Evaluation Manual

for the Authorisation of Biopesticides according to Reg. (EC) No 1107/2009

Part I: Micro-organisms

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Board for the Authorisation of
Plant Protection Products and Biocides
ctgb

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Document history

Version	Date	Amended paragraph(s)	General description of changes
Pre-separation history of the Micro-organism section			
Not considered relevant to keep a change log of the pre-separation version, because the document has been completely revised in the process.			
Post-separation history of the Micro-organism section			
2.0	December 2022	**-**	Initial version of the separated EM Biopesticides – Part I, dedicated to the assessment of micro-organisms, in accordance with Part B of Regulations (EU) No 283/2013 and (EU) No 284/2013 as amended.
2.1	April 2023	**-**	Addition of 'Appendix I to EM Biopesticides Part 1: Microorganisms – Roadmap for SANCO/2020/12258' (separate document). Update of references to Overview table in Appendix I. Occurrences: A.2.8, A.4.1
2.2	September 2023		Update of references to new Communications from the Commission concerning Part B of the Annex to (EU) No 283/2013 and (EU) No 284/2013. Occurrences: A.7.1.1.1, A.8, P.2.7, P.10

Regulatory framework and purpose of this document

The regulatory framework for PPP containing micro-organisms is set by the Plant Protection Product Regulation (PPPR; Regulation (EC) No 1107/2009). This regulation states that a plant protection product can only be authorised when the active substance has been approved, the product is sufficiently effective and use of the product does not have harmful effects on human health and have no unacceptable effects on the environment. These conditions should be met for all PPP independent on the type of active substance (microbial or chemical).

The rules to determine if these conditions are met are set by the decision and evaluation criteria and the data requirements. These criteria and requirements are given in four documents. The approval criteria for the active substance are given in an Annex to the PPPR itself (i.e., Annex II to Regulation (EC) No 1107/2009). The decision and evaluation criteria are given in an implementing Regulation commonly referred to as the 'Uniform Principles' (see Article 29, paragraph 6 of the PPPR). The data requirements for the active substance and the product are given in two separate implementing Regulations.

While the overarching conditions for the authorisation of PPP are fixed (they should be effective and safe), the precise elaboration of the evaluation to determine if these conditions are met can be amended (see Article 29, paragraph 6 of the PPPR). This is exactlty what happened at the 31st of August 2022: new implementing Regulations were adopted which provide updated requirements and criteria for microbial PPP. The requirements and criteria were updated to reflect the development of scientific insight and obtained experience with the evaluation of PPP containing micro-organisms. The relevant amending regulations with the requirements and criteria for microbial PPP which apply from the 21st of November 2022 are:

- Commission Regulation (EU) 2022/1438, amending Annex II to Regulation (EC) No 1107/ as regards **specific criteria for the approval of active substances** that are micro-organisms
- Commission Regulation (EU) 2022/1439, amending Regulation (EU) No 283/2013 as regards the information to be submitted for **active substances** and the specific **data requirements** for micro-organisms
- Commission Regulation (EU) 2022/1440, amending Regulation (EU) No 284/2013 as regards the information to be submitted for plant protection products and the specific **data requirements for plant protection products** containing micro-organisms
- Commission Regulation(EU) 2022/1441, amending Regulation (EU) No 546/2011 as regards specific **Uniform Principles** for evaluation and authorisation of plant protection products containing micro-organisms

As these regulations are amending regulations, the numbering of the regulations relevant for the requirements and criteria for microbial PPP will not change. For example, the regulation containing the data requirements for the active substance will still be Regulation (EU) No 283/2013. Consolidated versions of these regulations are made available (see EUR-Lex — Access to European Union law). As a result, this numbering will be used throughout the text of this document; all references to the regulations refer to the amended versions.

To include references in cases where a differentiation is needed between the versions of the regulations before and after the amendment, the correct wording is (taking Regulation (EU) NO 283/2013 as an example):

- *To refer to the "old" regulation: "…Regulation (EU) No 283/2013 as it stood before being amended by Regulation (EU) 2022/1439…"*
- *To refer to the "new" regulation: "…Regulation (EU) No 283/2013 as amended by Regulation (EU) 2022/1439…"*

This document aims to provide an interpretation to these four new implementing Regulations. Such interpretations may be useful for any legal text, as the options to explain the context of a certain requirement or criterium in the legal text itself are limited. For these implementing Regulations on microbial PPP, additional guidance may be even more relevant as the assessment of biological entities is inherently complex. The new criteria and requirements acknowledge this inherent complexity and are based on the biological properties of micro-organisms. In this way, the new implementing Regulations aim to be more fit-for-purpose.

