

Review of Precision Fermentation Applications to Identify Common Challenges for Safety Assessment

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FSA Research and Evidence

Executive Summary

Insufficient data on bioinformatics, cell line integrity, protein digestibility, nutritional disadvantage and allergenicity are key challenges that prevent the FSA from concluding on the safety of precision fermented products.

Introduction

The process of fermentation (using microorganisms to change naturally occurring ingredients), has been used by humans to produce food for thousands of years. Fermentation can be utilised in many ways, for example in traditional fermentation yeast is used to produce bread and beer. In biomass fermentation, the microorganisms used to produce proteins are left in the final product, and a well-known example includes the mycoprotein *Fusarium venenatum*.

The working definition of precision fermentation (PF) currently used by the Food Standards Agency (FSA) is “Precision fermentation is considered to be a technology that creates essential food components, like proteins and enzymes, through use of genetically modified microorganisms (GMM) to produce specific functional components”. A fuller definition includes “where whole micro-organisms are reproduced in a bio-reactor / closed system and refined for their fat or protein content”. Specific hazards from precision fermented products can include residual genetically modified (GM) DNA or microbe in the final version of the product, microbial toxins and chemical contaminants, novel allergen exposure and lower nutritional quality compared to traditional counterparts.

The aim of the Innovation Research Programme is to generate new knowledge about the risks and potential of innovative technologies and to use this knowledge to improve the risk analysis (risk assessment, risk management and risk communication), of innovative products. This review

sits under the science research workstream “1.1 Identifying and characterising toxicological hazards, microbiological hazards, allergenicity and nutritional quality”.

The first aim of this work is to identify the major challenges the FSA faces in concluding on the safety of PF products. The second aim is to ascertain whether the planned Innovation Research Program expert elicitation events are on the most relevant topics and identify areas for future research.

Key questions

- What typically are the data gaps/barriers to the FSA being able to conclude on the safety of PF products?
- Should any of these challenges be a higher priority for the FSA to focus on in knowledge generation or expert elicitation than those already identified under the IRP science workplan?

Materials and Methods

In collaboration with the Novel Foods Risk Assessment Team, market authorisation applications were identified which met the above full definition of a PF product, are in or have passed through the assessment stage and have been to at least one Advisory Committee on Novel Foods and Processes (ACNFP) meeting. For each application, ACNFP minutes were reviewed and resultant RFIs on the internal Case Management System (CMS) evaluated. To ensure accuracy, findings from each individual application were discussed with the risk assessors in the novel foods team responsible for each respective application.

Results

When discussing the major challenges with the risk assessors who dealt with the respective applications, risk assessors drew a distinction between challenges common to precision fermented product applications, and issues in common with cell-derived products and general novel food applications. These are outlined below.

A key challenge for PF product applications is understanding the identity of any microorganisms which have no qualified presumption of safety (QPS), and in some cases have no history of food use. To help risk assessments proceed, applicants could improve the description of the identity of the microorganism, i.e. genus and species classification. When a GMM is used,

inadequate information on the genetic modification and individual strain which has been modified can prevent conclusions about safety being reached.

Often a new genome sequence is provided in PF applications. To support robust bioinformatics analysis, a high-quality genome assembly with sufficient coverage is needed. Lack of a high-quality genome assembly is a common data gap which is important for the FSA to make conclusions on safety. Insufficient bioinformatics analysis to evaluate potential pathogenicity and toxicity of a microbe is also a common issue. If through bioinformatics analyses a safety concern is identified, applicants are required to demonstrate that the product is safe. For example, if bioinformatics analyses demonstrate that the genome encodes a pathway for a toxin, applicants need to demonstrate that the toxin is not present in the final form of the product. Similarly, if secondary metabolites are produced by the microbe, they need to be analysed with appropriate methods to assure product safety.

During production process, important data gaps which prevented the FSA from drawing conclusions which were observed to be in common with general novel food applications include a sufficiently detailed food safety management plan, for example a Hazard Analysis and Critical Control (HACCP) plan to ensure that no microbe is present in the final product. Challenges in common with other cell-derived products include adequate information on cell propagation (the number of passages of cells), the genetic and phenotypic stability of the microbe, how fermentation is controlled and detail on the management of cell banking.

Where a GMM is used to produce a product, the removal of the GMM from the final product needs to be adequately demonstrated. Applicants also need to provide sufficient detail on how the product is secreted from the GMM. Finally, the use of media and bacteria as a processing aid may lead to the presence of heavy metal contaminants or trace metals in the final product.

Further detail on product composition is often required from applicants by the FSA. If a GMM is used to produce a protein, applicants are required to check that the protein is functional and folded correctly. For example, it is not sufficient for an applicant to demonstrate that the amino acid sequence is identical. Applicants should check that the secondary or tertiary protein structure is equivalent between proteins produced by the GMM and the native protein.

When investigating protein quality, it would be helpful for applicants to calculate protein content based on amino acid composition, to give an accurate representation of whether a product confers a nutritional

disadvantage. Similarly, applicants are required to choose an appropriate protein digestibility assay (for example, a method which takes into account absorption in the small intestine) and justify their choice.

Many PF products have intended uses as meat or dairy analogues. Meat for instance is a good source of protein, vitamins and minerals. Therefore, applicants need to ensure that a PF product does not cause nutritional disadvantage for vulnerable groups, such as infants and the elderly if replacing high quality protein. To assist this judgement, applicants need to be clear on the proposed uses of the product. For the FSA to assess nutritional disadvantage, applicants need to perform estimated intake calculations correctly. Insufficient clarity on proposed uses and estimated intake calculations have prevented the FSA concluding on the nutritional disadvantage that PF products (and cell-derived products), may pose to a consumer.

Further data gaps with regards to composition include a consideration by the applicant of the RNA content of the novel food, as RNA can be metabolised in the body to uric acid. The level of dietary fibre in the novel food also needs to be explained by the applicant, for example whether it will impact absorption in the gut or adversely affect individuals with fibre intolerance.

A challenge with PF products is also allergenicity. If a PF product is a milk protein, and marketed as a dairy alternative, applicants need to demonstrate that products will be labelled with the appropriate allergens (this is a risk management issue). Appropriate bioinformatics need to be performed to assess similarity between the proteins and known allergens, and where potential allergens are identified applicants need to clarify whether they pose a risk to consumers.

Conclusion

During this review, the highest priority challenges identified which impact product safety include bioinformatics, cell line integrity, protein digestibility, nutritional disadvantage and allergenicity of PF products. Therefore, the topics identified for the expert elicitation events held by the FSA are relevant and some of the above challenges may be addressed in future work. Indeed, many of the challenges faced in determining the safety of PF products are in common with those of cell-derived products, and insights from the sandbox research programme may assist with the risk assessment of PF products (and vice versa).

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Supplementary Materials

Figure 1: Placeholder

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