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Recommendation for applicants on information requirements and assessment of applications for technical equivalence of active micro-organisms

Legal note

This document contains recommendations on fulfilling the information requirements for technical equivalence assessment for micro-organisms under Article 54 of Regulation (EU) No 528/2012 of the European Parliament and of the Council of 22 May 2012 concerning the making available on the market and use of biocidal products (Biocidal Products Regulation, BPR). This document describes the BPR obligations and how to fulfil them. However, users are reminded that the text of the BPR is the only authentic legal reference and that the information in this document does not constitute legal advice. The European Chemical Agency does not accept any liability with regard to the contents of this document.

1. Introduction

The BPR provides a centralised provision for the assessment of technical equivalence between active substances. The legal basis is Article 54, which sets out the procedure for the assessment of technical equivalence applications, under the responsibility of the Agency. The Guidance on the Biocidal Products Regulation Vol V, Guidance on applications for technical equivalence (1), provides exhaustive information on preparing an application for technical equivalence and its assessment. Since the above mentioned guidance is, however, not addressing active substances that are micro-organisms, the specific requirements applicable to micro-organisms are presented in this recommendation. For all details on information requirements for microbial active substances and on detection and quantification methods of microbial active substances and their impurities, please refer to Guidance on the Biocidal Products Regulation Vol V, Guidance active micro-organisms and biocidal products (2).

The prerequisite for technical equivalence is that both the alternative (new) source and the reference source have the same substance identity. Within the EU, micro-organisms are approved at strain level, and the current practice is to consider each new strain on its own for approval. Thus this recommendation for micro-organisms concerns applications for assessment of technical equivalence of the same microbial strain as the approved biocidal active substance (reference source). For the purposes of this document the same definition of a strain is used as for assessment of equivalence of microbial plant protection products: "a culture that is specifically linked to a collection number" (3, 4).

Technical equivalence needs to be demonstrated for micro-organisms when the properties of the technical grade active ingredient (TGAI) may change, e.g. when there is a:

- Change in the manufacturing location
- Change of the manufacturing process, like starting materials, processing steps, process conditions (e.g. temperature)

A tiered approach is followed in the assessment. Tier I consists of the evaluation of the identity and content of the active substance and metabolites/toxins relevant for the mode of action, and of the identity and content of impurities, additives and contaminating micro-organisms of the active substance (analytical data). The first step in the Tier I assessment is the confirmation of microorganism identity and verification that the active substance alternative has the same identity as the reference. If the Agency concludes during the technical equivalence assessment that the substance identities are different, the assessment will not proceed further and the application will be concluded negatively. If technical equivalence cannot be established on the basis of the Tier I data, further consideration relating to toxicological and ecotoxicological data is necessary under Tier II.

2. Applications for technical equivalence for micro-organisms

2.1 Information requirements

The general information requirements for technical equivalence applications of micro-organisms in Tier I are described below in Table 1. The first column of the table summarises the Tier I information that needs to be submitted in the technical equivalence application.

The second column of the table indicates for each Tier I requirement the related information requirements under BPR for micro-organisms to be fulfilled, and also where further guidance on these requirements can be found (in parentheses the corresponding section of Chapter 3.1.1 in *Guidance on the Biocidal Products Regulation Vol V, Guidance on active micro-organisms and biocidal products*). The applicant needs to follow the requirements in the indicated sections of the aforementioned Guidance document when preparing the technical equivalence application, and consider also the comments in Table 1.

The third column of the table includes comments about the requirements that the applicant should take into account, in addition to the general requirements in the aforementioned Guidance, when preparing the application.

Table 1. Tier I information requirements for technical equivalence applications for micro-organisms.

Required Tier I information to be submitted in the technical equivalence application	Related requirements under BPR for micro-organisms; for each requirement section in the Guidance on the BPR Vol V Chapter 3.1.1*	Comments
Applicant full name and address details	Applicant (name, address and contact person) (endpoints 1.1. and 1.2)	
Manufacturer of the active substance: full name and address details (office addresses) Manufacturing plant location full name and address details	Manufacturer of the active substance (name, address, head office and location of manufacturing plant (endpoint 1.3)	Only one manufacturer and one plant location can be included in one technical equivalence application. The actual plant location needs to be provided. If there are several locations during where the active substance is processed during the manufacturing, they all need to provided.

Manufacturing process description	Method of production and quality control (endpoint 2.6)	Only one manufacturing process can be included in one technical equivalence application. The description of the manufacturing process needs to clearly explain whether a stable TGAI is produced, or whether the active micro-organism is directly formulated into a biocidal product. When the technical equivalence application is for a change in the manufacturing process, the change(s) made to the process should be specifically described.
Identifiers for active substance	Common name of the micro-organism (including alternate and superseded names) (endpoint 2.1) Taxonomic name and strain (endpoint 2.2) Collection and culture reference number where the culture is deposited (endpoint 2.3)	Technical equivalence assessment for a change in the manufacturing location or manufacturing process can be submitted for the same microbial strain as the approved biocidal active substance (reference source).
Proposed specification by the applicant for the active substance and for the maximum concentrations of impurities, additives and contaminating micro-organisms	Content of the micro-organism (endpoint 2.7) Identity and content of impurities, additives, contaminating micro-organisms (endpoint 2.8) Specification of the technical grade active ingredient (endpoint 2.5)	The content of the active micro-organism in the technical grade active ingredient, TGAI, (or biocidal product) has to be submitted. If metabolites/toxins are responsible for the mode of action, also the biopotency information needs to be submitted. Level and nature of contaminating micro-organisms needs to be provided. The choice of providing information on TGAI or biocidal product should follow the same rationale as for the reference source. If deviating from this principle, sound justification should be provided.