However, it is important to realise that the consequence of these criteria and requirements being more fit-for-purpose for the assessment of complex biological entities (micro-organisms) is that dossier preparation and evaluation of a microbial PPP should also be based on these biological principles. As a result, the process of dossier preparation and evaluation of a microbial PPP and conventional chemical PPP is inherently different.

For conventional chemical active substances the outlines of the risk assessment are clear from the onset: the compound on which the assessment should focus is known (the active substance), the hazards which may apply to the use of this compound are listed in the data requirements (e.g., toxicity, persistence) and the criteria and data requirements provide information on what should be considered as a foreseeable risk (e.g., more than 10% of the amount applied for soil degradation studies – see also the section 'Introduction to general concepts and principles of the risk assessment of microbial PPP'). In contrast, for microbial active substances, it is not clear from the onset on which component of the active substance the assessment should focus (micro-organism and/or any metabolites of concern), the hazards will depend on the characteristics of the micro-organisms (pathogenicity, toxicity of metabolites, anti-microbial resistance genes) and perhaps most importantly: there is no quantitative threshold to determine what should be considered to be a foreseeable risk.

For the assessment of microbial PPP, the first step of dossier preparation and evaluation is therefore to use all available information to assess what needs to be assessed (problem formulation). Furthermore, information becoming available during dossier preparation from literature searches or experimental data may trigger (or exclude) the need for further information for other areas of the assessment – the initial strategy for the risk assessment needs to be adapted during this process. For those areas where a hazard has been identified, the assessment should conclude on whether this hazard leads to a foreseeable risk. In contrast to the assessment of conventional chemical substances, this assessment for microbial PPP will in most cases be a qualitative assessment, often using a weight-of-evidence approach.

This Evaluation Manual (EM) aims to provide relevant information for all these stages of dossier preparation and assessment. However, due to the complexity and diversity of micro-organisms, what this manual cannot (and should not) provide is a one-size-fits-all tick-the-box approach for microbial PPP. For each microbial PPP, the appropriate approach for the risk assessment for this specific microbial PPP should be determined.

For each area of the risk assessment, the EM does not only provide technical information on how the data requirements can be addressed or which guidance or guidelines may apply, but also on the purpose of the section for the risk assessment. By describing why the information is needed and how the information can be used in the risk assessment, the relevance of a section and the best approach to address the section for a particular micro-organism can be better determined. This is thought to be supportive to compile thorough and coherent dossiers. It might be worthwhile to discuss the chosen approach during a presubmission meeting. In this way, the EM aims to contribute to more efficient risk assessments for microbial PPP.

This EM has been derived from an Explanatory Notes document that has been drafted as a joint effort of the Danish Environmental Protection Agency and the Dutch board for the authorisation of plant protection products and biocides (Ctgb). Upon completion of the first

draft, these Notes have been made available to the EU Commission.

Glossary of abbreviations and acronyms

5-BA	Five-Batch Analysis
(A)AOEL	(Acute) Acceptable Operator Exposure Level
ADI	Acceptable Daily Intake
AMR	AntiMicrobial Resistance
AOAC	Association of Official Analytical Collaboration
ARfD	Acute Reference Dose
CA	Competent Authority
CFU	Colony-Forming Unit
CoA	Certificate of Analysis
CRS	Closely Related Strain
EM	Evaluation Manual
EPPO	European and Mediterranean Plant Protection Organization
FRAC	Fungicide Resistance Action Committee
GAP	Good Agricultural Practice (colloquially refers to GAP-table)
GD	Guidance Document
GEP	Good Experimental Practice
GMO	Genetically Modified Organism
HRAC	Herbicide Resistance Action Committee
IPM	Integrated Pest Management
IRAC	Insecticide Resistance Action Committee
ISR	Induced Systemic Resistance
IU	International Unit
LOQ	Limit Of Quantification
LWA	Leaf Wall Area
MED	Minimal Effective Dose
MPCA	Microbial Pest Control Agent
MPCA-AM	Microbial Pest Control Agent As Manufactured
MoA	Mode of Action
MoC	Metabolite of Concern
MoPC	Metabolite of Potential Concern
MPCP	Microbial Pest Control Product
NOAEL	No Observed Adverse Effect Level
NTO	Non-Target Organism
OB	Occlusion Body
PAE	Pesticide Application Equipment
PDI	Plant Defence Inducers
PEC	Predicted Environmental Concentration
PED	Predicted Environmental Density
PFU	Plaque-Forming Unit
PHI	Pre-Harvest Interval
PNEC	Predicted No Effect Concentration
PPP	Plant Protection Product
RRF	Relative Response Factor
SM/RF	Spent Medium / Rest Fraction
TTC	Threshold of Toxicological Concern
UVCB	Unknown or Variable composition, Complex reaction products or Biological materials

Definitions used in this document

Below, definitions are included other than those provided in the Regulations.

