
# EFSA Stakeholders' meeting on food enzymes

27th May 2014

# Introduction

- Many dossiers were submitted since our last meeting
  - Incl. 2 joint dossiers
  - More experience at EFSA and applicants
  - New challenges and open questions…
- Updated Explanatory note for guidance
  - We welcome the clarifications!
  - Certain items may deserve further discussion
- Scope of present process: enzymes already evaluated and/or on the market for many years

# Agenda

- Open questions from the present submission and evaluation process
- Feedback and questions about the updated Explanatory note for guidance
- Joint dossiers: Amfep's method and assumptions
- Examples of entries in the future EU list
- Procedural aspects

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# Amino-acid sequence (3.1.2.1.i)

- Amino-acid sequence should not be an absolute requirement for enzymes produced by non-GM sources
  - Sequences are not always available in literature
  - Enzymes are authorized and/or have been on the market for decades
  - Sequencing is a technical challenge, esp. for enzyme complexes

# Subsidiary/side activities (3.1.2.3.iii)

- Definition: enzyme activities that are not needed for the technological purpose
- No safety concern
  - Enzymes are authorized and/or have been on the market for decades
  - The side activities are enzymes which present in food raw materials
  - No negative indication from toxicological studies
  - Cf. uses as digestive aids

# Residual amounts of antifoams in the food enzyme

- Food-compatible substances
- Theoretical consumer exposure is extremely low
- Evaluated by FDA (2003) as being used in accordance with the principles of GMP

# Fate in food

- In almost all cases, food enzymes are used as processing aids:
  - Denatured, or…
  - Removed, or…
  - Present at residual levels in final foods but not functional
- Fate in food is not a safety concern
  - Toxicological studies or QPS status ensure a high margin of safety

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# Glycosylation

- ENFG p. 5 (iii)
  - *Post translational process means enzymatic/chemical modifications performed in the enzyme protein after its translation by the organism itself (i.e. glycosylation). In eukaryotic expression hosts the applicant should consider that glycosylation could influence the properties of the enzyme.*
- Glycosylation is not a safety concern
  - Decades of safe use and authorizations
  - (glycosylated) Enzymes are present in all food raw materials

# Subsidiary/side activities

- ENFG p. 6 (iii)
  - *Side/subsidiary activities are referring to other activities of the enzymes present in the food enzyme, including activities that may be expressed under different conditions than those intended in the application.*
- Clarification needed

# Stability of the food enzyme during storage and before use

- ENFG p. 6-7 (iv)
  - *The data on the stability of the food enzyme as such would have to cover at least the recommended time of use under the specified conditions of **use**.*
- Is the meaning “use”, or rather “storage”?
- Stability is not necessary in the conditions of **use**
  - It is OK that the enzyme gets denatured during its use, provided that it performs its function in the meantime

# Animal tissue

- ENFG p. 7 (i)
  - *An example can be given for rennet (chymosin): There are different types of rennet commercially available which may differ in their origin (e.g. animal, vegetable, microbial or recombinant rennet) or physical state (liquid, powder or paste). Rennet paste is a crude form of rennet and the dossiers for this form of rennet should follow the data requirements as laid down in this chapter.*
- Clarification needed
  - Biological origin and commercial form are independent from each other

# Mutants

- ENFG p. 8 (3.2.1.3)
  - *Mutants from a specific strain that has been thoroughly tested for safety, have to be re-tested if additional mutations are performed.*
- Clarification needed
  - Our understanding is that the production microorganism has to be evaluated for its potential to produce secondary metabolites of concern, even if it belongs to a safe strain lineage (i.e. no oral tox study on the enzyme from the present strain)

# CEF *vs.* GMM guidance

- ENFG p. 9 (ii)
  - *Recipient strain is the one receiving the genetic modification […] methodology (including sampling methodology) used.*
- Contents is fine, however…
- …should this belong to the CEF guidance or to the GMM guidance?

# Lipopeptides

- ENFG p. 10 (iv)
  - *Lipopeptides may also exert antibacterial or antifungal properties. Their absence would be dependent on the purification procedure so that when using production strains able to generate lipopeptides, their presence in the final product should be checked.*
- Lipopeptides are not a safety concern for consumers
  - Japanese food *natto* contains high levels of lipopeptides from *Bacillus*
  - Test for antimicrobial activity is part of the JECFA specifications

# Reactions catalyzed by the food enzyme

- ENFG p. 11-12 (ii)
  - *Reactions should refer to the foods covered by the proposed conditions of use. Specific issues to be addressed: matrix effects on activity in intended uses, side reactions depending on food.*
- No safety concern
  - A given enzyme activity is present in all food ingredients where its substrate is present
  - Food ingredients where side reactions would be a concern would not be safe for consumption to start with

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# Joint dossiers

- Enzymes covered by Regulation 562/2012
- Structure (headings) according to the checklist of the Practical Guidance for applicants of the Commission
- Contents according to the EFSA CEF Guidance on the submission of food enzyme dossiers
- About 16 different joint dossiers are to be expected

# Manufacturing process

- Generic description based on EFSA's advice (Jan. 2013)
- Generic list of possible raw materials
- HACCP certificates from all companies participating in the dossier

# Toxicity studies

- Provided by one company participating in the dossier
- NOAEL is used for the calculation of the safety margin for all uses in food processing
- Consumer exposure is calculated even when there is no toxicological study (QPS sources)

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# Producer-specific dossiers

| Name | Specifications | Foods | Conditions of use | Restrictions on the sale of the food enzyme directly to the final consumer | Specific requirements in respect of the labelling of food |
|---|---|---|---|---|---|
| Alpha-amylase | **IUB no: 3.2.1.1**<br>**Systematic name:** 1,4-alpha-D-glucan glucano-hydrolase<br>**Source:** A genetically modified strain of *Aspergillus oryzae*<br>**Strain designation:** STR-123456<br>**Identification:** Alpha-amylases catalyze the hydrolysis of (1,4)-alpha-D-glucosidic linkages in starch polysaccharides<br>**Purity criteria:** All preparations placed on the market shall comply with the general purity specifications set by JECFA (2006) for food enzymes | - Starch processing<br>- Beverage alcohol (distilling) processes<br>- Brewing processes<br>- Baking processes<br>- Fruit and vegetable processing | *Quantum satis* | Not intended for direct sale to final consumer | None – the food enzyme does not perform a technological function in final foods nor can its use mislead the consumers. |

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# Enzyme complexes

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|---|---|---|---|---|---|
| Cellulase | **IUB no: 3.2.1.4**<br>**Source:**<br>*Trichoderma reesei*<br><br>**[…]** | - Baking<br>- Brewing<br>- Fruit and vegetable processing<br>- Grain processing<br>- Potable alcohol production<br>- Wine production | *Quantum satis* | Not intended for direct sale to final consumer | None – the food enzyme does not perform a technological function in final foods nor can its use mislead the consumers. |
| Endo-1,3(-4)-beta-glucanase | (id.) | (variable) | (id.) | (id.) | (id.) |
| Endo-1,4-beta-xylanase | (id.) | (variable) | (id.) | (id.) | (id.) |

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# Validation criteria

- Several applicants have been asked for additional documentation before their dossier could be considered as valid
- What are the criteria for requesting such additional data?

# Pre-submission meetings

- Mentioned in Jan. 2013
- Still needed, esp. for SMEs
- SME front desk?


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