson 2001; Pariza & Cook 2010)</p>
66	Belgian Biosafety Advisory Council	BEL Comparative approach	<p>Line 353 and following ("Comparative approach") : The text between lines 354-377 focuses on the need to have complete information on the recipient/parental micro-organism. The choice of a good comparator is indeed an important step in the risk assessment of food or feed products as a basis for further identification of similarities/differences (intended and unintended) between the GMM and its non-GM equivalent.</p>

	ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT
				However, this section would gain in clarity if the principles and objectives of the comparative approach would be also addressed in more details, as it has been done in the guidances on GM plants.
67	Genencor, A Danisco Division	NLD	Comparative approach	Genencor, A Danisco Division, agrees with the comments submitted by AMFEP, the Association of Manufacturers and Formulators of Enzyme Products.
68	Novozymes A/S	DNK	Comparative approach	Novozymes A/S agrees with the comments submitted here by AMFEP.
69	FEFANA	BEL	Comparative approach	Lines 353-377: The document discusses QPS and the significance of QPS. It is mentioned that previous assessments on a host strain in the same pedigree can be used for the risk assessment and that the applicant then must focus on the differences. It is proposed to take the next step along this line of thinking and recognize the "safe strain lineage" concept and the Pariza Cook/Pariza Johnson and Pariza Foster peer-reviewed papers.
70	AMFEP	BEL	Comparative approach	(lines 353-377) The document discusses QPS and the significance of QPS. It is mentioned that previous assessments on a host strain in the same pedigree can be used for the risk assessment and that the applicant then must focus on the differences. It is proposed to take the next step along this line of thinking and recognize the "safe strain lineage" concept as developed by Pariza and Johnson (Evaluating the Safety of Microbial Enzyme Preparations Used in Food Processing: Update for a New Century. Regulatory Toxicology and Pharmacology 33, 173–186 (2001)), and Pariza and Cook (Determining the safety of enzymes used in animal feed. Regulatory Toxicology and Pharmacology 56 (2010) 332–342).
71	Federal Agency for Nature Conservation	DEU	Intended and unintended effects	<p>See General Comments to Chapter II for more comments on intended and unintended effects.</p> <p>Line 379-380 Consider a simpler wording: "Intended effects are the intended phenotypic changes of the genetic modification."</p> <p>Line 381 What is meant by the word consistent and what is the legal basis or scientific justification for it? Since unintended effects can be due to changes in expression which in turn can be affected by the environment some unintended effects might be identified under certain conditions only and therefore not consistent.</p> <p>Line 385-386 A strategy and a concept are missing on how to deal with unintended unpredicted effects during risk assessment.</p> <p>Line 387 The term predicted intended is a duplication in itself and should be deleted. The sentence should be changed to "Intended and predicted unintended effects should be analysed based on the most appropriate methodology."</p> <p>Line 387-389 What is the relevance of the differentiation between predicted unintended and not predicted unintended in terms of safety?</p>
72	Ministry of Rural Development	HUN	Intended and unintended effects	<p>Line:388-389 Change sentence „Unintended effects, including those which could not be predicted, are addressed in the safety and nutritional assessment of the product.”</p> <p>To:</p>

ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT
			Unintended effects should be addressed in the safety and nutritional assessment of the product
73	Ministry of Rural Development	HUN	Intended and unintended effects Line 386 Add sentence at the end of para: In spite of this, it is necessary to carry out a full safety assessment.
74	Belgian Biosafety Advisory Council	BEL	Intended and unintended effects Line 379 : it is said that intended effects are "genotypic or phenotypic changes", whereas in the ERA guidance of plants the description remains more general, as follows : "Intended effects are those that are designed to occur and which fulfil the original objectives of the genetic modification." Is there any particular reason, could it be clarified ?
75	Austrian Agency for Health and Food Safety	AUT	III. INFORMATION REQUIRED IN APPLICATIONS FOR GMMS AND/OR THEIR PRODUCTS We appreciate the effort of EFSA to update the guidance document on genetically modified microorganisms. This updated document provides on several occasions clear guidance what kind of and to which extent information is required to achieve a scientifically sound - up to date - risk assessment of GMMs. This is of substantial benefit for the applicant as well as for the involved risk assessors. However, there are several sections in this updated guidance document, where reasonable requirements, which had been compulsory in the old version of the document, have now been omitted or substantially relieved. This approach may be appropriate in some instances but for the overwhelming majority of the noted cases we are of the opinion that these requirements are vital parts for the risk assessment of GMMs helping to provide the necessary amount of data for a sufficient precise exclusion of adverse effects on human and animal health and the environment. Therefore we strongly recommend to revert to the old wording of the guidance document at the indicated positions in the text of the updated guidance document. Concerning the risk assessment of potentially involved antibiotic resistance genes – a pivotal part of the risk assessment of GMMs – we had to realize that the corresponding section was substantially shortened and partially replaced by referencing to a technical guidance document prepared by the EFSA FEEDAP Panel. This FEEDAP Panel guidance is missing vital information making it ineligible as proper basis for the risk assessment for antibiotic resistance genes because it is focusing mainly on the phenotypical determination of resistance and completely excludes any phenomenon mediated by the transfer and uptake of free DNA in natural habitats (no reference included to natural genetic transformation). We strongly recommend the EFSA GMO Panel to review this document for appropriateness as reference for providing enough information for a sufficiently reliable risk assessment of antibiotic determinants.
76	Federal Agency for Nature Conservation	DEU	III. INFORMATION REQUIRED IN APPLICATIONS FOR GMMS AND/OR THEIR PRODUCTS Line 391-397 Different from what is claimed here the headlines and structure of part III do not follow Annex III of Directive 2001/18/EC. Line 398-400 This para is simply to clarify that the present draft also applies to GMMs obtained by self-cloning. Actually this information is best placed under scope of the document.
77	Ministry of Rural Development	HUN	III. INFORMATION REQUIRED IN APPLICATIONS FOR GMMS AND/OR THEIR PRODUCTS Line:401-403 Change sentence „Not all the points included will apply to every case. Unless otherwise specified, the applicant is advised to refer to Figure 1 (page 43) and Table 1 (page 44) for an indication of which data must be supplied for applications belonging to each Category.” To: Because of intended and unintended effects all the points will apply to every case
78	Belgian Biosafety Advisory Council	BEL	III. INFORMATION REQUIRED IN APPLICATIONS FOR Line 391 : It is said that the structure of Chapter III of the Guidance is based on Annex III A of Directive 2001/18/EC. This is only partly true (for example section 2 on information relating to the product is not requested under Directive 2001/18/EC). Therefore, it should be made clear in the Guidance when information requirements come from Directive 2001/18/EC, for example by referring to the relevant section numbering and

	ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT
			GMMS AND/OR THEIR PRODUCTS	title of Annex III of the Directive.
79	FEFANA	BEL	III. INFORMATION REQUIRED IN APPLICATIONS FOR GMMS AND/OR THEIR PRODUCTS	Sentence in lines 396-397 should read "This guidance was developed to support applicants in preparation and presentation of applications submitted under Regulation 1829/2003, 1332/2008, 1333/2008, 1831/2003." (cf. above comments on legal background section).
80	Ministry of Agriculture	ARG	III. INFORMATION REQUIRED IN APPLICATIONS FOR GMMS AND/OR THEIR PRODUCTS	<p>CHAPTER III</p> <p>- Lines 522-524. The possibility of harm to immunocompromised individuals should be considered separated from the other issues in this bullet point, as it a different kind of risk. Literature reports indicate that several common microbial strains, generally considered harmless, may cause opportunistic infections in immunodeficient individuals.</p> <p>- Lines 551-554. (1.2. Characteristics of the origin of the inserted sequences [donor organism(s)]). It is not clear here the reference to a "donor", as we are dealing with a gene deletion in the recipient organism, and foreign DNA is not involved.</p> <p>However, there could be situations of "functional" deletions, that is, that this paragraph would refer not to a complete deletion of the gene but to a recombination with a donor sequence (e.g., in a plasmid) of the same gene which has been previously modified so it is no longer functional (a defective gene). The intended recombination will result in a recipient organism with the defective gene replacing the original, functional gene. In this case, the characterization of the donor has full meaning.</p> <p>- Lines 664-670. (1.4.3. Stability of the genetic traits in the GMM) Perhaps it would be advisable to require information on the method used for assuring the consistency of the geno/phenotype of the GMM under the conditions of their intended production or use, and how these consistency is checked over time.</p> <p>- Lines 694-695. Would it be advisable to require information on the selective pressure at which the advantage would be effective?</p> <p>- Line 901. Check wording</p> <p>- Lines 949-951. Suggested alternative wording:</p> <p>¿ a search for homology to toxic proteins should be conducted. Identified similarities should be evaluated; the database(s) and the methodology used to carry out the search should be specified;</p> <p>- Lines 1008-1010. The production of GMM involving the expression of proteins that undergo extensive post-translational processing in the donor organism should be discouraged. Such products, if intended for commercial use, will require a extensive study of the immune response in animals, as differential post-translational processing may be a safety concern.</p> <p>- Lines 1011-1017. Suggest to clarify. The heading states "Source of the protein" but it deals with the source of transgene.</p> <p>- Lines 1043-1045. Pepsin digestibility (more precisely, digestibility in simulated gastric fluid) should be requested independently from IgE binding tests.</p> <p>- Line 1069. A simple condition to be tested would be pH values different from the optimum for pepsin (which could be the case under certain abnormal situations in humans) .</p>

ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT
			- Line 1231. It is suggested that conjugative transposons may also be considered.
81	Austrian Agency for Health and Food Safety	AUT	A. General information Line 413: Please extend the bullet point to: Scope of the application considering the categorisation as defined in section "Categorisation of risk assessment of GMMs and their derived products" (p. 52)
82	Federal Agency for Nature Conservation	DEU	A. General information Line 403-404 The statement "reasons must be given for the omission of such data from the dossier" gives the applicant the possibility not to provide all requested (and necessary) data, as long as he can give reasons for this. It is not specified what reasons would be seen as sufficient for the omission of data. The concerning sentence should be deleted or specific criteria on what reasons would be perceived as sufficient should be supplied. Line 405-417 The requirement to provide information on the conditions for placing on the market, including specific conditions for use and handling, when appropriate, are no longer listed under General Information as in the present guideline (EFSA 2006), but hidden somewhere in the text. In doing so the present draft provides less clear guidance about what kind of information is required in applications.
83	Belgian Biosafety Advisory Council	BEL	A. General information Line 406 and other places in the document : The wording "information relating to the GMM" is used several times in the guidance in different contexts (lines 406, 438, 1322). This could be confusing for people not familiar with the risk assessment process. We suggest to delete the wording "information relating to the" in titles 1.1 and 1.2 on page 37.
84	United States of America, Food and Drug Administration	USA	B. Hazard identification and characterisation Section B Lines 434-435 state: "For human and animal health, this step [Hazard Characterization] is focused on possible quantification of the toxicological/nutritional potential of the genetically modified microbe (GMM) and/or food/feed derived from or produced with it." It may be useful to indicate more clearly what is meant by quantification of toxicological potential and quantification of nutritional potential and how such quantification is expected to be performed. From the text in this sentence, it is not clear what would be acceptable regarding a quantification of toxicological or nutritional potential.
85	EFFSACO	NLD	B. Hazard identification and characterisation 1. CLARITY, PRECISION & PRESCRIPTIVE: The guidance per se is clear, precise, easy to follow, prescriptive, & include key examples, hence a practical tool for anyone working in regulatory affairs. We would say definitely an improvement on the EFSA 2006 GMM guidance, with scope for reduced toxicology testing for Category 2 GMMs with QPS status of parental strain/s or otherwise established history of safe use (e.g. most feed & food enzymes have parental strains with an established history of safe use). 3. CONCLUSION & RECOMMENDATIONS: We congratulate EFSA on the improvements & further encourage the use of in vitro safety testing (e.g. on toxins, virulence factors, relevant transferrable antibiotic resistance, antimicrobial production, genetic stability) to replace in vivo safety testing in laboratory animals, wherever possible. To this end, & in relation to feed or food enzymes, We would suggest that EFSA consider the publication from Pariza M. and Cook M. 2010. Determining the safety of enzymes used in animal feed. Regulatory Toxicology and Pharmacology 56, 332-342. This publication can also be sent on request.
86	Federal Agency for Nature Conservation	DEU	B. Hazard identification and characterisation Line 418-437 These paras actually define terms relevant for risk assessment and should be moved to part II. (See general comment to Chapter II). Line 428

	ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT
				<p>The focussing of the hazard identification on the identification of differences between the GMM and appropriate comparators and the subsequent risk assessment of only these differences is problematic as unintended effects might be overlooked in this first step and thus be excluded from the risk assessment.</p> <p>Contrary to this, the principles of the environmental risk assessment laid down in the Directive 2001/18/EC clearly state that effects should not be discounted based on their improbability. The comparison to a comparator is proposed as a supporting method to determine unexpected effects and not, as in this guideline, as yardstick for the harmfulness of differences. Possible risks are excluded by this severe restriction in the first step of the risk analysis. It is necessary that the risk assessment should be independently performed from the comparator and that a base set of problem formulations and experimental strategies should be given to detect unexpected or unlikely effects.</p> <p>Furthermore, the handling of gaps of knowledge and uncertainties in the problem formulation, although mentioned a couple of times in Chapter III.D, is not discussed properly in the guideline.</p>
87	The Netherlands Commission on Genetic Modification (COGEM)	NLD	B. Hazard identification and characterisation	<p>According to EFSA, several analyses have to be performed in order to obtain information relating to the GMM or the products derived with or from the GMM. For categorization of a product in group 1 and 2, the absence of the GMM has to be determined. Guidance for the selection of the detection methods to be used for the demonstration of the absence of a GMM consists of descriptions like 'appropriate methods' (line 527), 'a proper sampling method' (line 800), or 'a recognized method' (line 824). The limit for detection of a GMM in a product is determined by the analytical sensitivity of the applied method, however, the document does not provide guidance which detection limit is acceptable for a chosen method. COGEM is of the opinion that more guidance is needed on the methods to be used and the quality requirements that should be met by those methods.</p>
88	Ministry of Rural Development	HUN	B. Hazard identification and characterisation	<p>Line:428-430 Who will decide and on what basis that in case of a GMM, when hazard identification is focused on the identification of differences between the GMM and appropriate comparators, that what is the appropriate comparator and what sort of changes are necessary to establish the differences?</p> <p>Line:436-437 Change sentence „Whenever an appropriate non-GM comparator is available, a comparative approach can be applied (see Chapter II.)”</p> <p>To:</p> <p>In each case an appropriate non-GM comparator should be available, a comparative approach will be applied (see Chapter II.).</p>
89	Belgian Biosafety Advisory Council	BEL	1. Information relating to the GMM	<p>Line 438 and following : In certain cases, some sections of Annex III A of Directive 2001/18/EC are not mentioned (e.g. II.A.11(b), II.A.11(c), II.A.12). This should be explained.</p>
90	Austrian Agency for Health and Food Safety	AUT	1.1. Characteristics of the recipient or (when appropriate) parental organism	<p>Lines 535-544: When the parental species has a QPS status, this should be indicated together with the information whether the strain used for the GMM construction fulfils the specific QPS qualifications (e.g., lack of transmissible antimicrobial resistance genes)</p> <p>We would like to point to the fact that also the QPS qualification scheme relies on the technical guidance concerning the “Update of criteria used in the assessment of bacterial resistance to antibiotics of human or veterinary purpose” prepared by the FEEDAP Panel. This guidance document completely ignores any horizontal gene transfer effects mediated by natural genetic transformation and, thus, has drawn unreliable conclusions (= chromosomal/genomic mutation leading to resistance = low risk of horizontal dissemination (= neglecting effects mediated by natural genetic transformation!) = resistant strain/resistance gene is acceptable). This rationale is misleading the applicant and does not reflect</p>

ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT
			<p>an up to date knowledge concerning horizontal gene transfer. Supporting this rationale is strongly discouraged and should not be supported by the EFSA GMO panel. In our opinion also chromosomally located antibiotic resistance genes impose a substantial capability to be transferred horizontally by transformation to competent acceptor bacteria and, thus, should be evaluated.</p> <p>Two crucial terms (“unintended presence”, “scientific evidence”), which have been elaborated in the old version of the GMM guidance document are now missing in this updated version.</p> <p>Therefore we recommend to add the following paragraph after line 544:</p> <p>Information should be provided relating to the previous use or unintended presence (e.g. as a contaminant) in food or feed. Information on the history of use in food or feed should, whenever possible, be supported by scientific evidence and applicants should provide evidence of safe use, preferably under conditions as close as possible to those anticipated for the derived GMM.</p>
91	Austrian Agency for Health and Food Safety	AUT 1.1. Characteristics of the recipient or (when appropriate) parental organism	<p>Line 525-530: We are not of the opinion that adherence to the mentioned reference (EFSA, 2008; “Update of the criteria used in the assessment of bacterial resistance to antibiotics of human or veterinary importance prepared by the Panel on Additives and Products or Substances used in Animal Feed”) is able to provide sufficient information for an appropriate risk assessment of antibiotic resistance genes for the following reasons:</p> <p>The concept of intrinsic vs. acquired antibiotic resistance appears to be somewhat arbitrary concerning the potential of free (genomic) DNA originating for instance from decaying – but resistant – bacterial cells to be taken up by viable – but sensitive - host bacteria. Thus virtually any kind of resistance function physically encoded in DNA irrespective of its location on plasmids, transposons, integrons (or other mobile genetic elements) or in the bacterial chromosome may be transferred via natural genetic transformation. This may take place at a significant rate equalling or succeeding the transfer rates for conjugative gene transfer. Chromosomal location does not provide a “security lock” per se for a reduced potential for gene transfer.</p> <p>Chromosomal DNA transferred via transformation is thought to be one of the major sources of resistance functions concerning initial introgression of these determinants into originally sensitive bacterial populations in the environment.</p> <p>The concept of natural genetic transformation is not mentioned in the technical guidance provided by the FEEDAP Panel (e.g. section 3.2.1 “Antimicrobial resistance gene exchange among bacteria”). The term “transformation” does not even appear in the whole text. Therefore this reference is neglecting a crucial aspect of horizontal gene transfer which is consequently also missing in this section of the new GMM guidance document. (However, it is properly addressed in section 3.2. “ERA of products produced from GMMs in which GMMs capable of replication or of transferring newly introduced genes are not present; but in which newly introduced genes are still present (Category 3); lines 1162ff)”) For an appropriate evaluation of the potential for transfer also the aspects concerning natural genetic transformation must be considered.</p> <p>We recommend the addition of a third bullet point as follows:</p> <p>* Information should also be provided on the location of the resistance genes within the genome and on their potential for transfer to other organisms including natural genetic transformation; detection of the presence of resistance determinants should be carried out using both phenotypic and genotypic methods. The techniques used should be justified. The use of at least one phenotypic technique associated with at least one molecular technique is strongly recommended. In particular, antibiotic resistances not normally associated with the GMM genus or species should be highlighted. Microorganisms in which antibiotic resistance is conferred by an inactivating mechanism encoded by a gene that is located on a mobile genetic element and targeting an agent(s) in clinical or veterinary use should not be used in the recipient. The level of gene expression and the potential for the induction of gene expression should be evaluated when antibiotic resistances of particular concern</p>

ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT
			are observed.
92	Austrian Agency for Health and Food Safety	AUT	1.1. Characteristics of the recipient or (when appropriate) parental organism Line 510ff: Please add the following bullet points (as stated in the old version of the Guidance Document): * Information on the doubling time and on the mode of reproduction should be provided * Information on survival, including the ability to form spores or other survival structures should be provided.
93	Austrian Agency for Health and Food Safety	AUT	1.1. Characteristics of the recipient or (when appropriate) parental organism Line 498ff: Please add (as stated in the old version of the Guidance Document): "Factors affecting the genetic stability should be specified (e.g., insertion sequences, transposons, integrons, plasmids, prophage). Taking into account the high level of mobility that is typical of microbial genomes, the absence of any negative effect on human and animal health related to the genetic mobility (instability) should be assessed."
94	Austrian Agency for Health and Food Safety	AUT	1.1. Characteristics of the recipient or (when appropriate) parental organism Line 486ff: Since entry of new resistance genes into usually sensitive bacterial populations is assumed to be mediated also to a considerable amount by the uptake of free DNA from the environment a reference to features concerning natural genetic transformation is missing. We suggest to add two additional bullet points asking for i) information about the presence of competence genes and genes responsible for DNA secretion - which are in a broader sense also components of the "host machinery for transfer" (compare with Streptococcus pneumoniae) - and ii) transformation frequencies and transformation rates achievable under naturally occurring conditions for the strain under evaluation . This is also relevant concerning the formation of mosaic genes by natural genetic transformation within the GMM and/or with potential host bacteria. Suggestion (to be added after line 497): * the presence of competence genes mediating uptake and/or secretion of free DNA * transformation frequencies and transformation rates under naturally occurring conditions
95	Austrian Agency for Health and Food Safety	AUT	1.1. Characteristics of the recipient or (when appropriate) parental organism Line 492-497: In line with the assessment of the possibility of gene transfer, also respective consequences should be assessed.
96	Austrian Agency for Health and Food Safety	AUT	1.1. Characteristics of the recipient or (when appropriate) parental organism Line 480: Please add (as stated in the old Guidance Document): The choice of detection and identification techniques should be justified and their sensitivity, reliability, specificity and validation, should be provided. Suggestion: The identification technique should be detailed and adequate to identify the recipient/parental organism unequivocally at the strain level. The choice of detection and identification techniques should be justified and their sensitivity, reliability, specificity and validation, should be provided.

ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT	
97	Austrian Agency for Health and Food Safety	AUT	1.1. Characteristics of the recipient or (when appropriate) parental organism	Line 479f: Please revert to the original text present in the old Guidance Document. Suggestion: The identification technique should be detailed and adequate to identify the recipient/parental organism unequivocally at the strain level to permit its detection and quantification in the environment. The use of the most recent and reliable molecular techniques and, if possible, more than one, is recommended.
98	Austrian Agency for Health and Food Safety	AUT	1.1. Characteristics of the recipient or (when appropriate) parental organism	Line 470: Please change "may" to "shall". Suggestion: Phenotypic characteristics shall include morphology, growth requirements, growth rates, temperature...
99	United States of America, Food and Drug Administration	USA	1.1. Characteristics of the recipient or (when appropriate) parental organism	Section B 1.1.3. Line 476 states: "The relationship between the recipient [microorganism] and donor(s) [organism(s)] should be described, when appropriate." It may be helpful to explain how this information will be used as part of the safety assessment and what particular criteria are of interest regarding the relationship between the recipient and donor(s) because it is not clear precisely when this information would be relevant for inclusion in a submission.
100	Federal Agency for Nature Conservation	DEU	1.1. Characteristics of the recipient or (when appropriate) parental organism	The requirement to name the source of the recipient organism (e.g. isolate or culture collection; see 1.8 of the present GD (EFSA 2006)) is missing and should be added again. The same applies to 1.2. 1.1 of the draft has not improved when compared to the corresp. chapters of the present GD, as there is a lack of demand to provide certain information. In 1.1 of the draft, general requirements are given in 442-447, which are more detailed in the the present GD (e.g. 1.4 and 1.8). 440-451 The present GD explains the meaning of "when appropriate", namely in the case of a micro-organism in which the endogenous genetic material has been modified. This information is missing here and therefore it is less clear. What is the reason for deleting the requirement to justify the use of micro-organisms as recipients that contain virulence determinants in the draft compared to the present GD? 447 Please add here human and animal health and the environment. 470-473 This para lists a couple of possibly relevant characteristics, but does not relate them or provides reason for their relevance as done in chapter 1.4 of the present GD. These aspects should be added again. 1.1.4. Information about the recipient strain should be provided on (i) the source from which it has been obtained (e.g. culture collection) or isolated, (ii) on the habitats in which it was found or has been isolated from and (iii) on its ecological role and interactions with other organisms therein.

ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT
			<p>1.1.4. of the draft is much shorter than 1.8 of the present GD and is less understandable as well.</p> <p>1.1.6.</p> <p>What is the justification for deleting the requirement to specify factors affecting the genetic stability (see 1.10. of the present GD)?</p> <p>1.1.7.</p> <p>Former requirements to provide information on growth and survival (1.1.1. b) and c) of the present GD have been incompletely shifted to 1.1.2. of the draft. Requirement for information on any survival structures, on doubling time and the mode of reproduction are missing and should be added again either in 1.1.2 or in 1.1.7.</p> <p>The draft cites a most recent EFSA GD (EFSA, 2008) for appropriate methods to analyse for introduced antibiotic resistance genes. However, this GD only deals with phenotypic methods (MIC determination) and not with genotypic once as required by the present GD, but absent from the draft. Other related details were also omitted, namely that (i) antibiotic resistances not normally associated with the GMM genus or species should be highlighted, that (ii) micro-organisms in which antibiotic resistance is conferred by an inactivating mechanism encoded by a gene that is located on a mobile genetic element and targeting an agent(s) in clinical or veterinary use should not be used in the recipient and that (iii) the level of gene expression and the potential for the induction of gene expression should be evaluated when antibiotic resistances of particular concern are observed. What is the justification for not transferring these specifications to the draft and thereby lessen the guidance?</p> <p>1.1.8.</p> <p>According to the present GD information on the history of use in food or feed should, whenever possible, be supported by scientific evidence and applicants should provide evidence of safe use, preferably under conditions as close as possible to those anticipated for the derived GMM. Both provisions are omitted in the draft and should be added again.</p> <p>539-540 “...product and an estimation of the final human or animal exposure should be given.” Also the exposure of the environment must be estimated.</p> <p>543-544 The provision that the previous history of use of the parental strain should be presented for organisms with a non-QPS-status only shall be deleted (see comment to Table 1).</p>
101	Ministry of Rural Development	HUN 1.1. Characteristics of the recipient or (when appropriate) parental organism	<p>line:518-521 Change sentence „Information on the ability to colonise plants, animals (including invertebrates) or humans should be provided. In particular, applicants should provide information on the viability and ability of the recipient/parental microorganism to survive in the gastrointestinal tract of humans or animals consuming the GMM (Category 4).”</p> <p>By deleting(Category 4) to:</p> <p>Information on the ability to colonise plants, animals (including invertebrates) or humans should be provided. In particular, applicants should provide information on the viability and ability of the recipient/parental microorganism to survive in the gastrointestinal tract of humans or animals consuming the GMM.</p>

	ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT
				<p>line:525-534 Please include:</p> <p>GMM with genes encoding antimicrobial resistance genes should not be authorised, since they should not become part of the food and feed chain and their presence should be minimised in the environment.</p> <p>Please remove lines 526-530</p> <p>line:540-543 Delete sentence „When the parental species has a QPS status, this should be indicated together with the information whether the strain used for the GMM construction fulfils the specific QPS qualifications (e.g., lack of transmissible antimicrobial resistance genes).”</p>
102	Ministry of Rural Development	HUN	1.1. Characteristics of the recipient or (when appropriate) parental organism	<p>line 476 Change sentence „The relationship between the recipient and donor(s) should be described, when appropriate.”</p> <p>To:</p> <p>The relationship between the recipient and donor(s) should be described.</p>
103	Ministry of Rural Development	HUN	1.1. Characteristics of the recipient or (when appropriate) parental organism	<p>Line:440-441 Change sentence „Comprehensive information relating to the recipient or (where appropriate) the parental strain should be provided:</p> <p>To:</p> <p>In each case comprehensive information relating to the recipient and the parental strain should be provided:</p> <p>Line:449-451 Delete sentence „The QPS status can be used to meet the information requirements.”</p> <p>Change sentence „The history of all previous modifications should be described. Information relating to the recipient or (when appropriate) the parental organism must include the following:”</p> <p>To:</p> <p>Information relating to the recipient and the parental organism must include the following:</p>
104	DSM	NLD	1.1. Characteristics of the recipient or (when appropriate) parental organism	<p>(line 449) The request "The history of all previous modifications should be described" for the microorganism is somehow ambiguous in its scope. We construe it as "all the modifications made by the applicant or described in previous notifications or literature".</p> <p>(lines 469-473) The paragraph is rather open ended, and we suggest to start the sentences by "Relevant phenotypic..." and "Relevant genotypic...".</p>

ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT
			<p>(lines 474-480) We are not certain what is meant here by "all relevant environmental samples". GMM-derived enzymes are produced in contained use, therefore the only methods available are those provided in the application for production approval. This paragraph seems to be relevant only for categories 3 and 4.</p> <p>(lines 486-492) A discussion of the host strains ability to exchange DNA by horizontal gene transfer with other microorganisms is requested. We construe this requirement as applying only to categories 3 and 4, as specified in the table. Its relevance for category 3 is even questionable since such products do not contain living organisms.</p> <p>(lines 499-503) The use of genetic fingerprinting is not mentioned later in Section 1.4.3. We suggest to remove "fingerprinting" from the text - to just leave "a genetic technique".</p> <p>(lines 535-544) The phrase "well characterised microbial species with a history of safe use, for example belonging to a safe strain lineage" should be included in addition to this section, to be in agreement with lines 355 to 357.</p>
105	Ajinomoto Eurolysine S.A.S.	FRA	<p>1.1. Characteristics of the recipient or (when appropriate) parental organism</p> <p>1) Lines 499-500 As regards the end of the 1st sentence (line 500), we wonder what is meant by "stable performance" and the importance of this point for risk assessment. If this concerns the product of interest obtained through the manufacturing process implemented, the recipient/parental strain usually shows (very) poor production performance for the product of interest. This is the reason why it is modified. In some cases the recipient/parental strain is devoid of the production capacity of the product of interest but is selected because belonging to a species/strain devoid of safety problem or easier to cultivate than a microorganism able to produce the product of interest.</p> <p>2) Lines 500 to 502 This sentence is somewhat confusing: it is referred to the (final) GMM obtained and its correspondence to the recipient/parental strain. We wonder whether this sentence should not rather be placed in section II, B, 1.4.1 (lines 636 to 657).</p> <p>3) Lines 499 to 503 For section 1.1.6, for this aspect of the risk assessment, the wording used in the 2006 version of the Guidance is considered adequate</p> <p>" Factors affecting the genetic stability should be specified (e.g., insertion sequences, transposons, integrons, plasmids, prophage). Taking into account the high level of mobility that is typical of microbial genomes, the absence of any negative effect on human and animal health related to the genetic mobility (instability) should be assessed."</p>
106	Ajinomoto Eurolysine S.A.S.	FRA	<p>1.1. Characteristics of the recipient or (when appropriate) parental organism</p> <p>Line 449 (General comment)</p> <p>"The history of all previous modifications should be described".</p> <p>This requirement is general. There may be cases where the recipient strain (used for the construction of a new strain) is itself a constructed strain described in another/previous application for authorisation (e.g. by the same applicant). In such situation it should be possible to refer to the previous application and only describe the new modifications resulting in the new strain. The purpose of this proposal is to avoid the repetition of a lengthy description.</p>
107	Belgian Biosafety Advisory Council	BEL	<p>1.1. Characteristics of the recipient or (when appropriate) parental organism</p> <p>Line 493 : It should be added: "the possible presence of relevant bacteriophages".</p>

	ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT
			appropriate) parental organism	<p>Lines 507-509 : In case the microorganism does not appear in the list provided in Annex III of Directive 2000/54/EC, the applicant should refer to other relevant lists of classification of hazard to determine to which risk group the microorganism belongs.</p> <p>Line 510 : information relating to host range could be added</p> <p>lines 523-524 : We suggest to replace the line 523-524 and to add a note below the page.</p> <p>This modified text could be :</p> <p>b) Information relating to pathogenicity, infectivity, toxigenicity, virulence, and allergenicity should be provided, as appropriate:</p> <ul style="list-style-type: none"> • Information should be provided on the history of safe use of the recipient/parental strain or any close relative, if available. Effects of any previous use or unintended presence (e.g. as a contaminant) in food or feed has to be considered. The whole human population, including vulnerable groups has to be taken into consideration (*). • Information on pathogenicity should be provided for the recipient/parental strain, and also for related strains and species, if relevant. • Information on the ability to colonise plants, animals (including invertebrates) or humans should be provided. In particular, applicants should provide information on the viability and ability of the recipient/parental microorganism to survive in the gastrointestinal tract of humans or animals consuming the GMM (Category 4). • Information regarding probiotic or immunomodulatory properties should be provided, taking into account the whole human population, including vulnerable groups (*) <p>(*)The vulnerable groups are represented by immunocompromised individuals, infants, pregnant women and the elderly.</p>
108	Genencor, A Danisco Division	NLD	1.1. Characteristics of the recipient or (when appropriate) parental organism	Genencor, A Danisco Division, agrees with the comments submitted by AMFEP, the Association of Manufacturers and Formulators of Enzyme Products.
109	Novozymes A/S	DNK	1.1. Characteristics of the recipient or (when appropriate) parental organism	Novozymes A/S agrees with the comments submitted here by AMFEP
110	FEFANA	BEL	1.1. Characteristics of the recipient or (when appropriate) parental organism	<p>Line 449: The request "The history of all previous modifications should be described" for the microorganism is somehow ambiguous in its scope. We propose to reword it as "The history of all the modifications made by the applicant should be described".</p> <p>Lines 469-473: The paragraph is rather open ended, and we suggest additional, more specific guidance to be provided here.</p> <p>Lines 474-480: We are not certain what is meant here by "all relevant environmental samples". As the products are produced in contained use, only the methods provided in the application for production approval are relevant.</p> <p>Lines 486-492: A discussion of the host strains ability to exchange DNA by horizontal gene transfer with other microorganisms is requested. We seek guidance on how this should be done and for which categories this applies. In table 1 this is only listed as a requirement for categories 3 and 4.</p>

	ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT
				<p>Lines 499-503 (see 1.1.6. INFORMATION ON THE GENETIC STABILITY OF THE RECIPIENT MICROORGANISM): The use of genetic fingerprinting as means to determine genetic stability of the GMM is not scientifically relevant. In addition it is not mentioned later in Section 1.4.3.</p> <p>Lines 535-544 (see 1.1.8. DESCRIPTION OF HISTORY OF USE): The phrase "well characterised microbial species with a history of safe use" should be included in addition to this section to be in agreement with lines 355 to 357.</p>
111	AMFEP	BEL	1.1. Characteristics of the recipient or (when appropriate) parental organism	<p>(line 449) The request "The history of all previous modifications should be described" for the microorganism is somehow ambiguous in its scope. We construe it as "all the modifications made by the applicant or described in previous notifications or literature".</p> <p>(lines 469-473) The paragraph is rather open ended, and we suggest to start the sentences by "Relevant phenotypic..." and "Relevant genotypic...".</p> <p>(lines 474-480) We are not certain what is meant here by "all relevant environmental samples". Enzymes are produced in contained use, therefore the only methods available are those provided in the application for production approval. This paragraph seems to be relevant only for categories 3 and 4.</p> <p>(lines 486-492) A discussion of the host strains ability to exchange DNA by horizontal gene transfer with other microorganisms is requested. We construe this requirement as applying only to categories 3 and 4, as specified in the table. Its relevance for category 3 is even questionable since such products do not contain living organisms.</p> <p>(lines 499-503) The use of genetic fingerprinting is not mentioned later in Section 1.4.3. We suggest to remove "fingerprinting" from the text - to just leave "a genetic technique".</p> <p>(lines 535-544) The phrase "well characterised microbial species with a history of safe use, for example belonging to a safe strain lineage" should be included in addition to this section, to be in agreement with lines 355 to 357.</p>
112	Austrian Agency for Health and Food Safety	AUT	1.2. Characteristics of the origin of the inserted sequences [donor organism(s)]	<p>Lines 561-573: Please return to the text of the old guidance document and add the following bullet points:</p> <p>Additionally, in cases where no QPS status is obtainable, the following information should be provided:</p> <ul style="list-style-type: none"> * Phenotypic and genotypic information relevant to identification, genetic stability and/or safety should be provided, not only for the donor strain, but also for related microorganisms, if appropriate. This should include any information relating to pathogenicity, potential immunological impact or human and animal health. * Description of identification and detection techniques: These should be described in detail. The use of the most recent and reliable molecular techniques is recommended. * Sensitivity, reliability and specificity of the detection techniques: The choice of detection and identification techniques should be justified and their sensitivity, reliability and specificity, including within-laboratory validation, should be provided. * Source and habitat of the organism: Information should be provided of the habitat(s) in which the microorganism is found naturally. The source should be specified, whether a wild strain or a commercial strain from a recognised culture collection.

	ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT
				<p>* Pathogenicity traits: Classification of hazard according to the existing Community rules concerning the protection of human health and/or the environment; pathogenicity, infectivity, toxigenicity, virulence, allergenicity, and the ability to act as a carrier of pathogenicity islands should be provided</p> <p>* History of use: Information should be provided relating to the past and present use, if any, in food and/or feed and of its unintended presence in food or feed (e.g. as a contaminant), if relevant.</p>
113	Anses	FRA	1.2. Characteristics of the origin of the inserted sequences [donor organism(s)]	<p>1.2.3. Nucleic acids directly extracted from environmental samples</p> <p>Line 586: Please add the following sentence "identification of dominant flora of the ecosystem using 16S ribosomal DNA sequencing."</p>
114	Federal Agency for Nature Conservation	DEU	1.2. Characteristics of the origin of the inserted sequences [donor organism(s)]	<p>1.2.1. DNA from defined donor organisms</p> <p>The few requirements including the exemption for donors with a QPS status do not comply with Annex IIIA of Directive 2001/18/EC which is the primary legal source. See also comment to Table 1.</p> <p>1.2.3. Nucleic acids directly extracted from environmental samples</p> <p>Line 589 If the extracted nuclei acid can be related to a defined organism than this organism should be regarded as donor and according information shall be required.</p>
115	Ministry of Rural Development	HUN	1.2. Characteristics of the origin of the inserted sequences [donor organism(s)]	<p>line:551-554 Change sentence „Alternatively, the genome of the recipient microorganism may be modified in such a way that it does not involve foreign DNA. An example of this would be the deletion of a gene. In these cases, the characteristics of the donor should be provided only when the strain used is different from the recipient.”</p> <p>To:</p> <p>The genome of the recipient microorganism may be modified in such a way that it does not involve foreign DNA. An example of this would be the deletion of a gene. In these cases, the characteristics of the donor should also be provided to prove that no unintended changes occurred in the genome.</p> <p>line:569-570 Change sentence „In cases when unspecified DNA is expected to be associated with the genes to be transferred, further detailed information is required.”</p> <p>To:</p> <p>When unspecified DNA is expected to be associated with the genes to be transferred, it should be checked and if it is found the GMM cannot be authorised.</p> <p>line:570-573 Delete sentences „This information should include the elements outlined above in 1.1.4 and 1.1.6. This information is not needed for</p>

ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT
			microorganisms with a QPS status or plants and animals with a history of safe use as food or feed."
116	DSM	NLD	1.2. Characteristics of the origin of the inserted sequences [donor organism(s)] The whole section should be checked for coherence of requirements between cases (with defined genes) where the donor is known, use of synthetic genes, environmental DNA metagenomics. (lines 547-592) Detailed info on donor species or environmental sample characteristics is only necessary when there was a possibility of introducing unknown DNA. When PCR fragment has been used and clones purified and sequenced (as is normal practise, see Amfep's trial dossiers) putative function is known and possibility of harmful sequences excluded. (lines 551-554) When no foreign DNA is used there is no donor, so it can't be different from the recipient. (lines 561-573) Detailed donor taxonomy should only be required under section 1.2.1 when the introduced DNA is not sufficiently characterized (cf. sections 1.22. and 1.2.3). (lines 569-573) "In cases when unspecified DNA is expected to be associated with the genes to be transferred...". This is not allowed in Class I GMMs. (lines 582-592) It is highly appreciated that the existence of "environmental DNA" and metagenomics is acknowledged and guidance is provided.
117	Ajinomoto Eurolysine S.A.S.	FRA	1.2. Characteristics of the origin of the inserted sequences [donor organism(s)] Lines 564 to 573 Under section 1.2.1, detailed information should only be required when the introduced DNA is not sufficiently characterized. Detailed information is not necessary when the DNA inserted is well characterised (PCR fragment, clones obtained purified and sequenced, function of the DNA inserted is known and possibility of harmful sequences excluded).
118	Belgian Biosafety Advisory Council	BEL	1.2. Characteristics of the origin of the inserted sequences [donor organism(s)] Lines 552-554 : "In these cases, ..." => This sentence is not clear, as it relates to a case where no donor microorganism is involved. Line 561 to 573 : To be consistent with what is requested under sections 1.2.2 and 1.2.3, we are of the opinion that information requested under 1.2.1. (DNA from defined donor organism) should include, in addition to the description of the donor organism, information on : - The DNA sequence, and the physical map of the functional elements; - Amino acid sequence(s) and function(s) of the encoded protein(s), including the role played in the metabolism and substrate specificity.
119	Genencor, A Danisco Division	NLD	1.2. Characteristics of the origin of the inserted sequences [donor organism(s)] Genencor, A Danisco Division, agrees with the comments submitted by AMFEP, the Association of Manufacturers and Formulators of Enzyme Products.
120	Novozymes A/S	DNK	1.2. Characteristics of the origin of the inserted sequences [donor organism(s)] Novozymes A/S agrees with the comments submitted here by AMFEP.
121	FEFANA	BEL	1.2. Characteristics of the origin of the inserted sequences [donor organism(s)] Lines 547-592: Detailed info on donor species or environmental sample characteristics is only necessary when there was a possibility of introducing unknown DNA. When PCR fragment has been used and clones purified and sequenced (as is normal practise, see our trial dossiers) putative function is known and possibility of harmful sequences excluded.

	ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT
				<p>Lines 551-554: When there is foreign DNA used in the modification of the genome there is no donor, so it can't be different from the recipient.</p> <p>Lines 561-573 (1.2.1. DNA FROM DEFINED DONOR ORGANISMS): Detailed donor taxonomy should only be required under section 1.2.1 when the introduced DNA is not sufficiently characterized (cf. sections 1.22. and 1.2.3).</p> <p>Lines 569-573 (1.2.1. DNA FROM DEFINED DONOR ORGANISMS): "In cases when unspecified DNA is expected to be associated with the genes to be transferred...". Since this is not allowed in Class I GMMs the requirement is irrelevant.</p> <p>Lines 582-592: It is highly appreciated that the existence of "environmental DNA" and metagenomics is acknowledged and guidance is provided.</p>
122	AMFEP	BEL	1.2. Characteristics of the origin of the inserted sequences [donor organism(s)]	<p>The whole section should be checked for coherence of requirements between cases (with defined genes) where the donor is known, use of synthetic genes, environmental DNA metagenomics.</p> <p>(lines (547-592) Detailed info on donor species or environmental sample characteristics is only necessary when there was a possibility of introducing unknown DNA. When PCR fragment has been used and clones purified and sequenced (as is normal practise, see Amfep's trial dossiers) putative function is known and possibility of harmful sequences excluded.</p> <p>(lines 551-554) When no foreign DNA is used there is no donor, so it can't be different from the recipient.</p> <p>(lines 561-573) Detailed donor taxonomy should only be required under section 1.2.1 when the introduced DNA is not sufficiently characterized (cf. sections 1.22. and 1.2.3).</p> <p>(lines 569-573) "In cases when unspecified DNA is expected to be associated with the genes to be transferred...". This is not allowed in Class I GMMs.</p> <p>(lines 582-592) It is highly appreciated that the existence of "environmental DNA" and metagenomics is acknowledged and guidance is provided.</p>
123	Austrian Agency for Health and Food Safety	AUT	1.3. Description of the genetic modification	<p>Line 633: Please add the following paragraph again, since it contains crucial information concerning the use and risk assessment of antibiotic resistance genes:</p> <p>* the methods and criteria used for selection: when a marker gene is necessary for the selection of the desired event, careful consideration should be given to the choice in view of the amount of information required for risk assessment and justifications for the choice should be provided. If a gene conferring antibiotic resistance is used, it should be justified and evidence that other marker genes could not be used should be provided. Whenever possible, the use of antibiotic resistance marker genes in GMM construction should be avoided to prevent the possibility that clinical therapy could be compromised.</p> <p>Alternative technologies that do not rely on antibiotic resistance marker genes should be used for selection purposes in GMMs.</p>
124	Austrian Agency for Health and Food Safety	AUT	1.3. Description of the genetic modification	<p>Line 620ff: Please include the following text of the original Guidance Document:</p> <p>c) the methods and criteria used for selection: when a marker gene is necessary for the selection of the desired event, careful consideration should be given to the choice in view of the amount of information required for risk assessment and justifications for the choice should be provided. If a gene conferring antibiotic resistance is used, it should be justified and evidence that other marker genes could not be used</p>

ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT
			<p>should be provided. Whenever possible, the use of antibiotic resistance marker genes in GMM construction should be avoided to prevent the possibility that clinical therapy could be compromised.</p> <p>Alternative technologies that do not rely on antibiotic resistance marker genes should be used for selection purposes in GMMs;</p>
125	Austrian Agency for Health and Food Safety	AUT	<p>1.3.2. Information relating to the genetic modification:</p> <p>Line 617: Please add: “...and in the case of insertions, the copy number of the inserts (both complete and partial) should be provided...”-“the detection methods should be detailed and their sensitivity demonstrated</p> <p>Line 618: Please add: ...and accompanied by experimental data e.g. Southern analysis or real time PCR. The detection methods should be detailed and their sensitivity demonstrated.</p> <p>Line 619: Please add: Any polar effects that the deletion event may have on downstream expression should be documented;</p> <p>Line 625: Please add: ... an estimate of the copy number of plasmids per cell (e.g. by quantitative real time PCR).</p>
126	Austrian Agency for Health and Food Safety	AUT	<p>1.3.1. Characteristics of the vector:</p> <p>Line 600: Please add: * the source and type (plasmid, phage, virus, transposon) of the vector used (including plasmid copy number). The choice of the vector should be justified and the procedures used to construct it detailed.</p> <p>Line 608: Please add: * the frequency of mobilisation of the inserted vector and its capacity for genetic transfer. Any information on the expected stability of the inserted vector in the recipient microorganism, and on its capacity to transfer genetic material to other organisms should be provided. The method(s) used to determine the transfer capabilities of the inserted DNA should be provided. When the origin of replication of the vector has a broad host range, this should be taken into account in the evaluation of the stability and transfer capabilities of the vector;</p> <p>* information on the degree to which the vector is limited to the DNA that is required to perform the intended function. It is always recommended to avoid or minimise the inclusion of extraneous DNA; all information relating to the host range of plasmid used as a vector should be given.</p>
127	Austrian Agency for Health and Food Safety	AUT	<p>Lines 593-597: Please add: “The use of carrier DNA is discouraged.” after “When helper plasmids are used, they should be described in detail.”</p>
128	Federal Agency for Nature Conservation	DEU	<p>1.3.1. Characteristics of the vector</p> <p>Requirements of Annex IIIA of the Directive 2001/18/EC are missing here to provide information (i) on the degree to which the vector is limited to the DNA required to perform the intended function and (ii) on the sequence, functional identity and location of the altered/inserted/deleted nucleic acid segment(s). While Annex IIIA actually requests the vector sequence, the present draft only demands the description of the</p>

ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT
			<p>(inserted, deleted etc.) sequence.</p> <p>Line 620-621 Please add here that the absence of certain elements shall not only be “tested experimentally”, but that the evidence shall actually be provided.</p> <p>1.3.2. Information relating to the genetic modification</p> <p>This chapter does not fully comply with the requirements of Annex IIIA of Directive 2001/18/EC. Information should be requested on the purity of the insert from any unknown sequence and information on if the insert is limited to sequences required to perform the intended function.</p> <p>Line 614 Other possible integration loci for DNA are bacterial plasmids. Therefore, "in plasmids" should be added following "in the chromosome".</p>
129	Ministry of Rural Development	HUN	<p>line:622-624 Change sentence „If a vector (mobile genetic element associated with the inserted DNA) is present in the final production strain, the following additional information should be provided based on literature data and/or experimental evidence:</p> <p>To:</p> <p>If a vector (mobile genetic element associated with the inserted DNA) is present in the final production strain, the following additional information should be provided based on experimental evidence:</p>
130	DSM	NLD	<p>(lines 594-595) It is pointed out that helper plasmids or carrier DNA must be described. To what level of detail is such a description needed? If part of the DNA is absent in the final construct (as demonstrated by test) a less detailed description should suffice.</p> <p>(line 625) The request does not bring any further information on the safety of the GMM and the product produced.</p>
131	Ajinomoto Eurolysine S.A.S.	FRA	<p>1) Lines 594-595 It is pointed out that helper plasmids or carrier DNA must be described. What level of detail is considered sufficient by EFSA?</p> <p>For parts of the DNA absent in the final construction (as demonstrated by tests) a less detailed description should suffice</p> <p>2) Line 625 We wonder whether an estimate of the copy number of plasmids per cell provides additional information on the safety of the GMM and the product produced. Moreover, no precise methodology to evaluate the number of plasmids does exist.</p>
132	Genencor, A Danisco Division	NLD	<p>Genencor, A Danisco Division, agrees with the comments submitted by AMFEP, the Association of Manufacturers and Formulators of Enzyme Products.</p>
133	Novozymes A/S	DNK	<p>Novozymes A/S agrees with the comments submitted here by AMFEP.</p>
134	FEFANA	BEL	<p>Lines 594-595: It is pointed out that helper plasmids or carrier DNA must be described. To what level of detail is such a description needed? For parts of the DNA absent in the final construct (as demonstrated by test) a less detailed description should suffice.</p> <p>Lines 598-608: A fully annotated sequence is requested for all plasmids. We seek guidance for the format of such sequence (paper or</p>

ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT
			<p>electronic format – if electronic, then what are the software requirements?).</p> <p>Line 625: The request does not bring any further information on the safety of the GMM and the product produced. In addition there is no clear methodology to evaluate the number of plasmids.</p>
135	AMFEP	BEL	<p>1.3. Description of the genetic modification</p> <p>(lines 594-595) It is pointed out that helper plasmids or carrier DNA must be described. To what level of detail is such a description needed? If part of the DNA is absent in the final construct (as demonstrated by test) a less detailed description should suffice.</p> <p>(line 625) The request does not bring any further information on the safety of the GMM and the product produced.</p>
136	Food Standards Agency	GBR	<p>1.4. Information relating to the GMM and comparison of the GMM with an appropriate comparator</p> <p>UK expert Committee (ACNFP) Comment 3 (section 1.4.4)</p> <p>The guidance focusses very strongly on foreign transgenes that encode new proteins. This certainly covers the majority of GMMs, but GMMs with modifications that alter the expression level of endogenous genes should also be considered, for example via targeted changes in promoter regions. The heading of section 1.4.4 (line 671) could be changed from 'rate and level of expression of the new genetic material' to 'rate and level of expression of the new genetic material or endogenous genes affected by recombinant DNA modification'.</p>
137	Novo Nordisk A/S	DNK	<p>1.4. Information relating to the GMM and comparison of the GMM with an appropriate comparator</p> <p>Paragraph 1.4.1 line 640 – 41 The guideline should explain the purpose of the deposition of the GMM in a "recognised culture collection".</p> <p>Likewise it is recommended to explain the characteristic of a "recognised" culture collection.</p> <p>Novo Nordisk has culture collections placed in at least two different places internally. This is due to the fact that the company shall be able to deliver our vital medicine to the patients no matter which incidents should occur to one of our culture collections.</p> <p>We do not see a need for depositing our production strain in a culture collection outside the company, and we do not at all understand this requirement, when the application concerns biomasses with no living GMMs.</p>
138	Austrian Agency for Health and Food Safety	AUT	<p>1.4. Information relating to the GMM and comparison of the GMM with an appropriate comparator</p> <p>Line 716f: Please include the following text of the original Guidance Document:</p> <p>The general population, as well as specific groups which might be particularly vulnerable, should be considered when the safety of a GMM is evaluated. When transformation events have been combined by transfer of existing approved GMM or by re-transformation of an existing GMM, the need for further molecular analysis will depend, on a case-by-case basis, on the nature of the genetic modifications involved. There is no a priori reason to assume that transfer of transgenic material between independent, safe GMMs will pose any additional risk through a compromised stability of copy number and insert structure. Additional unintended effects could arise through the effects of combined genes e.g. on biochemical pathways and, on a case-by-case basis, will require appropriate comparative analysis.</p>
139	Austrian Agency for Health and Food Safety	AUT	<p>1.4. Information relating to the GMM and comparison of the GMM with an appropriate comparator</p> <p>Line 705: Please include the following text of the original Guidance Document:</p> <p>a) information on any toxic, allergenic or other harmful effects on human or animal health arising from the GMM. Studies of pathogenicity appropriate to the GMM must be performed, when relevant. Genes inserted in a GMM should be evaluated for their potential impact on human and animal health. Documented evidence of safe use of the GMM must be provided. The GMM may have been significantly changed in comparison with its conventional counterpart so that effects on safety must be investigated. Genetic modification may stimulate or de-repress</p>

ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT
			endogenous toxin production so that the GMM should be tested for the production of relevant toxins;
140	Austrian Agency for Health and Food Safety	AUT	1.4. Information relating to the GMM and comparison of the GMM with an appropriate comparator Line 695: Please add: * Potential to transfer DNA by natural genetic transformation
141	Austrian Agency for Health and Food Safety	AUT	1.4. Information relating to the GMM and comparison of the GMM with an appropriate comparator Line 688ff: Please include the following text of the original Guidance Document: In the construction of GMMs, however, specific measures may be used to reduce the potential for the spread of an introduced recombinant construct or gene. Such measures include the following...
142	Austrian Agency for Health and Food Safety	AUT	1.4. Information relating to the GMM and comparison of the GMM with an appropriate comparator Lines 682-684: Information should be provided on the sensitivity, reliability and specificity of the methods.
143	Austrian Agency for Health and Food Safety	AUT	1.4. Information relating to the GMM and comparison of the GMM with an appropriate comparator Line 671ff: Please include the following text of the original Guidance Document: The precise function of the new gene product(s), together with a phenotypic description of the new trait(s), should be detailed. The level of expression of the new gene(s) and the location in the GMM of the gene product(s) as well as the expression during growth cycle should be defined. Applicants should provide information on the level of expression of the modified DNA under the conditions envisaged during use of the GMM in food or feed. This information should be derived using several batches. The requirements for information on developmental expression should be considered on a case-by-case basis taking into account the promoter used, the intended effect of the modification and the potential for effects on non-target organisms. Any new substance that may be produced by the GMM and that is not present in its non-GM counterpart should be identified and assessed for risk.
144	Austrian Agency for Health and Food Safety	AUT	1.4. Information relating to the GMM and comparison of the GMM with an appropriate comparator Line 658ff: Please include the following text of the original Guidance Document: The organisation of the inserted genetic material at the insertion site, including sequence information, the location of primers used for detection, and the methods used for the characterisation should be provided. The size and copy number of all detectable inserts, both complete and partial, and the methods used for their detection should be detailed and their sensitivity demonstrated. Applicants should demonstrate that the sequence inserted in the GMM is the one intended. Sequence determination at both 5' and 3' ends of the inserts should extend into the genome of the recipient. This serves two primary functions. Firstly, it provides information on unique identification sequences for detection purposes (traceability). Secondly, flanking sequence data may identify insertion into, and interruptions of, known ORFs (open reading frames) or regulatory regions and/or the potential for insertional events to produce novel chimeric proteins. Risk assessment of any changes observed should be provided according to the appropriate section of this guidance document. If potential chimeric ORFs are identified, bioinformatic analyses should be conducted to investigate the possibility for similarities with known toxins or allergens. Depending on the information gathered, further analyses may be needed to complete the information necessary for a comprehensive risk assessment. For example, transcriptional and/or translational data may be required to investigate if novel proteins and RNA molecules are synthesised. Thirdly, genomic fingerprints (using PFGE) would be useful to identify any gross genomic changes. Line 661: Please complement:

ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT
			This should be analysed by using appropriate methods, e.g. Southern analysis or real time PCR.
145	Austrian Agency for Health and Food Safety	AUT	1.4. Information relating to the GMM and comparison of the GMM with an appropriate comparator All relevant phenotypic and genotypic traits of the comparator should be described. The methods used to establish the identity of the comparator should be detailed. The most relevant key components (metabolic activity, physiology, safety, etc.) to be considered in the comparative risk assessment should be identified, justified and described. In microorganisms, the presence of mobile genetic elements (plasmids, transposons, integrons and prophage) may lead to natural changes in the genome of the selected comparator strain. Therefore, the genetic stability and variability of the comparator should be demonstrated. A genetic fingerprint using the most recent reliable techniques available should be provided for the comparator to enable its identification and comparison to the GMM. When the comparator belongs to a group of closely related strains, the genetic variability within the group should be demonstrated using molecular techniques. This is important to avoid the attribution of observed differences to the genetic modification when they were already present among the closely related strains.
146	Austrian Agency for Health and Food Safety	AUT	1.4. Information relating to the GMM and comparison of the GMM with an appropriate comparator Line 648-657: Please replace the term "comparator" by "conventional counterpart".
147	Austrian Agency for Health and Food Safety	AUT	1.4. Information relating to the GMM and comparison of the GMM with an appropriate comparator Line 650: Please clarify why the term "isogenic" was changed to "identical".
148	Anses	FRA	1.4. Information relating to the GMM and comparison of the GMM with an appropriate comparator Line 663: Please precise at the end of the paragraph "It is always recommended to avoid or minimize the inclusion of extraneous DNA that is not required to perform the intended function. Whenever possible, the presence of antibiotic resistance marker gene should be avoided."
149	United States of America, Food and Drug Administration	USA	1.4. Information relating to the GMM and comparison of the GMM with an appropriate comparator Section B 1.4.4. Line 681 states: "When the final product is an enzyme, its activity and specificity should be given." We presume that this provision is intended to apply to the activity and specificity of the enzyme under the conditions of its intended use. It may be useful to specify that the activity and specificity of interest are those under the intended conditions of use as these parameters may vary with reaction conditions.
150	United States of America, Food and Drug Administration	USA	1.4. Information relating to the GMM and comparison of the GMM with an appropriate comparator Section B 1.4.4. Line 673 states: "The rate and level of expression of the inserted genetic material should be determined." It may be useful to clarify what is meant by "rate of expression." For instance, is rate of expression intended to mean simply to ascertain whether expression is constitutive, whether expression occurs only under specific conditions, or something else entirely (such as the rate at which something is produced relative to a specific standard)?
151	Federal Agency for Nature	DEU	1.4. Information relating to the GMM and comparison of the GMM with an appropriate comparator

ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT
	Conservation	to the GMM and comparison of the GMM with an appropriate comparator	<p>Line 640-641 What is the reason for the introduced requirement for the applicant to deposit the GMM in a recognised culture collection? Please clarify whether the requirement for the applicant to deposit the GMM in a recognised culture collection refers to the primary transformation event and whether it absolves the applicant from any of his duties. Culture collections shall not only be recognised, but also suitable and qualified to handle GMM.</p> <p>Line 644-647 The intended trait, anticipated phenotypic changes and expected by-products shall not merely be described, but reported information shall be supported by experimental evidence. This requirement is not absolved by referring to chapter 1.4.4 as 1.4.4 is about protein expression only.</p> <p>Lines 648-657 The selection of comparators is briefly explained in this section. For easier accessibility of the document, this section should be moved to Chapter II.</p> <p>1.4.2. Structure and amount of any vector and/or donor nucleic acid remaining in the GMM</p> <p>In the present guideline (EFSA 2006), the gene-region surrounding the insertion has to be considered in order to evaluate if chimeric proteins are formed or if essential ORFs or regulatory elements are disturbed. This aspect is missing from this draft and should be added again. This could be achieved by adding “and surrounding” in line 659 in front of “the inserted DNA...”.</p> <p>Further appropriate methods, such as PCR and sequencing, to analyse and document the presence or absence of any DNA not intended to be inserted, should be mentioned as well.</p> <p>1.4.3. Stability of the genetic traits in the GMM</p> <p>Line 667-670 Definitions of representative batches are necessary. This also applies to line 675, 783-784 and 878-879.</p> <p>1.4.4. Rate and level of expression of the new genetic material and activity of the expressed proteins</p> <p>The evaluation of the expression under the conditions of food and feed has been omitted from the draft compared to the present guideline (EFSA 2006) and should be added again.</p> <p>Line 675-677 Definitions of representative batches are necessary. Data should also be provided about variation of expression under suboptimal fermentation conditions.</p> <p>1.4.5. Description of identification and detection techniques</p> <p>Line 683-684 The sentence “The sensitivity, reliability (in quantitative terms) and specificity should be demonstrated and supported scientifically” (Directive 2001/18/EC, Annex IIIA, II.C.2.(g)) has been omitted from the draft in comparison to the present guideline (EFSA 2006) and should be added again.</p>

	ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT
				<p>The chapter 5.7 "Information on the interaction of the GMM with other organisms, when appropriate" has been deleted in the draft compared to the present guideline (EFSA 2006) and should be added again.</p> <p>1.4.8. Safety for humans and animals</p> <p>Line 712-715 The requirement expressed here relates to the viability and residence time of the GMM in the alimentary tract of the target host species. This is not identical with information on capacity for colonisation as required in Directive 2001/18/EC, Annex IIIA, C.2.(i) (iii) which is much more general and covers e.g. the respiratory tract as well. Please rephrase here to fully comply with the requirement of Annex IIIA.</p>
152	Ministry of Rural Development	HUN	1.4. Information relating to the GMM and comparison of the GMM with an appropriate comparator	<p>line:649-651 Please replace the sentence „In most cases, the most appropriate comparator is the parental or recipient strain that is identical except for the introduced trait(s).</p> <p>with</p> <p>The most appropriate comparator is the parental or recipient strain that is identical except for the introduced trait(s).</p> <p>line:651-652 Please delete the following sentence: "Provided that systematics is properly applied, taxonomic relatedness may be used as a criterion to select a comparator other than the parental microorganism.</p> <p>line:655-658 Please change the sentence „When the recipient strain does not have a history of safe use, the choice of a different strain as comparator must be justified; all the available information should be provided and evaluated on a casenby-case basis.</p> <p>to:</p> <p>When the recipient strain does not have a history of safe use, the choice of this strain cannot be justified and will not be allowed.</p> <p>line:661-664 Please change the text „The presence of any vector and/or donor DNA not intended to be inserted in the GMM should also be documented. This is especially important when antimicrobial resistance markers are present in the vector or donor DNA.</p> <p>to:</p> <p>The presence of any vector and/or donor DNA is undesirable therefore should be removed.</p> <p>line:708-711 Please change the sentence „information on the potential for DNA transfer to take place; such information should also take into account any capacity for enhanced gene transfer to occur; thus, on a case by-case basis, specific experimental data on gene transfer and its consequences may be required;</p> <p>to:</p>

	ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT
				<p>information on the potential for DNA transfer to take place; such information should also take into account any capacity for enhanced gene transfer to occur; thus, on a case by-case basis, specific experimental data on gene transfer and its consequences must be required;</p> <p>line:712-717 Please change the sentence " if the GMM remains viable in the final food or feed, information on the viability and residence time of the GMM in the alimentary tract of the target host species should be provided; this is particularly important if the viability of the GMM is affected by the genetic modification; information on any impact that the GMM may have on the microbiota of the human or animal gastrointestinal tract."</p> <p>to:</p> <p>if the GMM remains viable in the final food or feed, data on the viability and residence time of the GMM in the alimentary tract of the target host species should be provided; this is particularly important if the viability of the GMM is affected by the genetic modification; data on any impact that the GMM may have on the microbiota of the human or animal gastrointestinal tract.</p>
153	DSM	NLD	1.4. Information relating to the GMM and comparison of the GMM with an appropriate comparator	<p>(lines 640-641) GMM deposition for category 1 and 2 products is not useful from an authority control / monitoring point of view (as opposed to GM plants) and does not add value for the safety assessment. It constitutes a very significant threat to the manufacturer's intellectual property. Microbial strains used for the production of enzymes are the key for innovation in this field, and mistakenly release of a strain by the culture collection to a third party would gravely compromise the competitive situation of the concerned company.</p> <p>(lines 667-670) It is stated that usually 5 representative batches need to be analyzed to assess genetic stability. This number is not scientifically justified and in our experience much too high - and it would be difficult to comply with it in the case of new products. We question the overall relevance of this requirement in terms of safety assessment and suggest its deletion. Genetic stability is however an economic driver for the producer since it ensures consistent high fermentation yields.</p> <p>Lines 685-695 request information on the ability to transfer genetic material to other organisms. This is not relevant for category 1 or category 2 which involve contained use of the GMM. Table I implies that transfer is not an issue in these conditions (e g III. B. 1.1.5; III. B. 1.4.6).</p>
154	Ajinomoto Eurolysine S.A.S.	FRA	1.4. Information relating to the GMM and comparison of the GMM with an appropriate comparator	<p>1) Lines 640-641 We wonder what is the additional/useful information for risk assessment provided by the knowledge that a strain has been deposited.</p> <p>2) Lines 667 to 670 It is stated that the stability of the GMM "should be demonstrated using representative batches, normally five"</p> <p>Could EFSA be more specific for what is meant by 'representative batches'.</p> <p>For products already on the market, for which an application for renewal of the authorisation is sought, this could be cultures from industrial fermenters or large size pilot fermenters. However this is not possible for a new product. Would culture in laboratory tanks of a few litres be considered representative?</p> <p>What is the basis considered by EFSA for opting for 5 batches? For new products in development 5 batches is difficult to comply with; 3</p>

ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT
			batches are suggested instead. Moreover, this would be consistent with the '3 independent batches of product preparation' mentioned at e.g. line 799 (section III, B, 2.2.1)
155	Belgian Biosafety Advisory Council	BEL	1.4. Information relating to the GMM and comparison of the GMM with an appropriate comparator
			<p>Lines 634-717: 4) In paragraph 1.4, the information asked to the notifier, relative to the GMM and comparison of the GMM with an appropriate comparator, could be more exhaustive.</p> <p>Despite the lack of universal methods for evaluating the potentially hazardous effects of genetic modification, Food and Agriculture Organization and the European Food Safety Authority recommendations call for targeted approaches to evaluate macro-, micro-, and anti-nutrients, toxins, allergens, and secondary metabolites.</p> <p>Kuiper et al. (2003) and Battista (2008) proposed some molecular profiling methods to increase the chances of detecting unintended effects of transgenic modifications. One of the mentioned profiling techniques is microarrays. This technology allows for monitoring the expression of thousands of genes simultaneously.</p> <p>In parallel of investigation on transcriptome and on the targeted direct product of transgene expression, proteome analysis could be necessary to identify the proteins which are collaterally over or down-expressed in the GMO. Finally, these studies must be completed by metabolomic approach able to diagnose the major and the minor effects of the transgenic modification.</p> <p>Kuiper HA, Kok EJ, Engel K-H (2003) Exploitation of molecular profiling techniques for GM food safety assessment. <i>Curr Opin Biotechnol</i> 14:238–243.</p> <p>Batista R, Saibo N, Lourenço T, Oliveira MM. (2008) Microarray analyses reveal that plant mutagenesis may induce more transcriptomic changes than transgene insertion. <i>Proc Natl Acad Sci U S A</i>. Mar 4;105(9):3640-5. Epub 2008 Feb 26.</p> <p>Lines 648-657 : the whole paragraph on the comparator should be moved between lines 635 and 636, because the use of a comparator is relevant for several sub-sections of section 1.4 (not only 1.4.1 but also 1.4.4 and 1.4.8).</p> <p>In 1.4.4, line 671, It seems that anything that is expressed should result in a protein (and the applicant needs to test the protein activity). However, I think that towards the future there will also be cases where microRNAs will be expressed, maybe in combination with their target genes. Although miRNAs are probably not present in bacterial genomes, expression of these short RNA sequences may have effects on the cell.</p>
156	Genencor, A Danisco Division	NLD	1.4. Information relating to the GMM and comparison of the GMM with an appropriate comparator
			Genencor, A Danisco Division, agrees with the comments submitted by AMFEP, the Association of Manufacturers and Formulators of Enzyme Products.
157	Novozymes A/S	DNK	1.4. Information relating to the GMM and comparison of the GMM with an appropriate comparator
			Novozymes A/S agrees with the comments submitted here by AMFEP.
158	FEFANA	BEL	1.4. Information relating to the GMM and
			Lines 640-641 request that the GMM be deposited in a recognised culture collection but makes no suggestions on who can retrieve these deposits and under what conditions. We propose to delete this requirement for category 1 and 2 products as we fail to understand why and

	ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT
			comparison of the GMM with an appropriate comparator	<p>how this requirement would increase food/feed safety.</p> <p>Lines 664-670 (see 1.4.3. STABILITY OF THE GENETIC TRAITS IN THE GMM): "Genetic stability:".</p> <p>Lines 667-670: It is stated that usually 5 representative batches need to be analyzed to assess genetic stability. What is the basis for this number? What is meant by "representative batches"? Will lab tank fermentations in volumes below 10 l be considered representative? Overall the requirement for 5 batches seems difficult to comply with in the case of new products (we suggest 3 batches instead). In addition, if strains from the same strain lineage are used the number could be reduced as well because strain lineages have the same inactivation characteristics.</p> <p>Lines 685-695 request information on the ability to transfer genetic material to other organisms. This is not relevant for category 1 or category 2 which involve contained use of the GMM. Table I implies that transfer is not an issue in these conditions (e.g. III. B. 1.1.5; III. B. 1.4.6).</p>
159	AMFEP	BEL	1.4. Information relating to the GMM and comparison of the GMM with an appropriate comparator	<p>(lines 640-641) GMM deposition for category 1 and 2 products is not useful from an authority control / monitoring point of view (as opposed to GM plants) and does not add value for the safety assessment. It constitutes a very significant threat to the manufacturer's intellectual property. Microbial strains used for the production of enzymes are the key for innovation in this field, and mistaken release of a strain by the culture collection to a third party would gravely compromise the competitive situation of the concerned company.</p> <p>(lines 667-670) It is stated that usually 5 representative batches need to be analyzed to assess genetic stability. This number is not scientifically justified and in our experience much too high - and it would be difficult to comply with it in the case of new products. We question the overall relevance of this requirement in terms of safety assessment and suggest its deletion. Genetic stability is however an economic driver for the producer since it ensures consistent high fermentation yields.</p> <p>Lines 685-695 request information on the ability to transfer genetic material to other organisms. This is not relevant for category 1 or category 2 which involve contained use of the GMM. Table I implies that transfer is not an issue in these conditions (e.g. III. B. 1.1.5; III. B. 1.4.6).</p>
160	Federal Agency for Nature Conservation	DEU	2. Information relating to the product	<p>2. Information relating to the product</p> <p>Major parts of this chapter are related to categorisation and the scope of the product. They could be moved to chapters I or II or remain here under a separate subtitle.</p> <p>Line 721 While we agree with EFSA that only a limited amount of information is required to perform a risk assessment on GMMs of Category 1, information that is required, is an assessment of the process by which the GMMs will be removed from the product and how it is ensured that no recombinant DNA is maintained in the product. This should be mentioned explicitly in this section and should be included in Table 1 (cf. comments on Table 1).</p> <p>Furthermore, as it is stated in the text that it is necessary to understand the process by which the GMM has been inactivated in the product in GMMs of the Categories 2 AND 3, it is not understandable why in Table 1 Category 2 is exempted from this requisition. This information is essential for the risk assessment of Category 2 GMMs and it should thus be indicated in Table 1 (cf. comments on Table 1).</p> <p>Line 730-732 Once more, only differences to the comparator should be assessed which significantly narrows the risk assessment and might lead to the overlooking of unintended effects.</p> <p>Line 745-750 and footnotes 31-32</p>

ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT
			<p>If understood correctly this para in combination with footnotes 31 and 32 suggests that applications for biomass used as feed material (Category 3 and 4) are prepared and presented following Regulation (EC) No 1829/2003, but risk assessed following Council Directive 83/228/EEC. Council Directive 83/228/EEC, which is of 18 April 1983, contains guidelines for the assessment of certain products used in animal nutrition, but does not cover GMO-specific aspects. Therefore, the risk assessment should be made following Regulation (EC) 1829/2003 and additionally take into account the Council Directive 83/228/EEC.</p>
161	The Netherlands Commission on Genetic Modification (COGEM)	NLD 2. Information relating to the product	<p>III.B.2. Information relating to the product</p> <p>EFSA states that applicants should indicate in which of the four categories the GMM or the products derived with or from the GMM belongs. For products belonging to category 2 and 3 it must be demonstrated that the GMM has been inactivated. According to the document, for both product categories it has to be confirmed that viable but non-culturable cells (VBNCs) are absent (line 724-725). Bacteria and fungi may also produce spores that permit survival. Therefore, in COGEM's view the absence of both viable spores and VBNCs has to be confirmed in products belonging to category 2 and 3.</p>
162	DSM	NLD 2. Information relating to the product	<p>(lines 721-727) The following sentence is inappropriate: "For categories 2 and 3, it will be necessary to understand the processes by which the GMM has been inactivated in the product and the degree to which traces of recombinant DNA may be detected in the product.": GMM inactivation is not part of the food or feed product manufacturing but of the Contained Use.</p> <p>(line 724) The phrase "full length" should be added before "DNA" to be in agreement with other parts of the document.</p> <p>(lines 751-758) specifies that section B.2.2 applies to food enzymes. We understand food enzymes as belonging to Category 2, as stated in lines 341-342. This seems however to be in contradiction with Figure 1 and Table 1.</p>
163	Ajinomoto Eurolysine S.A.S.	FRA 2. Information relating to the product	<p>1) Lines 722 to 724 We believe that in line 724 the words 'full-length coding sequences of' should be added before "DNA" to be in agreement with other parts of the document.</p> <p>For category 3 products we believe this is an important parameter to consider- please see comment made in regard of lines 345 – 347 – which conditions other evaluations to be made or not.</p> <p>2) Lines 730 - 731 For the statement "Comparison of the product with an appropriate comparator should be carried out."</p> <p>The words 'where appropriate' or 'when an adequate comparator does exist' should be added at the end of the sentence.</p> <p>Indeed, there are cases where comparators do not exist. This could be, for example, the case of microbial biomasses for feed (or food) use produced from GMM but not, previously, from a 'conventional' counterpart of the same microorganism.</p> <p>3) Lines 747- 749 (Comment just for the sake of legal soundness.)</p> <p>To take into account legal developments EFSA should no longer refer to</p> <p>Directive 83/228 and Directive 82/471 because both have been repealed by Regulation (EC) No 767/2009. According to Regulation (EC) No 767/2009 for biomasses used as feed materials not falling within the scope of Regulation (EC) No 1829/2003, contrary to Directive 82/471 no</p>

ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT
			<p>authorisation prior the placing on the market of the biomass is (anymore) necessary (this aspect is indicated in the Guidance (in preparation) for the risk assessment of biomasses used as feed materials).</p> <p>This sentence should be structured in a different way e.g. using the wording utilised in the lines 13 to 17 of the Guidance for the assessment of biomasses for use in animal nutrition (also submitted to public consultation).</p>
164	Belgian Biosafety Advisory Council	BEL	2. Information relating to the product Suggestion for addition after line 776 : "According to the EU legislation, food supplements (such as vitamins and minerals) are to be considered as foods."
165	Genencor, A Danisco Division	NLD	2. Information relating to the product Genencor, A Danisco Division, agrees with the comments submitted by AMFEP, the Association of Manufacturers and Formulators of Enzyme Products.
166	Novozymes A/S	DNK	2. Information relating to the product Novozymes A/S agrees with the comments submitted here by AMFEP.
167	FEFANA	BEL	2. Information relating to the product <p>Lines 721-727: The following sentence is inappropriate: "For categories 2 and 3, it will be necessary to understand the processes by which the GMM has been inactivated in the product and the degree to which traces of recombinant DNA may be detected in the product.": GMM inactivation is not part of the food or feed product manufacturing but of the Contained Use.</p> <p>Line 724: The phrase "full length" should be added before "DNA" to be in agreement with other parts of the document.</p> <p>Lines 745-750: The Directive 83/228/EEC respectively the e basic Directive 82/471/EEC have been withdrawn and replaced by Regulation 767/2009/EC. According to that Regulation biomasses not falling under the Regulation 1829/2003 are out of the scope of further assessment. Thus this link should be deleted in case of non-GMM biomasses. Proposed wording : "To take into account legal developments EFSA should no longer refer to Directive 83/228 and Directive 82/471, to which it is associated, because both have been repealed by Regulation (EC) No 767/2009. According to Regulation (EC) No 767/2009 for biomasses used as feed materials not falling within the scope of Regulation (EC) No 1829/2003, contrary to Directive 82/471 no authorisation prior the placing on the market of the biomass is (anymore) necessary.</p>
168	AMFEP	BEL	2. Information relating to the product <p>(lines 721-727) The following sentence is inappropriate: "For categories 2 and 3, it will be necessary to understand the processes by which the GMM has been inactivated in the product and the degree to which traces of recombinant DNA may be detected in the product.": GMM inactivation is not part of the food or feed product manufacturing but of the Contained Use.</p> <p>(line 724) The phrase "full length" should be added before "DNA" to be in agreement with other parts of the document.</p> <p>(lines 751-758) specifies that section B.2.2 applies to food enzymes. We understand food enzymes as belonging to Category 2, as stated in lines 341-342. This seems however to be in contradiction with Figure 1 and Table 1.</p>
169	Federal Office of Consumer Protection and Food Safety (BVL)	DEU	2. Information relating to the product <p>Lines 749/750: The statement "for these applications, Section B.2.2. of the Chapter will apply" is misleading since Section B 2.2. of the chapter does not apply to products of Category 4, cf. Table 1.</p> <p>Furthermore, it is not clear why Section B.2.3. will not apply for biomasses used as feed materials.</p> <p>Lines 770 - 772: The sentence is misleading since Section B.2.2. of the chapter does not apply to food consisting of or containing GMMs (Category 4), cf. Table 1.</p>

ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT	
170	Austrian Agency for Health and Food Safety	AUT	2.1. Information relating to the production process	<p>Lines 782-784: Please include the following text of the original Guidance Document:</p> <p>The key stages of the production process that may lead to any difference between the GM product and its conventional counterpart should be identified. The parameters most relevant for the characterisation of the product from a safety and nutritional point of view should be considered. A flowchart showing the key stages is recommended. The applicant should provide the scientific rationale for the risk assessment. Experimental data may be required on a case-by-case basis.</p>
171	Federal Agency for Nature Conservation	DEU	2.1. Information relating to the production process	<p>Line 783-784 No details are provided here and guidance is missing on what kind and amount of information is required. This lack of guidance is hardly acceptable. Production conditions shall be described in detail. Possible variation of parameters (e.g. temperature, pH, substrate, medium, oxygen supply, foaming etc.) shall be considered with a view to whether they can effect the composition of the product and the reliability and efficacy of the methods to remove or inactivate cells and recombinant DNA. It is also relevant to know what conditions apply to so-called representative batches. See also comments on line 667-670, 678 and 878-879.</p>
172	DSM	NLD	2.1. Information relating to the production process	<p>(lines 789 et seq.) It is suggested for clarity to rewrite the headline into "2.2.1. Demonstration of the absence of GMM in the product". Similarly, the second sentence should read: "The technique used to remove microbial cells in the course of the production process should be detailed and the absence of the microbial cells in the product should be experimentally verified."</p> <p>(lines 839-865) We welcome the clarification that one functional gene must be targeted for residual recombinant DNA detection. In this respect we suggest that line 859 is changed into "At least one functional gene of concern has to be targeted".</p> <p>If a PCR assay is requested despite absence of sequences of concern, it is important that it is possible to design a generic assay. We strongly wish to develop generic assays for residual DNA determination and believe that a generic sequence, specific for a lineage of production strains from a company having the size of a typical gene (e.g. 1 kb) would be the right target for such an analysis (could e.g. be the sequence resulting from a central gene disruption). Does the Panel agree to that?</p> <p>It is requested that the analysis is done by PCR and that all functional genes of concern must be targeted specifically as DNA degradation can be sequence dependant. What is the basis for the latter statement regarding sequence dependence of DNA degradation? We seek guidance on understanding which sequences are of concern.</p> <p>(lines 840-841) The Panel is respectfully invited to provide a reason why the presence of residual (recombinant) DNA is relevant for the safety of the GMM or its product. For example, during the evaluation of a food enzyme produced by a GMM in France, AFSSA only requires the demonstration of absence of biologically active DNA when there is a toxicological effect demonstrated during the safety tests on the product. At most, the demonstration of absence of DNA should only apply when sequences of concern are present in the final GMM.</p> <p>(line 844) "a cell lysis step should be introduced in the DNA extraction procedure when the product belongs to Categories 2 or 3". This is not necessary, see comments on 789 et seq. above.</p>
173	Belgian Biosafety Advisory Council	BEL	2.1. Information relating to the production process	<p>- Line 417 and line 783 : several microbial derived products or other organic chemicals can be further converted using microbial cells or enzymes as catalysts (biocatalysts) into very useful derivatives; biocatalysis is now also an important way/method of manufacturing fine bio-chemicals, nutraceuticals, food additives..., in addition to fermentation.</p> <p>In line 783, we suggest to amend the text as follows : "The stages of the production process of the GMM (e.g. fermentation, cultivation,</p>

	ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT
				biocatalysis...) should be detailed.
174	Austrian Agency for Health and Food Safety	AUT	2.2. Information relating to the product preparation process	Lines 833-835: Please include the following text of the original Guidance Document: When, after killing treatment, viable cells are still present, they should be identified and quantified.
175	Austrian Agency for Health and Food Safety	AUT	2.2. Information relating to the product preparation process	Line 789-804: Please include the following text of the original Guidance Document: The absence of microbial cells should be established, using both a recognised culture-based method for the enumeration of viable microorganisms, if available, and molecular methods. The use of molecular methods allows the detection of cells that are viable but that cannot be cultivated under laboratory conditions. Different kinds of PCR may be used, using either primers specific for the GM event or primers that can detect a broader group of microorganisms (strain, species, genus or family) to which the GMM belongs. The use of detection techniques with different specificities should be evaluated on a case-by-base basis and should be justified.
176	United States of America, Food and Drug Administration	USA	2.2. Information relating to the product preparation process	Section B 2.2.2. Lines 805-838 describe analytical methods for ensuring the inactivation of genetically engineered organisms in category three products. This section suggests describing the technique used to inactivate the microbial cells, demonstrating the absence of genetically engineered microorganisms using a recognized method for detection of viable microorganisms, and verifying the absence of stressed cells using a resuscitation step in the culturing method. The section also suggests the use of non-culturing techniques such as flow cytometry or microscopy targeting different metabolic functions and reverse transcriptase PCR (RT-PCR) targeting mRNAs for which there is a short half-life to detect genetically engineered viable but non-culturable (VBNC) microorganisms. The section then recommends the use of microscopy or flow cytometry for the detection of genetically engineered physically intact dead cells. The analytical techniques described for the detection of genetically engineered VBNC microorganisms and genetically engineered physically intact dead cells suggest going to lengths beyond those commensurate with the risks ordinarily associated with genetically engineered VBNC microorganisms and genetically engineered physically intact dead cells intended to be present in food. Based on the foregoing safety assessment that includes consideration of the pathogenicity and toxigenicity of the host and donor and the safety of the transferred DNA and its expression product, presumably such organisms would be non-pathogenic and non-toxigenic; and, therefore, would seem to present little, if any, safety concerns if present in food in the VBNC or physically intact dead states. Additionally, it is not clear whether use of microscopy, flow cytometry and RT-PCR) would ordinarily be practical, especially when complicated by the presence of the food matrix. It is also unclear how EFSA would evaluate and apply the data obtained from such analyses. Rather than turning to methods such as flow cytometry, microscopy, and RT-PCR to assess the possible presence of VBNC microorganisms or genetically engineered physically intact dead cells, perhaps it would be more feasible and appropriate for applicants to indicate whether there would be any safety concerns associated with the possible presence of genetically-engineered VBNC microorganisms or genetically engineered physically intact dead cells in the final food/feed product.
177	Federal Agency for Nature Conservation	DEU	2.2. Information relating to the product preparation process	2.2. Information relating to the product preparation process It is appreciated that requirements on the removal of the GMM cells, on the inactivation of the cells and assessment of the presence of remaining physically intact cells as well as on information on the possible presence of recombinant DNA (Chapters 2.2.1, 2.2.2, 2.2.3) have been specified. However, this should be complemented by an indication whether data should be sampled from small, pilot or industrial scale fermentation, especially since this was an issue during evaluation of recent GMM applications (see comments in the mentioned chapters). 2.2.1. Information on the removal of the GMM cells from the product

	ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT
				<p>Line 793 Please complete this sentence as follows: "...should be established for industrial scale production." This applies to line 821-823 accordingly.</p> <p>Line 796 Efficacy and suitability of the resuscitation step shall be demonstrated for the production strain grown under representative fermentation conditions using cells which have not been completely inactivated. The same applies to line 826-827 in chapter 2.2.2.</p> <p>2.2.2. Information on the inactivation of the GMM cells and assessment of the presence of remaining physically intact cells</p> <p>Line 812-813 The efficacy of any inactivation technique shall be established under conditions of industrial production scale.</p> <p>Line 812-819 It is possible to deduce and assess the potential and risk of inactivated cells or cells of different variability stages to interact with various hosts on the basis of their specific properties provided they are known. However, they might be different for the recipient and the GMM due to unintended effects including those which cannot be predicted. Therefore, in case of Category 3 products, this assessment should be based on experimental data with the GMM obtained in animal studies.</p> <p>Line 821-823 Please alter this sentence as follows: ".....should be established for industrial scale production, taking into consideration the following literature."</p> <p>Line 826-827 Efficacy and suitability of the resuscitation step shall be demonstrated for the production strain grown under representative fermentation conditions using cells which have not been completely inactivated. The same applies to line 796 in chapter 2.2.1.</p>
178	The Netherlands Commission on Genetic Modification (COGEM)	NLD	2.2. Information relating to the product preparation process	<p>III.B.2.2.1. Information on the removal of the GMM cells from the product</p> <p>According to the guidance, removal of the GMM is required in products belonging to categories 1 and 2 (lines 790-792). For verification of the removal, the performance of a resuscitation step is recommended. Resuscitation should be done with a longer incubation time compared to the normal culturing of viable organisms (line 796-798). 'A longer incubation time' is too vague and should be specified more precisely, e.g. the incubation time will be at least 1000 times the generation time of the GMM.</p>
179	Ministry of Rural Development	HUN	2.2. Information relating to the product preparation process	<p>line:856-858 Please change the sentence „Should PCR inhibition be encountered when testing the product, samples taken before formulation may be used.”</p> <p>To:</p> <p>Should PCR inhibition be encountered when testing the product, the product cannot be used.</p>
180	Ajinomoto Eurolysine S.A.S.	FRA	2.2. Information relating to the product preparation process	<p>1) Lines 789 and 805 We understand that the Guidance intends to cover a diversity of products and manufacturing processes. For products of interest not presenting a risk of degradation by heat or chemical (acid) treatment, the 'inactivation treatment' often takes place immediately after the culture step, i.e. prior to the removal of the GMM cells from the product.</p>

	ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT
				<p>As previously commented in regard of lines 345 to 347 this has an effect on the 'quality' of the recombinant DNA present in category 3 products ('Type 1 products).</p> <p>2) Lines 840-81 For residual (recombinant) DNA, i.e. recombinant below the size of full-length coding sequences or, even, the size of a gene we wonder how this presence is relevant for safety – risk assessment. A clarification is respectfully requested to the Panel.</p>
181	Belgian Biosafety Advisory Council	BEL	2.2. Information relating to the product preparation process	<p>Line 788: It is not clear why exactly it is referred to section B.2.2.3 only.</p> <p>After line 788 : Suggestion to add a new subsection 2.2.1 "Information relating to the purification of the product"</p> <p>Line 790 : Removal of the GMM is NOT required in products belonging to Category 1. The text should be modified accordingly (also to be coherent with Table 1 on page 46).</p> <p>Line 815 : The exact meaning of the term "host" should be clarified.</p>
182	Genencor, A Danisco Division	NLD	2.2. Information relating to the product preparation process	Genencor, A Danisco Division, agrees with the comments submitted by AMFEP, the Association of Manufacturers and Formulators of Enzyme Products.
183	Novozymes A/S	DNK	2.2. Information relating to the product preparation process	Novozymes A/S agrees with the comments submitted here by AMFEP.
184	AMFEP	BEL	2.2. Information relating to the product preparation process	<p>(lines 789 et seq.) It is suggested for clarity to rewrite the headline into "2.2.1. Demonstration of the absence of GMM in the product". Similarly, the second sentence should read: "The technique used to remove microbial cells in the course of the production process should be detailed and the absence of the microbial cells in the product should be experimentally verified."</p> <p>(lines 839-865) We welcome the clarification that one functional gene must be targeted for residual recombinant DNA detection. In this respect we suggest that line 859 is changed into "At least one functional gene of concern has to be targeted".</p> <p>If a PCR assay is requested despite absence of sequences of concern, it is important that it is possible to design a generic assay. We strongly wish to develop generic assays for residual DNA determination and believe that a generic sequence, specific for a lineage of production strains from a company having the size of a typical gene (e.g. 1 kb) would be the right target for such an analysis (could e.g. be the sequence resulting from a central gene disruption). Does the Panel agree to that?</p> <p>It is requested that the analysis is done by PCR and that all functional genes of concern must be targeted specifically as DNA degradation can be sequence dependant. What is the basis for the latter statement regarding sequence dependence of DNA degradation? We seek guidance on understanding which sequences are of concern.</p> <p>(lines 840-841) The Panel is respectfully invited to provide a reason why the presence of residual (recombinant) DNA is relevant for the safety of the GMM or its product. For example, during the evaluation of a food enzyme produced by a GMM in France, AFSSA only requires the demonstration of absence of biologically active DNA when there is a toxicological effect demonstrated during the safety tests on the product. At most, the demonstration of absence of DNA should only apply when sequences of concern are present in the final GMM.</p> <p>(line 844) "a cell lysis step should be introduced in the DNA extraction procedure when the product belongs to Categories 2 or 3". This is not</p>

ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT
			necessary, see comments on 789 et seq. above.
185	FEFANA	BEL	2.2. Information relating to the product preparation process <p>Lines 789-804 (see 2.2.1. INFORMATION ON THE REMOVAL OF THE GMM CELLS FROM THE PRODUCT): "removal of the GMM cells from the product": the "product" is in this guideline the food or feed product. From F&F products there is no removal of GMMs. Inactivation is part of Contained Use and not necessary to demonstrate for F&F products because i) no viable cells are present for protection of our Intellectual Property, and ii) we are in violation if live cells were present in our enzyme products. In addition this section is way too prescriptive.</p> <p>Lines 805-838 (see 2.2.2. INFORMATION ON THE INACTIVATION OF THE GMM CELLS AND ASSESSMENT OF THE PRESENCE OF REMAINING PHYSICALLY INTACT CELLS): Same comments as per lines 789-804.</p> <p>Lines 824-825: The panel is respectfully invited to define recognised methods for detecting viable microorganisms.</p> <p>Lines 840-841 (see 2.2.3. INFORMATION ON THE POSSIBLE PRESENCE OF RECOMBINANT DNA): The Panel is respectfully invited to provide a reason why the presence of residual (recombinant) DNA is relevant for the safety of the GMM or its product. Additionally information should be provided about the definition of present residuals and possible detection limits to give clear advice to the applicant.</p> <p>Line 844 (see 2.2.3. INFORMATION ON THE POSSIBLE PRESENCE OF RECOMBINANT DNA): "a cell lysis step should be introduced in the DNA extraction procedure when the product belongs to Categories 2 and 3".</p> <p>Not necessary, see comments on 789 et seq above. Alternatively, enzyme preparations should be Category 1 instead of 2.</p>
186	Food Standards Agency	GBR	2.3. Description of the product <p>UK expert Committee (ACNFP) Comment 4 (section 2.3.4)</p> <p>Sections 2.3.4 (lines 884 - 888) and 2.3.5 (lines 889 - 893) : These sections could be a little better focussed on the likely use and form in which GMMs would be consumed, ranging from highly refined ingredients to the organism itself and could be combined. Such a section could then consider the physical form and attributes of purified products versus the whole organism and then discuss the potential formulations in which the ingredient might be delivered and then consumed. Whilst guidance is necessary, it is unclear why these sections appear to be so prescriptive. For example why ask for data on surface tension? This seems a bizarre request for a whole organism although it might be relevant for a purified ingredient. Surely if the assessment is done on a case-by-case basis the applicant has to provide the risk assessor with data appropriate to undertaking the assessment. Why is the information on the "efficiency" of analytical methodology required here, but not in section 2.3.3 on composition?</p>
187	Austrian Agency for Health and Food Safety	AUT	2.3. Description of the product <p>Line 874ff: Please include the following text of the original Guidance Document:</p> <p>The qualitative and, when possible, quantitative composition of the product, should be provided, including all ingredients and impurities. The extent of batch-to-batch variation should be determined. For products that are single substances, the chemical characteristics (molecular weight, molecular formulae) and the presence and nature of contaminants should be provided. The techniques used to identify the product and to define its chemical composition should be detailed.</p>
188	United States of America, Food and Drug Administration	USA	2.3. Description of the product <p>Section B 2.3.5</p> <p>Lines 890-891 state: "The technological attributes of the product should be specified for its intended use and for any other potential uses." The intended use of a product bounds the risk assessment for that product. "Any other potential uses" requires speculation and is not relevant to the risk assessment of a product for an intended use; and, therefore, we recommend that the phrase "and for any other potential uses" be</p>

	ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT
				deleted.
189	United States of America, Food and Drug Administration	USA	2.3. Description of the product	Section B 2.3.2 Lines 872-873 state: "The intended use of the product and its mode(s) of action, where applicable, should be described. Any other potential uses should also be specified." The intended use of a product bounds the risk assessment for that product. "Any other potential uses" requires speculation and is not relevant to the risk assessment of a product for an intended use; and, therefore, we recommend that the sentence, "Any other potential uses should also be specified," be deleted.
190	Federal Agency for Nature Conservation	DEU	2.3. Description of the product	2.3.3. Composition Line 876 Only in "appropriate" cases quantitative composition data is required. The guideline should specify what cases are regarded as appropriate (e.g. only potentially toxic or allergenic components, anti-nutrients etc.). Line 878-879 This para shall be supplemented as follows: "At least three representative batches should be included in each analysis. Relevant experimental data has to be provided in cases of any introduced changes in the production process; the effects on the composition should be assessed." Line 880-883 Applicants shall justify the selection of substances which are analysed with a view to the intended use of the product, the genetic modification, possibly variation in the fermentation conditions and the provision to indentify any adverse effects through the genetic modification.
191	DSM	NLD	2.3. Description of the product	(lines 884-888) What is assessed in the present guidance is the safety of the genetic construction. The physical properties of the product, which can be marketed in multiple physical forms, are not relevant in this context. (lines 889-893) What is assessed in the present guidance is the safety of the genetic construction. The technological properties of the product, which can be marketed in multiple physical forms and for multiple uses, are not relevant in this context.
192	Genencor, A Danisco Division	NLD	2.3. Description of the product	Genencor, A Danisco Division, agrees with the comments submitted by AMFEP, the Association of Manufacturers and Formulators of Enzyme Products.
193	Novozymes A/S	DNK	2.3. Description of the product	Novozymes A/S agrees with the comments submitted here by AMFEP.
194	AMFEP	BEL	2.3. Description of the product	(lines 884-888) What is assessed in the present guidance is the safety of the genetic construction. The physical properties of the product, which can be marketed in multiple physical forms, are not relevant in this context. (lines 889-893) What is assessed in the present guidance is the safety of the genetic construction. The technological properties of the product, which can be marketed in multiple physical forms and for multiple uses, are not relevant in this context.
195	Norwegian Scientific Committee for Food Safety	NOR	2.4. Considerations of the GM product for human health	Paragraph 2.4.2. Assessment of proteins expressed by the newly introduced genes: The GMM production is in some cases not completely known. In such cases one has probably to perform various toxicological tests. In para 2.4.2 one get the impression that toxicological tests only in exceptional cases should be done.

ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT
			Paragraph 2.4.3. Toxicological tests carried out in 90-days rat study is not well suited to detect unknown components. These tests are designed to determine the toxicity of known chemicals. When testing complex components, such as nutrients, the design of testing should be more comprehensive, involving other animals e.g. fish, which are fed by the GMM-feed.
196	Food Standards Agency	GBR	<p>2.4. Considerations of the GM product for human health</p> <p>UK expert Committee (ACNFP) Comment 8 (section 2.4.6)</p> <p>Section 2.4.6 (lines 1087 - 1107) Nutritional assessment: This is quite straightforward and the logic followed in the opinion is that the standard procedure used for any novel food ingredient can be applied to GMMs. The question is how deep the analysis profile should go. To measure every possible nutrient and metabolite is not feasible. However, there may be a case for more detailed analysis in the case of some GM products. Take the example of Golden Rice (genetically modified to produce vitamin A). The genetic modification involves a number of genes which provide alternative pathways to synthesise vitamin A. This apparently gives rise to an unusual profile of carotenoids, which in turn, may give rise to health concerns (beta-carotene intake and lung cancer progression). It may be that many applicants would anticipate this type of problem and provide the equivalent of a full carotenoid profile but some may not. The advice should include an explicit direction to consider the potential effect of the genetic modification on metabolism, both direct and indirect, and provide a detailed analysis of any relevant compounds and the rationale for considering these.</p>
197	Food Standards Agency	GBR	<p>2.4. Considerations of the GM product for human health</p> <p>UK expert Committee (ACNFP) Comment 7 (section 2.4.5.2)</p> <p>Page 30 (line 1015) states that genes derived from wheat, barley, rye and oats should be assessed for a role in the elicitation of gluten-sensitive enteropathy. How should this be addressed? Is it sufficient initially to look for homology of the transgene with prolamins and/or test for prolamins content?</p>
198	Food Standards Agency	GBR	<p>2.4. Considerations of the GM product for human health</p> <p>UK expert Committee (ACNFP) Comment 6 (section 2.4.5)</p> <p>Section 2.4.5.3 and 4 (lines 1073 – 1086): This section needs to be better thought through with regards GMMs. The ways in which GMMs and their products are used in foods are somewhat different to the concept of a GMO plant-derived food and hence the consideration of how the matrix processing and formulation affects potential allergenicity is different. Adding a fungal enzyme which may come in a powdered form alongside other baking ingredients, for example, and which is mixed in to a food and then baked is different to considering a whole microbe which might be encapsulated and then added. This text appears to have been simply cut and pasted from the 2010 EFSA Opinion on allergenicity. It needs to be adapted properly for GMMs otherwise it is going to confuse rather than enlighten.</p>
199	Food Standards Agency	GBR	<p>2.4. Considerations of the GM product for human health</p> <p>UK expert Committee (ACNFP) Comment 5 (section 2.4.5)</p> <p>Section 2.4.5 (lines 977 - 1086) dealing with allergenicity draws heavily on the EFSA 2010 Opinion which is focussed on plants. This document should be more explicit regarding whether the safety considerations are focussed on allergens from foods or should include inhalant and other types and sources of allergens and allergenic organisms. There are many moulds/fungi which trigger inhalant allergies which maybe relevant to the allergenic risk assessment of GMMs which were not alluded to in the 2010 opinion on plants (except for pollen allergens, especially in terms of cross-reactive allergies to foods). This might be worth greater consideration with regards GMMs, as many food grade processing aids are produced in moulds/fungi.</p>
200	Austrian Coeliac Society	AUT	<p>2.4. Considerations of the GM product for human health</p> <p>Line 1093 - 1107 Consumption of larger quantities of certain foods</p> <p>Coeliacs are obliged to consume larger quantities of the products gluten-free by nature due to medical reasons compared to the general population. Therefore we kindly ask to consider that special emphasis should be given to the safety profile of gluten-free GM food like maize,</p>

	ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT
				<p>soy etc. It is also our opinion that before such GM food being released in the general circulation, studies have to be held to determine the actual quantities consumed by the general population versus coeliac population, clearly stating the guidelines to be used to quantify the daily intakes as well as the upper tolerated amounts of GM containing foods, however we kindly ask to consider in general:</p> <p>European population with autoimmune and/or gastro-intestinal disorders</p> <p>Coeliac disease is one of several other autoimmune disorders. How can these population be 100% sure that they are tolerating GM food in the same manner as the general population? Especially in coeliac disease the risk to develop other autoimmune disorders (diabetes typ 1 etc.) is much more increased compared with the general population. How long should a long-term study been undertaken to get absolute reliable results that e.g. other autoimmune disorders will not be additionally provoked or how can we be sure that a weak or very sensitive gastro-intestinal system is tolerating GMO foods in the same manner as healthy individuals?</p> <p>Hoping that our comments will be taken into account, I remain with kind regards</p>
201	Austrian Coeliac Society	AUT	2.4. Considerations of the GM product for human health	<p>Line 1014 – 1017 Please do not permit the transfer of genes from gluten containing foods or newly developed proteins into gluten-free foods!</p> <p>We kindly ask to take over the full protection what we obtained by the Codex ad hoc Intergovernmental Task Force on Foods Derived from Biotechnology (adopted by the Codex Alimentarius Commission in July 2003).</p> <p>We noted that in 1014 – 1017 part of the text is similar, however we have not seen in your paper the explicit request to avoid genes which code for a protein involved in coeliac disease. For better understanding we quote the relevant texts of the both Guidelines and kindly ask to insert them into the EFSA Scientific Opinion:</p> <p>"Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Plants</p> <p>42. The newly expressed proteins in foods derived from recombinant-DNA plants should be evaluated for any possible role in the elicitation of gluten-sensitive enteropathy, if the introduced genetic material is obtained from wheat, rye, barley, oats, or related cereal grains.</p> <p>43. The transfer of genes from commonly allergenic foods and from foods known to elicit gluten-sensitive enteropathy in sensitive individuals should be avoided unless it is documented that the transferred gene does not code for an allergen or for a protein involved in gluten-sensitive enteropathy.</p> <p>Guideline for the Conduct of Food Safety Assessment of Foods Produced Using Recombinant-DNA Microorganisms</p> <p>47. Genes derived from known allergenic sources should be assumed to encode an allergen and be avoided unless scientific evidence demonstrates otherwise. The transfer of genes from organisms known to elicit gluten-sensitive enteropathy in sensitive individuals should be avoided unless it is documented that the transferred gene does not code for an allergen or for a protein involved in gluten-sensitive enteropathy."</p> <p>In the past we were informed about research projects aiming to implement wheat genes into rice and buckwheat grains to improve the baking qualities in these cereals. With these developments by implementing wheat genes in cereals gluten-free by nature coeliacs would have to avoid also these cereals leading to the consequence to have no gluten-free bread, flour etc. at all.</p> <p>Therefore we urgently request not to permit the transfer of proteins involved in gluten-sensitive enteropathy.</p>

	ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT
				Thanks for your attention and kind regards
202	Anses	FRA	2.4. Considerations of the GM product for human health	Line 965: a paragraph present in the last guidance was missing corresponding to the "6.4 Information on natural food and feed constituents." page 33. In case of significant changes in the composition of nutrients and/or antinutrients: the nutritional assessment requirement is indicated line 1098 in the point 2.4.6 related to the "Nutritional assessment" but indication for a need of toxicological assessment is now missing in the new document guidance.
203	Anses	FRA	2.4. Considerations of the GM product for human health	2.4.2. Assessment of proteins expressed by the newly introduced genes Line 938: the concept of history of safe consumption use should be defined.
204	United States of America, Food and Drug Administration	USA	2.4. Considerations of the GM product for human health	Section B 2.4.5.4 Lines 1080-1086 suggest that the safety assessment include an assessment for adjuvanticity. Adjuvanticity has not been routinely considered in the safety assessment of food from genetically engineered organisms. EFSA's 2010 public consultation "Scientific Opinion on the assessment of allergenicity of GM plants and microorganisms and derived food and feed" outlines the difficulties associated with assessing adjuvanticity including the fact that there is no definite test for adjuvanticity, that examples of species differences in adjuvanticity are known, and that experimental work to reveal adjuvant activity of a substance must consist of immune function studies in the intact host with concurrent exposure to a known antigen. FDA recommends further research and development on this topic before adjuvanticity is routinely considered as part of a food safety assessment.
205	United States of America, Food and Drug Administration	USA	2.4. Considerations of the GM product for human health	Section B 2.4.5.3. Lines 1073-1076 discuss changes in the level of known allergens (e.g., endogenous allergens) in genetically engineered organisms. While this concept might be applicable to eukaryotic microbes it is unlikely to be useful in evaluating genetically engineered prokaryotes. To date, a number of fungal species (which would be considered eukaryotic microbes under the definitions used in this document) have been identified as allergens (primarily aeroallergens) and in many cases the allergenic proteins have been identified. However, there are very little data regarding endogenous allergens in prokaryotic species. This paragraph should be modified to clarify this distinction. It would also be appropriate for this paragraph to include a statement indicating that allergenicity assessment should be based on the nature of the final product and particularly on the likelihood that any endogenous allergens would be present in the final product Lines 1078-1079 suggest that the use of protein profiling has potential applicability in relation to allergenicity. While this emerging technology has potential, there are a number of significant challenges with respect to interpreting the data that can be obtained within the context of uncharacterized levels and patterns of normal variation. There are also significant differences in the way that this technology could be applied for eukaryotic and prokaryotic microbes. Therefore, we suggest that this sentence be removed or significantly modified to indicate that these methods may not be appropriate for use in a regulatory context at this time.
206	United States of America, Food and Drug Administration	USA	2.4. Considerations of the GM product for human health	Section B 2.4.5.2. Lines 1070-1072 state: "Although additional tests including in vitro cell based assays or in vivo tests on animal models have not been validated so far, they may be considered useful to provide additional information (e.g., on the potential of the product for de novo sensitization)." FDA agrees that an animal model of human allergy has yet to be validated. Given that currently there are no validated animal models of human allergy, it is not clear how data from a study using an animal model of human allergy would be interpreted and applied as part of a food safety

	ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT
				assessment. It is also unclear whether data from such a study would be predictive of potential public health risk. FDA recommends that animal models of human allergy be validated for their use in safety assessment prior to using data from such studies as part of a food safety assessment.
207	United States of America, Food and Drug Administration	USA	2.4. Considerations of the GM product for human health	<p>Section B 2.4.4.</p> <p>Lines 966-976 recommend animal feeding trials using the whole genetically engineered product in certain situations, such as when there is no corresponding conventional counterpart or if there are any indications from the risk assessment for further testing of the genetically engineered product. It may be helpful to clarify what is meant by use of the term "whole GM product" in this section. For example, it is not clear if "whole GM product" is intended to mean the final food product produced by the addition of a genetically engineered microorganism (e.g., yogurt) or a product derived from a genetically engineered microorganism (such as a cell extract or starter culture) intended as an ingredient of a product. We note that paragraphs 12 and 13 of the Codex Alimentarius "Guideline for the Conduct of Food Safety Assessment of Foods Produced Using Recombinant-DNA Micro-Organisms CAC/GL 46-2003" describe some of the difficulties associated with animal feeding trials using whole foods. If the intent of this section is to suggest feeding trials of purified living microorganisms, such as those described in the guidance as being in Category 4, we note that paragraph 14 of the Codex Alimentarius "Guideline for the Conduct of Food Safety Assessment of Foods Produced Using Recombinant-DNA Micro-Organisms CAC/GL 46-2003" describes some of the difficulties associated with these kinds of studies. FDA believes that in most cases a thorough food safety assessment can be conducted in the absence of the animal feeding trials described in lines 966-976 and that such animal feeding trials would only be warranted in extraordinary cases. Consequently, FDA does not think that the animal feeding trials described in lines 966-976 would routinely be warranted. Rather than relying on animal feeding trials using whole foods, FDA believes that analyses targeted to the specific substance of concern (e.g., the safety of a newly introduced protein, the level of a metabolite in the food, etc.) provide for greater sensitivity and precision while also avoiding many of the difficulties associated with animal feeding trials using whole foods. Prior to resorting to animal feeding trials using whole foods, FDA encourages EFSA to consider whether the questions such trials are intended to address could be addressed by analyses targeted to the specific substance of concern.</p>
208	Federal Agency for Nature Conservation	DEU	2.4. Considerations of the GM product for human health	<p>896 Again, the comparison of the GM product to an appropriate comparator is regarded as the first and main step in r.a. This could significantly narrow the r.a. and might lead to overlooking u.e.</p> <p>903 and 907-908 It is not explained how the "safety assessment per se" or "a most extensive safety evaluation" should be performed. Instead of relying exclusively on the comparison to a comparator (and only supplying the requirements on the comparison), the requirements of the safety assessment should be clearly formulated and the use of comparators should only be offered as a supplement of the process.</p> <p>916-917 The applicant is exempted from providing toxicological tests if the molecular and compositional analyses do not indicate an increased toxicity of the GMM compared to the comparator. This cannot be accepted as u.e. might enhance toxicity of the GMM and the molecular and compositional analyses might not necessarily identify all u.e. Depending on the use of the GMM a repeated dose animal toxicity study should be mandatorily required.</p> <p>919 Although u.e. are mentioned several times in the draft, there is no concept or strategy about how to detect and handle them, especially unexpected or unpredicted u.e.</p> <p>936-938 The applicant is exempted from providing an assessment on the toxicity of the newly expressed proteins, if the protein has a history of safe</p>

	ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT
				<p>consumption. This might refer to the protein in a different organismic context and/or the unmodified protein. The newly expressed protein might be differently modified in the donor organism than in the GMM and the transgene might be altered for better performance. Therefore, even though information on the safe history of consumption is relevant, it should not allow to omit toxicological evaluation of the newly expressed protein and the suggested repeated dose animal toxicity study (955 and following) should be mandatory.</p> <p>939-942 Other than with GMPs extraction of sufficient protein test material from the original source should not be a problem with GMMs, especially in case of large scale fermentation. Therefore, using an alternative protein source should be the exception and only possible when reasonably justified. Specifications for experimental details to demonstrate equivalence of both proteins are insufficient (line 940).</p> <p>945-948 The description of the protein's function shall be complemented by experimental data about its activity and substrate specificity.</p> <p>967-968 Once more, the applicant is exempted from supplying tox. data if a conventional product exists or if the r.a. does not indicate any toxic components. As the r.a. is based on limited data, overlooking of potential toxic components cannot be excluded. Therefore, the applicant should always provide conclusive data that the product he wishes to market is indeed safe for consumption and not draw conclusions on incomplete or not applicable information.</p> <p>1031 et seq. Provisions for serum screening and their compliance with recent EFSA's requests to applicants are appreciated.</p> <p>1059-1060 A reference to standardised methodology and or a definition of the appropriate conditions for pepsin degradation is missing.</p> <p>1081-1086 The possible variation in the composition of the GMM/product shall be considered here as well.</p> <p>1096-1097 "Compositional equivalence" is not defined or explained. Also, specifications for the comp. analysis are insufficient (see comment to 2.3.3.). This para requires further studies for nutritional assessment when the GM product is not compositional equivalent to a corresponding product without providing details how to perform them and what to consider.</p> <p>1106-1107 The bioavailability of nutrient components should be considered with a view to the intended purposes of the product</p>
209	The Netherlands Commission on Genetic Modification (COGEM)	NLD	2.4. Considerations of the GM product for human health	<p>III.B.2.4.4. Testing of the whole GM product</p> <p>Line 967-968 states that, if no corresponding conventional product exists, or if there are any indications from the risk assessment for further testing of the GM product, toxicological testing should be considered. 'Any indication' is vague. The guidance document should indicate in which cases toxicological testing is needed.</p>
210	Ministry of Rural Development	HUN	2.4. Considerations of the GM product for human health	<p>line:961-962 Change sentence „This may include toxicological testing on a case by-case basis.</p>

ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT
			<p>to:</p> <p>This must include toxicological testing in each case.</p> <p>line:967-968 Delete sentence „ If no corresponding conventional product exists, or if there are any indications from the risk assessment for further testing of the GM product, toxicological testing should be considered.”</p> <p>line 970 delete: (if available)</p> <p>line:1054-1069 Why is it that if, as it is quoted, „Although it has been established that no absolute correlation exists (Fu et al., 2002; EFSA Panel on Genetically Modified Organisms (GMO), 2010), resistance of proteins to pepsin digestion,” EFSA still proposes in vitro protein digestion „as an additional criterion to be considered in an overall risk assessment? Therefore the rest of the para is still irrelevant!</p> <p>line:1080-1086 Adjuvanticity We consider it dangerous to use an adjuvant in a food/food matrix. Therefore, for an adjuvants to become part of the food chain should not be allowed.</p> <p>line:1096-1097 Change sentence „When compositional equivalence of the GM product to a corresponding product is demonstrated, no further studies are required.”</p> <p>Please specify: When compositional equivalence of the GM product, such as enzymes, vitamins etc. to a corresponding product is demonstrated, no further studies are required.</p> <p>line:1098-1100 Change sentence „If significant changes in the composition of nutrients and/or antinutrients have been identified in the GM product, their nutritional relevance should be assessed based on current knowledge and taking into account the anticipated intake.”</p> <p>to:</p> <p>If significant changes in the composition of nutrients and/or antinutrients have been identified in the GM product, their nutritional relevance should be established experimentally taking into account the anticipated intake.</p>
211	Ministry of Rural Development	HUN 2.4. Considerations of the GM product for human health	<p>line:902-903 Change sentence „In case no appropriate comparator is available, the safety assessment per se should be carried out.”</p> <p>to:</p> <p>In case no appropriate comparator is available, the safety assessment should not be carried out.</p> <p>line:912-913 Change sentence „Thus, specific experimental data on gene transfer and its consequences may be required on a case-by-case basis (See</p>

ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT
			<p>Section B.3).”</p> <p>to:</p> <p>Thus, the use of such an organism or product is not allowed (See Section B.3).</p> <p>line:914-919 The toxicological impact of any changes in the GMM and/or derived product resulting from th genetic modification should be assessed.</p> <p>Change sentence „The need for toxicological testing should be considered based on the outcome of the molecular and comparative analysis (see Sections B.1. and B.2.), i.e. the differences identified between the GMM and/or derived product and its comparator, including intended as well as unintended changes.</p> <p>to:</p> <p>Because of intended as well as unintended changes the need for toxicological testing should be paramount in each and every single case for all GMM or derived products-</p> <p>line:928-930 Change sentence „There may be circumstances, when the applicant considers that a decision on safety can be taken without conducting some of the tests recommended in this chapter and/or that other tests are more appropriate.”</p> <p>to:</p> <p>There may be circumstances, when the applicant considers that a decision on safety can be taken without conducting some of the tests recommended in this chapter, although toxicological testing should be accried out in each case.</p> <p>line:933-938 Delete sentences „The studies required to investigate the toxicity of a protein should be selected on a case-by-case basis, depending on the knowledge available with respect to the source of the protein, its function and activity and its history of consumption by humans and/or animals. The studies required to</p> <p>investigate the toxicity of a protein should be selected on a case-by-case basis, depending on the knowledge available with respect to the source of the protein, its function and activity and its history of consumption by humans and/or animals. In the case of proteins expressed in the GMM, when the parental microorganism has a QPS status (or otherwise established history of safe use), and the new proteins have a history of safe consumption, specific toxicity testing as outlined below is not required.</p> <p>line:939-942 Change sentence „ If sufficient test materials cannot be extracted either from the GMM or from the product, a protein from an alternative source should be used. The structural, biochemical and functional equivalence of the substitute protein to the protein expressed by the recombinant genes in the GMM must be demonstrated.</p> <p>to:</p> <p>The excuse that sufficient test materials cannot be extracted either from the GMM or from the product, the product should not be allowed to be</p>

ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT
			released. No protein from an alternative source should be allowed to be used. line:949-950 Delete sentences „ • a search for homology to proteins should be conducted. Identified similarities should be evaluated, paying special attention to toxic proteins; the database(s) and the methodology used to carry out the search should be specified;
212	DSM	NLD	2.4. Considerations of the GM product for human health (lines 966-976) Products manufactured by fermentation in contained use are not "GM products", therefore we understand this section does not apply for categories 1 and 2. Enzymes for food and feed use are toxicologically tested anyway. (lines 998 et seq.) Food enzymes are evaluated for their possible allergenicity by ingestion according to the EFSA CEF Panel guidelines. Allergenicity by ingestion is generally not considered a concern for food enzymes. If the sequence homology research required by the food enzyme guidelines does not identify any concern, section 2.4.5.2 of the present guidance should not apply.
213	Ajinomoto Eurolysine S.A.S.	FRA	2.4. Considerations of the GM product for human health Line 977 to 1086 (General comment) Contrary to the previous version of 2006 ('Guidance document of the scientific panel on GMOs for the risk assessment of GMMs and their derived products intended for food and feed uses ') it is no longer stated that "Regarding animal health, allergenicity is not a significant issue that needs to be addressed specifically". This takes into account the new developments in this area, as described in the 'Scientific opinion on the assessment of allergenicity of GM plants and microorganisms and derived food and feed' (EFSA Journal 2010; 8(7): 1700). However, data and methods available for animal allergies are still at a very early stage of knowledge and mainly concern plant proteins. Therefore, providing data on target species (food producing animals, companion animals) on this aspect appears very difficult at this stage, especially if no signs are observed in common toxicity studies on laboratory animals.
214	Belgian Biosafety Advisory Council	BEL	2.4. Considerations of the GM product for human health Lines 1106-1107.. The bioavailability of a nutrient in a product does not only depend on the composition of the product itself but also on host factors and on the composition of the meal. In turn, consumption of a product could affect the bioavailability of nutrients not present in the product but in the meal (van het Hof KH, West CE, Weststrate JA, Hautvast JGAJ, 2002 . Dietary factors that affect the bioavailability of carotenoids 132:503-506). A possibility to take this into account would be to rephrase lines 1106-1107 for example as follows: "In addition to the nutrient content, the bioavailability of nutrient components in the product should be considered taking into account the composition and the preparation of the meal in which it is likely to be incorporated and the effect of the product on the bioavailability of nutrients present in such a meal." From a nutritional point of view, bioefficacy is more important than bioavailability (but harder to determine) (van Lieshout M, West CE, van Breemen RB, 2003. Isotope tracer techniques for studying the bioavailability and bioefficacy of dietary carotenoids, particularly beta-carotene, in humans. A review. Am J Clin Nutr 77:12-28). Therefore I suggest to insert after line 1107: "If appropriate, the bioefficacy of components of the product should be considered as well."
215	Belgian Biosafety Advisory Council	BEL	2.4. Considerations of the GM product for human health Lines 919-920 : Suggestion to change the sentence "The risk assessment should focus on the metabolites produced by the GMM during the fermentation process and in the food" by "The risk assessment should focus on the metabolites produced by the GMM during the fermentation process and in the food, as a result of the expression of newly introduced genes and/or possible changes in the level of natural constituents beyond normal variation and associated with the genetic modification". Lines 955-958 : We agree with the fact that the repeated dose animal toxicity study should not be carried out when there are convincing data about the safety of the protein from e.g. earlier studies. But if these data are not available, we are of the opinion that the 28 days study

	ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT
				<p>(repeated dose) should be performed automatically. This does not appear clearly from the document.</p> <p>Line 1073 : Assessment of allergenicity of the whole GM product should be mandatory when the host is known to be allergenic.</p> <p>After line 1086 : There is no mention in the text of possible allergic effects of food haptens (see e.g. Matsuda T et al., 2010. Phtalate esters reveal skin-sensitizing activity of phenethyl isothiocyanate in mice. Food Chem Toxicol 48:1704-1708; Kuchaska E, Bober J, Jedrichovski L, 2009. Involvement of haptens in allergic and non-allergic hypersensitivity. Polish J Environ.Studies 18:325-330). Phenethyl isothiocyanate for instance is present in cruciferous vegetables and has protein-binding activity.</p>
216	Genencor, A Danisco Division	NLD	2.4. Considerations of the GM product for human health	Genencor, A Danisco Division, agrees with the comments submitted by AMFEP, the Association of Manufacturers and Formulators of Enzyme Products.
217	Novozymes A/S	DNK	2.4. Considerations of the GM product for human health	Novozymes A/S agrees with the comments submitted here by AMFEP.
218	AMFEP	BEL	2.4. Considerations of the GM product for human health	<p>(lines 966-976) Products manufactured by fermentation in contained use are not "GM products", therefore we understand this section does not apply for categories 1 and 2. Enzymes for food and feed use are toxicologically tested anyway.</p> <p>(lines 998 et seq.) Food enzymes are evaluated for their possible allergenicity by ingestion according to the EFSA CEF Panel guidelines. Allergenicity by ingestion is generally not considered a concern for food enzymes. If the sequence homology research required by the food enzyme guidelines does not identify any concern, section 2.4.5.2 of the present guidance should not apply.</p>
219	Norwegian Scientific Committee for Food Safety	NOR	3. Potential environmental impact of GMMs and derived products	<p>General remark on chapter 3.</p> <p>An application for using GMO should include description of the following:</p> <ol style="list-style-type: none"> 1) The probability that GM may escape or be released to the environment 2) The fitness of the GMO in the environment. Competitiveness to related or similar species, and other organisms using the same niches 3) The effect of the GMO on the environment: <ol style="list-style-type: none"> a) Pollutions b) Competitiveness (feeding or spacing) c) Predation (feeding on other organisms) d) Interbreeding or horizontal gene transfer <p>The VKM GMO Panel want a chapter on Reversibility.</p> <ol style="list-style-type: none"> 4) Reversibility. If GMO released or escaped to the environments have a fitness that makes it capable to reproduce, what is the possibility, and by what means, can the system be reversed either by catching or killing the GMO in question.

ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT
220	Austrian Agency for Health and Food Safety	AUT 3. Potential environmental impact of GMMs and derived products	<p>General comment:</p> <p>This guidance document is focusing on genetically modified microorganisms (GMMs) for food and feed purposes. However research and development activities for GMM-applications are ongoing, which are not aimed primarily at food & feed purposes, like the development of GMMs for the production of biofuels and of GMMs for generating paratransgenic arthropods. Since these applications are either designed for intentional release into the environment or have a certain potential for accidental release of GMMs into the environment, there is a need for developing guidance for risk assessment as regards these applications. We note that the draft guidance document at hands is not specifically addressing the characteristics of applications, like e.g. large scale releases into the environment of GMMs associated with certain arthropods intended to reduce vector competence in these arthropod species or to facilitate population suppression of arthropod pests (Coutinho-Abreu et al. 2010). Therefore the current document should be amended to better accommodate such applications or supplemented with additional specific guidance as recommended e.g. in Benedict et al. (2010).</p> <p>The use of GMMs for the production of biofuels is an emerging issue which is receiving considerable attention directed to develop large scale applications in the near future (Keasling 2010, Simmons 2011). GM- algae or -microorganisms grown in large scale facilities are difficult to contain and may therefore pose specific risks for the environment. These risks also need to be covered by appropriate guidance for ERA.</p> <p>Benedict M., Eckerstorfer M., Franz G., Gaugitsch H., Greiter A., Heissenberger A., Knols B., Kumschick S., Nentwig W. and Rabitsch W., 2010. Defining environmental risk assessment criteria of genetically modified insects to be placed on the EU market. Scientific/technical report contracted by EFSA.</p> <p>Coutinho-Abreu I.V., Zhu K.Y. and Ramalho-Ortigao M., 2010. Transgenesis and para-transgenesis to control insect-borne diseases: Current status and future challenges. Parasitology International 59, 1-8.</p> <p>Keasling J.D., 2010. Manufacturing molecules through metabolic engineering. Science 330, 1355-1358</p> <p>Simmons B.A., 2011. Opportunities and challenges in advanced biofuels production: the importance of synthetic biology and combustion science. Biofuels 2 (1), 5-7]</p>
221	Federal Agency for Nature Conservation	DEU 3. Potential environmental impact of GMMs and derived products	<p>We appreciate the exhaustive requirements for the environmental risk assessment of GMMs of the categories 3 and 4. In case of GMMs/products of the 1st or 2nd category, the consideration of potential environmental damage caused by possible contaminations should be explained in more detail. A list on the possible causes that could lead to a contamination should be included as well as an assessment on the probability of occurrence. Furthermore, in line 1132, information on the source and natural habitat of the recipient micro-organism should be additionally demanded, so that a risk assessment of a potential contamination with viable cells can be performed.</p> <p>A general comment is missing at the beginning of chapter B.3 that the information requested in B.2 is relevant for e.r.a. as well. The same applies to Table 1.</p> <p>The draft does not consider cumulative long-term effects for e.r.a. as foreseen in Directive 2001/18/EC (recital 19 and Annex II) which are especially relevant for GMMs and products of category 3 and 4 where continuously large amounts of products might enter the environment over a long period.</p> <p>Line 1109-1115 The definition for possible exposure of the environment, other than human and animal gut or respiratory tract, should not be limited to entries of solid waste or manure. Depending on its application and use and also on handling and storage the GMM or its product might enter terrestrial and aquatic ecosystems directly and additionally indirectly via spillage or animal transport. Furthermore the exposure of natural ecosystems</p>

	ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT
				<p>especially protected habitats and species must be taken into account.</p> <p>Line 1113-1114 Please alter the sentence as follows: „...which are exposed to the GMM or to their products during production, application and waste disposal, e.g. human respiratory tract, human and animal gut,”</p>
222	Federal Office of Consumer Protection and Food Safety (BVL)	DEU	3. Potential environmental impact of GMMs and derived products	<p>Lines 1109/1110: This sentence is misleading. It should be made clear that “precondition” is not meant in the sense of a legal requirement. Legally, an environmental risk assessment (ERA) is only required for the authorisation of products containing or consisting of GMMs (products of category 4), but not for products made from, with or by GMMs (products of categories 1, 2 and 3). If EFSA is of the scientific opinion that an assessment of (certain) potential impacts on the environment should also be carried out for products of categories 1, 2 and 3, this should not be confused with the legally indispensable full-scale environmental risk assessment according to Directive 2001/18/EC which is only required for products containing or consisting of GMMs.</p> <p>In a broader perspective, it should also be considered that no environmental risk assessment is required for non-food/non-feed products made from GMMs (products outside the scope of Directive 2001/18/EC and Regulation 1829/2003).</p>
223	Ministry of Rural Development	HUN	3.1. Environmental risk assessment (ERA) of GMM-derived products belonging to categories 1 and 2	<p>line:1130-1131 Change sentence „Since contaminations with trace amounts of GMM or recombinant genes cannot always be excluded, consideration of potential environmental damage is required.”</p> <p>to: Since contaminations with trace amounts of GMM or recombinant genes cannot always be excluded, in all four categories of GMM, in each case a full environmental assessment is required.</p> <p>line:1132-1133 delete sentence „This can be based on the nature of the DNA sequences incorporated and must take into account the use of the product.”</p>
224	DSM	NLD	3.1. Environmental risk assessment (ERA) of GMM-derived products belonging to categories 1 and 2	(lines 1128-1135) This is not necessary when the production strain has been confirmed by Contained Use competent authority as Class I (i.e. no significant risk to man, animal or environment). In fact when the production strain has been confirmed by Contained Use competent authority as Class I (i.e. no significant risk to man, animal or environment) reduced requirements in general should apply.
225	Genencor, A Danisco Division	NLD	3.1. Environmental risk assessment (ERA) of GMM-derived products belonging to categories 1 and 2	Genencor, A Danisco Division, agrees with the comments submitted by AMFEP, the Association of Manufacturers and Formulators of Enzyme Products.
226	Novozymes A/S	DNK	3.1. Environmental risk assessment (ERA) of GMM-derived products belonging to categories 1 and 2	Novozymes A/S agrees with the comments submitted here by AMFEP.

ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT
227	AMFEP	BEL	3.1. Environmental risk assessment (ERA) of GMM-derived products belonging to categories 1 and 2 (lines 1128-1135) This is not necessary when the production strain has been confirmed by Contained Use competent authority as Class I (i.e. no significant risk to man, animal or environment). In fact when the production strain has been confirmed by Contained Use competent authority as Class I (i.e. no significant risk to man, animal or environment) reduced requirements in general should apply.
228	FEFANA	BEL	3.1. Environmental risk assessment (ERA) of GMM-derived products belonging to categories 1 and 2 Lines 1128-1135: This is not necessary when the production strain has been confirmed by Contained Use competent authority as Class I (i.e. no significant risk to man, animal or environment). In fact when the production strain has been confirmed by Contained Use competent authority as Class I (i.e. no significant risk to man, animal or environment) reduced requirements in general should apply.
229	Austrian Agency for Health and Food Safety	AUT	3.2. ERA of products produced from GMMs in which GMMs capable of replication or of transferring newly introduced genes are not present; but in which newly introduced genes are still present (Category 3)" Lines 1173ff: A theoretical assessment based on available relevant literature may not be sufficient to assess novel properties with regard to their effect in providing selective advantages in specific environments and under specific environmental conditions. The guidance should include appropriate criteria to outline when a theoretical assessment needs to be supplemented by empirical evidence.
230	Federal Agency for Nature Conservation	DEU	3.2. ERA of products produced from GMMs in which GMMs capable of replication or of transferring newly introduced genes are not present; but in which newly introduced genes are still present (Category 3)" Line 1152-1153 Consider production/manufacturing in line 1152 and respiratory tract in 1153 as well.
231	Ajinomoto Eurolysine S.A.S.	FRA	3.2. ERA of products produced from GMMs in which GMMs capable of replication or of transferring newly introduced genes are not present; but in which newly introduced genes are still present (Category 3)" Lines 1136 to 1179 Please see comments previously made in regard of lines 345 to 347. For the category 3 products referred to as of 'type 1'(*)the products should not be submitted to the ERA described in Section III, B, 3.2 lines 1136 to 1179. A risk evaluation, as described for category 2 should suffice. In figure 1 for category 3, 'type 1' products the flow diagram should be adapted to take this situation into account. In the same way, Table 1 (bottom of page 46), the box for the ERA f category 3 product should be adapted. (*) - Type 1: the inactivation treatment(s) implemented during the manufacturing process of the product– and as part of the contained use of the producer microorganism – result(s) not only in the absence of viable cells of the microorganism but also in the degradation of its DNA, with sizes of DNA fragments below full-length coding sequences, or even below the size of small genes. These fragments which are not functional will not transfer, even in very special conditions. This is the situation usually sought by applicants e.g. for biomasses intended to be used as feed materials.

	ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT
232	Belgian Biosafety Advisory Council	BEL	3.2. ERA of products produced from GMMs in which GMMs capable of replication or of transferring newly introduced genes are not present; but in which newly introduced genes are still present (Category 3)"	<ul style="list-style-type: none"> - Line 1172 : use more recent references : - Dubnau,D. (1999) DNA uptake in bacteria . Ann.Rev.Microbiol.,53, 217-244 - Dale,J.W. & Park, S.F. (2004) Molecular genetics of bacteria (4thed.); John Wiley & Sons
233	Testbiotech	DEU	3.2. ERA of products produced from GMMs in which GMMs capable of replication or of transferring newly introduced genes are not present; but in which newly introduced genes are still present (Category 3)"	<p>Release</p> <p>Line 1136 ff and line 1180 ff The Guidance lacks clear cut off criteria for organisms that contain genes from pathogenic organisms and/or synthetic genes and/or genetic information that has not previously existed in the receiving environment.</p> <p>These organisms and their genetic information should not be released into the environment because there is no sufficiently reliable way of predicting their future impact on ecological systems or human health. They should be perceived as a hazard per se, especially, if these organisms are able to survive (persist) and proliferate in the receiving environments. Therefore, these organisms should be excluded from release into the environment in general.</p>
234	Austrian Agency for Health and Food Safety	AUT	3.3. ERA of products consisting of or containing GMMs capable of replication or of transferring genetic material (Category 4)	<p>Lines 1189 – 1193: The draft guidance should more specifically indicate that indirect effects caused by the application of certain GMMs (e.g. to generate paratransgenic arthropods) need to be assessed comprehensively. Other-wise supplementary guidance detailing the assessment for such applications need to be drafted.</p>
235	Federal Agency for Nature Conservation	DEU	3.3. ERA of products consisting of or containing GMMs capable of replication or of transferring genetic material (Category 4)	<p>It has to be taken into account that also unintended effects may have altered the survivability, interactions with the environment, the likelihood of the gene transfer etc.</p> <p>Although it is appropriate to consider receiving and neighboring environments in a first step, e.r.a. must not solely focus on them if the GMM is generally able to survive and proliferate in the environment. Once released into the environment, there are several means and routes for micro-organisms to be dispersed and to reach favouring environments, especially when they form survival structures.</p> <p>Line 1204 Please add temperature range for growth.</p> <p>Line 1207 The GMM might be able to interact and associate with other micro-organisms if the genetic modification has conferred a new metabolic characteristic. This in turn could support and favour its survival in a certain environment. Therefore interaction with other organisms shall be considered here along with competition. This idea is also missing in the following para (lines 1210-1223).</p> <p>Line 1234 Please replace the term environmental microorganisms with other microorganisms.</p>

	ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT
				<p>Line 1237-1240 Is there a reference for the assumption that conjugation is regarded as the most likely gene transfer mechanism?</p> <p>Line 1231-1249 The evaluation of the probability of gene transfer from a GMM to other micro-organisms shall be based on data and studies from the literature. Prerequisites and efficiencies of the three gene transfer mechanisms can vary depending on the conditions, e.g. natural transformation is assumed to be increased in biofilms and when antibiotics are applied. Therefore, the evaluation requested in this para shall consider to what extent results and data obtained from literature apply to the environments in which the GMM and its products are released and remaining uncertainties and knowledge gaps.</p>
236	The Netherlands Commission on Genetic Modification (COGEM)	NLD	3.3. ERA of products consisting of or containing GMMs capable of replication or of transferring genetic material (Category 4)	<p>III.B.3.3. ERA of products consisting of or containing GMMs capable of replication or of transferring genetic material (Category 4)</p> <p>The ERA of category 4 products includes the assessment of potential ecological effects (lines 1210-1223). This part of the guidance document also applies to microbial plant protection products, which are developed for agricultural use. Therefore, in COGEM's view, the potential effect of the GMM on the agro-ecosystem should receive particular attention in the ERA of genetically modified microbial plant protection products.</p> <p>In addition, in the guidance document it is mentioned that potential effects of toxic compounds produced by the GMM on other microorganisms should be assessed (line 1215-1216). The term 'ecotoxicity' should be used in this context.</p> <p>The guidance document states that if the GMM causes an adverse effect and disrupts vital ecological processes the consequences of the effect should be assessed (line 1220-1223). The document does not state which ecological processes are considered 'vital'. More guidance is needed in this respect.</p>
237	Ministry of Rural Development	HUN	3.3. ERA of products consisting of or containing GMMs capable of replication or of transferring genetic material (Category 4)	<p>From lines 1279 and 1284 delete: When appropriate</p> <p>Please modify Fig. 1. and Table 1. accordingly</p>
238	Federal Agency for Nature Conservation	DEU	C. Exposure assessment/characterisation	<p>This section would be better located in Chapter II.</p>
239	Association of European Coeliac Societies	BEL	D. Risk characterisation	<p>The Association of European Coeliac Societies is of the opinion that the lines in question, though clearly stating the guidelines to be used to quantify the daily intakes as well as the upper tolerated amounts of GM containing foods, should be expanded to include the Codex recommended guidelines of 2003, in relation to the safety of GM foods. We believe that special emphasis should be given to the safety profile of GM food like maize, soy etc., within specific populations that for medical reasons, are obliged to consume larger quantities of the product when compared to the general population. It is also our opinion that before being released in the general circulation studies have to be held to determine the actual quantities consumed by the population as well as the determination of the presence of any compound that could exacerbate the condition.</p> <p>We are reproducing the relevant articles for your information.</p> <p>3.4.1 Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Plants</p> <p>Two paragraphs are important for the gluten intolerant population:</p>

ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT
			<p>"42. The newly expressed proteins in foods derived from recombinant-DNA plants should be evaluated for any possible role in the elicitation of gluten-sensitive enteropathy, if the introduced genetic material is obtained from wheat, rye, barley, oats, or related cereal grains.</p> <p>43. The transfer of genes from commonly allergenic foods and from foods known to elicit gluten-sensitive enteropathy in sensitive individuals should be avoided unless it is documented that the transferred gene does not code for an allergen or for a protein involved in gluten-sensitive enteropathy."</p> <p>3.4.2 Guideline for the Conduct of Food Safety Assessment of Foods Produced Using Recombinant-DNA Microorganisms</p> <p>"47. Genes derived from known allergenic sources should be assumed to encode an allergen and be avoided unless scientific evidence demonstrates otherwise. The transfer of genes from organisms known to elicit gluten-sensitive enteropathy in sensitive individuals should be avoided unless it is documented that the transferred gene does not code for an allergen or for a protein involved in gluten-sensitive enteropathy."</p>
240	Federal Agency for Nature Conservation	DEU	<p>D. Risk characterisation</p> <p>This section would be better located in Chapter II.</p> <p>Line 1307 A reference to the EFSA Scientific Opinion on Statistical considerations for the safety evaluation of GMOs (EFSA Journal 2010; 8(1):1250) might be appropriate.</p>
241	Federal Agency for Nature Conservation	DEU	<p>2. Conclusions from the risk characterization of GMMs and derived food/feed</p> <p>Line 1388-1390 The meaning of this statement remains unclear. If management strategies are proposed, these should be an objective of a new assessment to conclude on their efficacy and of case specific monitoring to verify the expected efficacy of the strategies or measures.</p>
242	United States of America, Food and Drug Administration	USA	<p>E. Post-market monitoring regarding use of the GM product for food or feed</p> <p>Section E.</p> <p>Lines 1391-1408 describe post-market monitoring regarding use of the genetically engineered product for food or feed. The section states that post-market monitoring should address, among other things, whether known effects and side-effects are as predicted. If there are known effects and side-effects, we presume that a pre-market safety assessment would have confirmed that such effects and side-effects do not present public health risks when taking into account the intended use of the product. Consequently, we are uncertain of the utility of trying to monitor for such effects and side-effects absent some reason to believe that these effects represent hazards. We note that within the context of the entire diet it may be difficult to link an effect or side-effect to a particular food or a specific ingredient in a particular food. If there is concern about effects or side-effects due to use of the product other than as predicted or recommended, then it may be useful to focus efforts simply on whether the product is used as predicted or recommended. Such information may inform whether the safety assessment should encompass additional uses of the product.</p> <p>Section E also suggests that post-market monitoring should address whether the product induces unexpected side-effects. Within the context of the overall diet it may be very difficult to identify unexpected side-effects and accurately attribute them to a specific food or a specific ingredient in a particular food, especially if one is not looking for a specific side-effect. We also note that many side-effects may not necessarily represent hazards. It would be of greater utility to monitor whether the product is being used as predicted or recommended and consider whether the safety assessment needs to encompass additional uses of the product.</p> <p>If monitoring for effects or side-effects is to be required, we recommend that any such monitoring be driven by a testable hypothesis that relates to the characteristics of the food and focuses on effects or side-effects that have a reasonable possibility of being a hazard given the</p>

	ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT
				characteristics of the food.
243	Belgian Biosafety Advisory Council	BEL	E. Post-market monitoring regarding use of the GM product for food or feed	Lines 1402-1403 : Suggestion to delete "are difficult to predict"
244	Federal Office of Consumer Protection and Food Safety (BVL)	DEU	F. Post-market environmental monitoring (PMEM) of GM products	Figure 1: It should be made clear that "environmental risk assessment (ERA)" for products of categories 1, 2 and 3 in Fig. 1 is not the same as the full-scale environmental risk assessment according to Directive 2001/18/EC which is only required for products containing or consisting of GMMs (category 4).
245	Austrian Agency for Health and Food Safety	AUT	1. General	Lines 1441-1448: As stated in Annex VII of Directive 2001/18/EC the scope of the monitoring is "to confirm that any assumption regarding the occurrence of potential adverse effects of the GMO or its use in the ERA are correct". The objectives for the PMEM of GMMs of Category 4 as outlined in the draft guidance should therefore be revised to reflect the above aim. The guidance should require that CSM is implemented to confirm that "assumptions in the ERA regarding potential adverse effects arising from the GMO and its use are correct", as outlined by the guidance notes to Annex VII of Directive 2001/18/EC. [Council Decision of 3 October 2002 establishing guidance notes supplementing Annex VII to Directive 2001/18/EC of the European Parliament and of the Council on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC. Official Journal of the European Communities, L 280/27, 2002/811/EC.]
246	Federal Agency for Nature Conservation	DEU	1. General	Line 1417-1420 See general comment to Chapter II
247	Ajinomoto Eurolysine S.A.S.	FRA	1. General	Lines 1428 to 1432 For products belonging to category 3, PMEM should be envisaged/decided on a case-by-case basis. As previously commented in regard of Lines 345 – 347 for category 3 products two types may be distinguished. For 'type 1' products, no PMEM should be necessary/required. In figure 1 for category 3, 'type 1' products the flow diagram should be adapted to take this situation into account. In the same way, Table 1 (top of page 46), the box for the PMEM should be adapted. [Type 1: the inactivation treatment(s) implemented during the manufacturing process of the product– and as part of the contained use of the producer microorganism – result(s) not only in the absence of viable cells of the microorganism but also in the degradation of its DNA, with sizes of DNA fragments below full-length coding sequences, or even below the size of small genes. These fragments which are not functional will not transfer, even in very special conditions. This is the situation usually sought by applicants e.g. for biomasses intended to be used as feed materials.]

ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT	
248	Federal Office of Consumer Protection and Food Safety (BVL)	DEU	1. General	Line 1418: Delete "their products". Directive 2001/18/EC requires a post-market environmental monitoring for GMOs, but not for products made from GMOs.
249	Federal Agency for Nature Conservation	DEU	2. Case-specific GM monitoring	Line 1463 The phrasing should be specified in the way that CSM should be targeted at all environmental factors, which are likely or not adversely affected. Further, it should be clarified, what is meant with environmental hotspots in this context. Exposure pathways, relevant environments and the presence of relevant coexisting micro-organisms have to be considered within the monitoring.
250	The Netherlands Commission on Genetic Modification (COGEM)	NLD	3. General surveillance of the impact of the GMM	General surveillance is a legal requirement which purpose is to detect unforeseen or unanticipated adverse effects of a GMO. The detection of unforeseen, unanticipated effects is difficult because no hypotheses can be formulated with regard to the type of effect or the place where an effect might occur. In case of a GMM the detection of unforeseen, unanticipated adverse effects is even more difficult. The variety of possible applications is broad and potential effects will take place in environments which are notoriously difficult to characterize, like soil. In COGEM's view the provided guidance is too general. More guidance should be given with regard to the methods that should be used to detect unexpected effects caused by GMMs.
251	Federal Agency for Nature Conservation	DEU	3.1. Approach and principles	Line 1486-1487 Please add: "where gene transfer may occur or where sensitive environments are affected." Especially endangered or protected environments should be in the focus of the monitoring. Line 1493-1497 Additionally, it should be stated that monitoring of the accumulation and the establishment of the transgenes is an important measure to clarify the relevant cause-effect chains when indirect and delayed adverse effects occur and should therefore be integrated within the monitoring.
252	Federal Agency for Nature Conservation	DEU	3.2. Main elements of General Surveillance	Line 1509-1512 It should be added: "identify the monitoring areas."
253	Federal Agency for Nature Conservation	DEU	4. Monitoring systems	Line 1518-1521 With regard to the Directive 2001/18/EC, the applicant is responsible for the monitoring. The applicant should use existing monitoring programs, where appropriate. There may be deficiencies in existing environmentally focused monitoring programs covering effects of microorganisms. In order to fulfil the requirements of the Directive, the applicant may have to develop more focussed monitoring systems. Questionnaires might not be suitable in this context. Line 1527-1533 The results should be reported annually, raw data should be provided upon request.
254	The Netherlands Commission on Genetic Modification (COGEM)	NLD	4. Monitoring systems	In addition, in the guidance document it is stated that for GMM products under category 3 post-market environmental monitoring should be considered for identified environmental risks (line 1429-1430). In this category newly introduced genes are still present, but GMMs capable of replication or of transferring newly introduced genes are absent. The guidance states that the risk assessment for category 3 products should focus on the potential risks of recombinant DNA such as horizontal gene transfer to other micro-organisms (line 1140-1141). Due to the broad variety of the many possible applications of GMMs and due to the inevitably rather vague description of recombinant DNA the specific cases for which environmental monitoring is needed, should be specified.
255	DSM	NLD	5. Reporting the results	Figure 1: Flow diagram showing the approach to the categorisation and risk assessment (Figure 1, line 1535) We could not assess for certain

	ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT
			of monitoring	that the guidance text and this figure are completely correlated (cf. above comment lines 751-758). Given that this figure is very important and useful, we respectfully suggest that perfect coherence be ensured and checked.
256	AMFEP	BEL	5. Reporting the results of monitoring	(Figure 1, line 1535) We could not assess for certain that the guidance text and this figure are completely correlated (cf. above comment lines 751-758). Given that this figure is very important and useful, we respectfully suggest that perfect coherence be ensured and checked.
257	Austrian Agency for Health and Food Safety	AUT	G. SUMMARY OF THE RISK ASSESSMENT REQUIREMENTS	Line 1557: An "X" is missing in Category 1: "1. Information on the removal of the GMM cells from the product." Please add this letter again, as it is also requested on page 24 line 790.
258	Federal Agency for Nature Conservation	DEU	G. SUMMARY OF THE RISK ASSESSMENT REQUIREMENTS	Figure 1 Post-market monitoring is not envisaged for GMMs of the first two categories, even though in chapter C "Exposure assessment/Characterisation" it is stated that e.g. "GMM and/or derived products aimed at modifying the nutritional quality" are products that should be monitored in a PMM. Such products can be produced with GMMs of the first two categories. The possibility of a PMM should not be excluded from GMMs of the first two categories but should strictly be dependent on if the conclusions of the risk assessment deem PMM necessary. The term VBNC should be explained in the legend for better understandability. Table 1 As already stated in the comment on chapter 2 "Information relating to the product", information on the removal of the GMM cells from the product is also required for GMMs of the category 1. This should accordingly be indicated in the table. Furthermore, as it is stated in chapter 2, information on the inactivation and the assessment of the presence of remaining intact cells is required for GMMs of the 2nd category and should therefore be indicated in the table. The footnote b "information not required if proposed QPS status is authorised" absolves the applicant from providing information on the source and natural habitat of the recipient organism, on genetic stability, pathogenicity, ecological and physiological traits and a description of history of use. In order to perform a sensible environmental risk analysis (especially for GMMs of the 4th category), information on these points is necessary and should be provided. Accordingly, the provision in chapter 1.1.8 that the previous history of use of the parental strain should be presented for organisms with a non-QPS-status only (line 543-544) shall be deleted. A guideline on how to collect the data (desk studies, literature reviews, lab studies, greenhouse studies etc.) and in what quality should be given.
259	DSM	NLD	G. SUMMARY OF THE RISK ASSESSMENT REQUIREMENTS	(Table 1, line 1545) We welcome a clear description of the requirements for the individual classes given in the form of a table. That provides a lot of clarity to the rest of the document. However we could not assess for certain that the guidance text and this table are completely correlated (cf. above comment lines 751-758). Given that this table is very important and useful, we respectfully suggest that perfect coherence be ensured and checked. Table 1: information required for applications for the placing of GMMs and their derived food and feed products. (Table 1, line 1557) An ERA is

ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT
			not necessary when the production strain has been confirmed by Contained Use competent authority as Class I (i.e. no significant risk to man, animal or environment). In fact when the production strain has been confirmed by Contained Use competent authority as Class I (i.e. no significant risk to man, animal or environment) reduced requirements in general should apply. (Table 1, line 1559) The required information on the possible presence of recombinant DNA (which only can be originating from the host cell or a donor cell of the same or related species) is not relevant for the safety assessment of the GMM and also not in line with figure 1.
260	Belgian Biosafety Advisory Council	BEL	G. SUMMARY OF THE RISK ASSESSMENT REQUIREMENTS Line 1545 : To facilitate the use of table 1 as a self-standing table, the definition of categories 1, 2, 3 and 4 as mentioned on page 12 should be repeated here rather than at the end of the document. Line 1557: Table 1, page 46 : In line with previous comment, suggestion to add a new sub-item entitled "Information relating to the purification of the product" under "Information relating to the product preparation process". The new sub-item should be "x" for Category 1 and "(x)" for Category 2.
261	Genencor, A Danisco Division	NLD	G. SUMMARY OF THE RISK ASSESSMENT REQUIREMENTS Genencor, A Danisco Division, agrees with the comments submitted by AMFEP, the Association of Manufacturers and Formulators of Enzyme Products.
262	Novozymes A/S	DNK	G. SUMMARY OF THE RISK ASSESSMENT REQUIREMENTS Novozymes A/S agrees with the comments submitted here by AMFEP.
263	AMFEP	BEL	G. SUMMARY OF THE RISK ASSESSMENT REQUIREMENTS (Table 1, line 1545) We welcome a clear description of the requirements for the individual classes given in the form of a table. That provides a lot of clarity to the rest of the document. However we could not assess for certain that the guidance text and this table are completely correlated (cf. above comment lines 751-758). Given that this table is very important and useful, we respectfully suggest that perfect coherence be ensured and checked. (Table 1, line 1557) An ERA is not necessary when the production strain has been confirmed by Contained Use competent authority as Class I (i.e. no significant risk to man, animal or environment). In fact when the production strain has been confirmed by Contained Use competent authority as Class I (i.e. no significant risk to man, animal or environment) reduced requirements in general should apply. (Table 1, line 1559) The required information on the possible presence of recombinant DNA (which only can be originating from the host cell or a donor cell of the same or related species) is not relevant for the safety assessment of the GMM and also not in line with figure 1.
264	FEFANA	BEL	G. SUMMARY OF THE RISK ASSESSMENT REQUIREMENTS Table 1, line 1557: We fail to understand the relevance of an ERA for category 1 and 2 products. Table 1, line 1559: The required information on the possible presence of recombinant DNA (which only can be originating from the host cell or a donor cell of the same or related species) is not relevant for the safety assessment of the GMM and also not in line with figure 1.
265	United States of America, Food and Drug Administration	USA	References Lines 1781-1782 refer to the OECD (Organisation for Economic Co-operation and Development) 2003b. Guideline for the conduct of food safety assessment of foods produced using recombinant-DNA microorganisms. We are not aware of such a document published by OECD. We believe this reference is to the Codex Alimentarius Commission's Guideline for the conduct of food safety assessment of foods produced using recombinant-DNA micro-organisms (CAC/GL 46-2003).
266	on behalf of the Association of Veterinary	ESP	References References, Lines 1784-1785: The AVC suggest that EFSA include the following references:

	ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT
	Consultants			<p>Pariza MW, and Johnson EA, 2001. Evaluating the safety of microbial enzyme preparations used in food processing: update for a new century. Regulatory Toxicology and Pharmacology, 33, 173-186 (was available on-line at http://www.ideallibrary.com, now www.elsevier.com).</p> <p>Pariza MW and Cook M, 2010. Determining the safety of enzymes used in animal feed. Regulatory Toxicology and Pharmacology, 56, 332-342 (www.elsevier.com/locate/yrtph)</p>
267	United States of America, Food and Drug Administration	USA	Glossary and abbreviations	<p>Glossary and Abbreviations</p> <p>Lines 1842-1845 define microorganism as, "Microorganisms: Any microbiological entity, cellular or non-cellular, capable of replication or of transferring genetic material, including viruses, viroids, animal and plant cells in culture. For the purpose of this guidance document, microorganisms cover archaea, bacteria and eukarya. Eukarya includes filamentous fungi, yeasts, protozoa and microalgae." We find that the inclusion of "viruses, viroids, animal and plant cells in culture" in this definition to be confusing. Given that these are specifically excluded in the scope section of the document on page 6, we recommend adding the following sentence, "This document does not cover the use of tissue cultures of plant or animals cells, or viruses or viroids" to the end of the definition of microorganism for the sake of clarity.</p>
268	Federal Agency for Nature Conservation	DEU	Glossary and abbreviations	<p>It is problematic to define terms which are central to risk assessment without providing a legal reference and therefore should be omitted.</p> <p>What is the scientific justification to define unintended effects as unintended consistent phenotypic changes in the GMM resulting from its genetic modification lacks?</p>