Representative 5-batch analysis	Analytical profile of batches (endpoint 2.9)	Five representative batches of the TGAI (or biocidal product, as duly justified; see above) must be analysed for the content of the active micro-organism, toxins responsible for the mode of action as well as other relevant metabolites and contaminating micro-organisms. The following information needs to be provided for the batches analysed in the 5-batch analysis: dates of manufacture, batch weights/volumes, justification for their representativeness (e.g. based on quality control (QC) data). In general, the age of the 5-batch analysis and the ages of the batches (dates of manufacture) shall not exceed 5 years (see BPR guidance Vol V on Technical Equivalence).
Method descriptions and validations for the analytical methods used in the 5-batch analysis	Methods, procedures and criteria used to establish the presence and identity of the micro-organism (endpoint 2.4) Analytical methods for the micro-organism as manufactured (endpoint 4.1)	All methods and method validation parameters used in the 5-batch analysis must be described (for identification, detection and quantification of the micro-organism and, if appropriate, of the toxin(s) responsible for the mode of action; and for determination of other relevant metabolites and contaminating micro-organisms). The application should also include a justification for how the stability and integrity of the strain are maintained, e.g. explanation on how frequently new master cultures and seed stocks are prepared from the strain which is preserved unchanged in the culture collection.
Quality control data (optional)		Quality control data can be submitted as supportive information. However, it must be noted that such data cannot replace the 5-batch analysis.
Other information depending on the case		Other information may be needed for the assessment depending on the active substance (e.g. additional requirements indicated in the Assessment Report (AR) for the approval of the active substance). If such information is needed, the Agency will request it from the applicant.

* Please note that there will be some amendments into the endpoints with the foreseen revision of BPR Annexes II and III. These amendments will be reflected in an update of this recommendation in due time.

2.2. Assessment of technical equivalence of micro-organisms

The assessment compares the active micro-organism from the reference source to the active micro-organism from the alternative (new) source. This recommendation concerns applications for assessment of technical equivalence of the same microbial strain as the approved biocidal active substance (reference source). For establishing strain identity and stability, collection and culture reference numbers as well as master and seed stock information is assessed.

The aim of the Tier I assessment is to ensure that the active micro-organism from the alternative source is equivalent to the one from the reference source for the following parameters:

- Content of the **active microorganism** (determined in relevant units, e.g. colony forming units, CFU)
- Content/potency of the **relevant metabolites/toxins**[1] (determined in relevant units, e.g. International Toxic Units, ITU)
- Content of **microbial contaminants** (determined in relevant units, e.g. CFU)

When there is only a change in a manufacturing location, but there is no change in the manufacturing process, the aim of the assessment is also to ensure that:

- composition of material for production (e.g. inoculum, culture media), and
- manufacturing conditions and processes (e.g. temperature, duration, aeration)

are equivalent for the active micro-organism from the alternative source and from the reference source.

The alternative source is considered technically equivalent in Tier I when the strain or isolate is established as the same as the one from the reference source, and the following criteria are fulfilled based on the 5-batch analysis:

- Content of the active micro-organism (determined in relevant units, e.g. CFU) is in agreement with the specifications for the reference source;
- Content/potency of metabolites/toxins responsible for the mode of action is in agreement with the specifications for the reference source;
- Content/potency of relevant metabolites/toxins regarded as impurities are lower than or equal to the limit specified for the reference source:
- Content of microbial contaminants is lower than or equal to the limits specified for the reference source.

In case the above criteria are not fulfilled, a Tier II assessment should be conducted to demonstrate that changes in the composition (chemical and/or microbiological) do not significantly affect the overall (eco)toxicity, pathogenicity, and other characteristics relevant to the hazard profile of the micro-organism, such as infectivity, persistence and clearance. In case any new potential relevant metabolite/toxin or existing relevant metabolite/toxin above the maximum limit is identified in Tier I assessment, further information and/or studies should be provided. The information requirements may, however, differ on a case by case basis for the micro-organisms, and thus it is advisable to contact ECHA before conducting any additional studies.

[1] As indicated in *Guidance on the Biocidal Products Regulation Vol V Guidance on Active Micro-organisms and Biocidal products*, relevant metabolites include metabolites that:

- form a major part of the mode of action, and/or
- are present in significant amounts, and/or
- produce an adverse effect on humans or the environment under practical conditions of use.

Thus a relevant metabolite can be either a required part responsible for the mode of action of the microbial active substance, or a side-product regarded as an impurity.

2.3. References to guidance and further information

1. Guidance on the Biocidal Products Regulation Vol V, Guidance on applications for technical equivalence. Version 2.0 July 2018. https://echa.europa.eu/documents/10162/23036412/guidance_applications_technical_equivalence_en.pdf
2. Guidance on the Biocidal Products Regulation Vol V Guidance on active micro-organisms and biocidal products. Ver 2.1 March 2017. https://echa.europa.eu/documents/10162/23036412/biocides_guidance_micro_organisms_en.pdf
3. SANCO/12823/2012: Guidance document for the assessment of the equivalence of technical grade active ingredients for identical microbial strains or isolates approved under regulation (EC) No 1107/2009. Rev 4. 12 December 2014. https://ec.europa.eu/food/sites/food/files/plant/docs/pesticides_guidance_equivalence-micro-organisms.pdf
4. OECD Series on Pesticides No 96: Guidance document for the assessment of the equivalence of technical grade active ingredients for identical microbial strains and isolates Series on Pesticides ENV/JM/Mono(2018)8 http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2018)8&doclanguage=en