'Claimed active metabolite' means a metabolite present in the MPCA-AM that is claimed to contribute to the plant protection action and whose quantitative presence in the final product is considered indispensible to the effect (see A.1.4.1 for further explanation). Claimed active metabolites are included in the specification.

'Consort' means an individual strain or isolate that is part of a consortium of strains or isolates.

'Deactivated micro-organism' means a micro-organism that is no longer capable of replication or transfer of genetic material.

'Formulation (process)' means the part of the production process that starts with combining the MPCA-AM (hypothetical or not) with co-formulants, other active substances and/or safeners/synergists, and ends with a finished MPCP. This part of the process is absent in process flows where the MPCA-AM is the MPCP.

'Framework' means the totality of regulatory texts (e.g., Regulations, Directives, guidances, working documents, and technical reports) that apply in the context of active substance approval under (EC) No 1107/2009.

'Manufacturing (process)' means the part of the production process that starts with the first operation performed with the seed stock and/or starting materials, and ends with a finished MPCA-AM (hypothetical or not).

'Part A active substance' means a substance for which a dossier shall be submitted in accordance with Part A (of (EU) No 283/2013 and (EU) No 284/2013). This group concerns chemical substances, extracts from biological material, semiochemicals, and metabolites produced by a micro-organism (either purified or as part of a fermentate in which the micro-organism has been deactivated).

'Part B active substance' means a substance for which a dossier shall be submitted in accordance with Part B (of (EU) No 283/2013 and (EU) No 284/2013). This group concerns (consortia of) micro-organisms, either with or without metabolites that significantly contribute to the substance's overall plant protection action.

'Production process' means the total of the manufacturing process and the ensuing formulation process (if any). In line with the definitions of the two sub-processes, the production process starts with the first operation performed with the seed stock and/or starting materials, and ends with a finished MPCP.

'Specification element' means a component, either an active (component), additive, contaminating micro-organism, relevant impurity, or MoC, that has been included in the specification.

'Viability' means the potential of spores to develop into colonies. Quantitatively, this parameter is approximated as %(CFUs per g (or mL) / spores per g (or mL)).

Efficient referencing to key guidance documents

'AMR GD' refers to SANTE/2020/12260, d.d. 23 October 2020

'FAO Manual' refers to the FAO/WHO JMPS Manual on development and use of FAO and WHO specifications for pesticides (2016) – ed.1, rev.3

'Literature GD' refers to the Guidance of EFSA – Submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009. EFSA J. 2011;9(2):2092

'Metabolite GD' refers to SANCO/2020/12258, d.d. 23 October 2020

'**OECD 67**' refers to the OECD guidance to the environmental safety evaluation of microbial biocontrol agents, Series on Pesticides No. 67

'OECD 85' refers to the OECD Guidance document on storage stability of microbial pest control products, Series on Pesticides No. 85

'OECD 98' refers to the OECD Working document on the risk assessment of secondary metabolites of microbial biocontrol agents, Series on Pesticides No. 98

Introduction to general concepts and principles of the risk assessment of microbial PPP

SELECTION OF THE APPROPRIATE ASSESSMENT TYPE
(Regulation (EU) No 283/2013, Annex I, Introduction)

Before starting to prepare a dossier for active substance approval, it is important to determine the 'best fit' with the available regulatory framework so as to avoid ending up with a set of requirements that demand a lot of information that is ultimately of little use to serve the clear-cut purpose of the assessment, which is to make sure an active substance is effective as claimed and safe in its use for plant protection.

For some time now, the separation of the framework into Part A (for chemical active substances) and Part B (for micro-organisms including viruses) has been in effect. Both domains have been designed to include all reasonably thinkable aspects that may need to be covered to satisfy the assessment purpose for either of the two groups of highly distinct substances.

In contrast to the previous version, amendment (EU) 2022/1439 to (EU) No 283/2013 provides practical criteria for active substance categorization that also covers previous boundary cases (see ANNEX I, Introduction).

Part A covers:
- Chemical substances (including semiochemicals and botanicals);
- Metabolites that are purified from the MPCA-AM by physical means (e.g., filtration, solvent-extraction, crystallization, (co-)precipitation);
- Metabolites that are part of an MPCA-AM in which the microbial active substance has been rendered incapable of replication or genetic transfer.

