CLARIFICATION OF THE INFORMATION NECESSARY TO DETERMINE THE FORMATION OF UNINTENDED INGREDIENTS IN MICROBIAL PESTICIDE PRODUCTS

OCSPP Guidelines 885.1200 and 885.1300

The intent of this document is to provide additional clarification to applicants of novel microbial pesticides and facilitate the development of complete submission packages. The document is not intended to augment or supersede any existing OPP guidance.

I. General considerations. Data and information needed to satisfy the OCSPP Guidelines 885.1200 (manufacturing process) and 885.1300 (formation of unintentional ingredients) for new microbial active ingredients must be accompanied by a full description of the production process, ingredients used, and quality assurance (QA) and quality control (QC) measures.

II. Identify critical control points. Critical control points (CCPs) identify steps in the manufacturing process (MP) at which microbial contamination may be introduced. CCPs should be identified prior to submission of the application and mitigating QA measures incorporated into the MP. The Hazard Analysis and Critical Control Points (HACCP) approach[1] may be consulted to identify CCPs, for guidance on applicable QC tests to detect microbial contamination, and to identify procedures that reduce the likelihood for contamination to occur.

III. Address the likelihood for product contamination. Manufacturing processes are vulnerable to the introduction of unintentional ingredients that can contaminate the pesticidal end-use product. Because some of these introduced substances may be harmful to human health or the environment, the likelihood of their presence warrants further review to adequately assess the potential risks. Examples of harmful contaminants are: Pathogenic microbes (bacteria and fungi); microbial metabolites and toxins produced though microbial activity during the manufacture, such as mycotoxins; and non-biological substances, such as those resulting from chemical reactions between inert ingredients formulated into the product. A description of the methods employed by the manufacturer for testing for contaminant presence should be submitted and accompanied by a discussion of the likelihood for introduction to occur. [2] Human health concerns stemming from the presence of metabolites/toxins may be partly addressed if the product-specific toxicity, irritation, and pathogenicity exposure assays demonstrate a low toxicity profile *and* if the test substance used in these studies is toxicologically/biologically equivalent to those reasonably expected to be present in the final pesticide product. Because additional confirmatory tests may still be required on a case-by-case basis, the need for such testing should also be discussed in the application, both in the context of the genotype/phenotype of the microbe and for every CCP.

Note that the methods proposed for detecting contaminants should be up-to-date and practical, and that analytical tests should be commercially available or well established. In the latter case, and if other test endpoints are proposed, a review copy must be submitted along with results, including any raw data such as plate counts, dilutions, diluents and selective or differential media employed.

IV. Mitigating measures. HACCP furthermore describes elements that can be consulted in designing an MP and associated standard operating procedures (SOPs) that ensures the production of a pure microbial product. These include widely accepted sterile techniques, such as rigorous cleaning of equipment and autoclaving of growth media prior to use. They also include measures that ensure consistency in water quality and growth medium between production batches.

[1] https://www.fda.gov/food/guidanceregulation/haccp/ucm2006801.htm

[2] Some of the applicable criteria are also discussed in the OECD issue paper on Microbial Contamination Limits for Microbial Pest Control Products No. 65 (2011). Please note that this paper discusses both major pathogenic organisms associated with food borne disease and indicator organisms for contamination that may be more practical to monitor.

At the beginning of the production process, QA procedures should be in place to ensure the purity of the seed stock. After the growth phase is completed, a stable culture may be maintained by reducing the availability of water, or through the incorporation of preservative techniques, including the addition of stabilizing compounds, e.g., those that lower the water potential. Please note that once the microbial active ingredient has grown on sterilized media and containment is broken, the purity and identity of the product should be confirmed before subsequent processing. If conditions allow for regrowth after processing and formulation, it may be prudent to perform a contamination check on the final product destined for commercial sale.

V. Special considerations for microbial active ingredients proposed for food or feed use. While use of any microbial product contaminated with a potential human or animal pathogen would be unacceptable, application to food, especially foods eaten with minimal processing or cooking (i.e. fresh produce) or uses that include food contact surfaces would be especially serious. In these cases, a low threshold for pathogen presence should be applied. The current reports of serious morbidity and mortality from foodborne illnesses is often traced to *Escherichia coli* O157:H7, *Salmonella* spp. and/or *Listeria monocytogenes*. For example, FDA's guidance to industry is that ready-to-eat foods should be free of these contaminants in 25g of product using an enrichment method.[3]

[3] https://www.fda.gov/food/foodscienceresearch/laboratorymethods/ucm2006949.htm