Part B covers:
- Micro-organisms, either as single strain or as multi-strain consortium;
- Micro-organisms, either as single strain or as multi-strain consortium, and one or more metabolites that are claimed to contribute to the overall efficacy. In this situation, the *direct or indirect* contribution of the micro-organisms themselves is always significant.

  NB: Here, it is pragmatically assumed that, as long as a micro-organism is capable of replication or genetic transfer, it will always provide a significant contribution to the overall efficacy, even when the metabolites are solely responsible for the actual pest control activity in terms of the MoA. In those cases, the micro-organisms will at least act as metabolite vector or 'sustained releaser' of the claimed active metabolites.

Despite the amendment, cases are conceivable that defy above ordering, like an MPCA-AM consisting of dead micro-organisms, lacking any identifiable metabolites that contribute to efficacy, but nonetheless showing useful elicitor activity. In such a situation, neither Part A nor Part B will by itself set out a satisfactory course for dossier drafting. In fact, the same may even apply for certain active substance dossiers that do meet the exact definitions above. Though not exhaustive, this EM provides some general considerations on assessment type selection and possible customization that should inspire a more critical way of dealing with the requirements that is more acutely aware of the prime purpose of the assessment.

Interpretation of the framework in specific cases

Part A and B crossover
An active substance based on rigorous purification of certain components from a fermentation broth generally produces a technical grade active substance that is perfectly primed for characterization according to Part A requirements. This is however not the case for other part A active substances that appear as unmodified fermentation broths with deactivated micro-organisms.
Having UVCB-like characteristics while lacking dedicated framework to deal with this, this category is prone to complicate the assessment when proceeding following a strictly formal route. To avoid the practical impossibility of attempting to achieve ≥ 980 g/kg analytical closure for the material, characterization according to Part B may be accepted as alternative.

Here, the Competent Authority may reason as follows: microbial active substances are approved based on Part B-characterization. Upon deactivation, micro-organisms will not change in any way that would justify a different approach towards composition-analysis. The deactivated – or rather: dead – micro-organisms will undergo common degradation processes that are logically not considered in the assessment.

As such, unmodified broth with dead micro-organisms, with or without any identified efficacy-supporting metabolites, is considered adequately characterized once it has been assessed according to SANCO/2020/12258 to check the possible presence of any residual, hazardous metabolites that may have been produced by the micro-organism when it was still alive.
In such cases, the active substance itself is simply quantified in terms of dry weight broth.

QUALITATIVELY DEFINED COMBINATIONS OF STRAINS; CONSORTIA
(Regulation (EU) No 283/2013, Annex I, Introduction)

In contrast to the previous version of the data requirements and Uniform Principles, the currently into force regulations explicitly include the possibility of having a qualitatively defined combination of strains (a microbial consortium) as a single active substance. From an ecological point of view, the benefits which may result from the use of combinations of micro-organisms are clear. The consortium can for example have a more robust efficacy when the separate strains function optimally under different environmental conditions or have differences in their host range. Alternatively, the efficacy of the consortium can be increased if the members have different modes of actions against the target, or when certain strains act as helper strains to the micro-organisms responsible for the biocontrol activity. It should be noted that also in the case of microbial consortia more is not always better; strains can also negatively affect each other and thereby lower overall efficacy of the active substance.
While in plant protection most uses of micro-organisms currently rely on the use of a single strain, in many other areas where micro-organisms are used in the food chain, the use of consortia is more common. This holds not only for brewing, fermenting and bread making, but also for probiotics for humans and animals and for biostimulants. Although the previous regulations didn't explicitly include the possibility of using a consortium as active substance, approved active substances which are viruses commonly consist of a combination of several isolates.
The revised regulations are a step forward for PPP based on microbial consortia becoming available to farmers. By including this possibility in the regulations, it is expected that applications for the approval of microbial consortia will follow. Currently, no guidance is

available on the risk assessment for microbial consortia for plant protection purpose; experience from other regulatory frameworks which regulate microbial consortia intentionally added to the food chain may be helpful. It is advised to start a dialogue between notifier and competent authority at an early stage of dossier preparation.
The relevance of data requirements for specific consortium members or for the full consortium (active substance) will depend on the characteristics of the consortium and on the proposed use. While certain data requirements will apply unequivocally to all members of a consortium (e.g., the absence of relevant AMR genes for bacterial strains), for other data requirements it may be justified not to provide certain data for all strains in the consortium. A minimum requirement is the qualitative definition of the consortium: all strains must be identified and deposited in a culture collection. Efficacy should be demonstrated for the full consortium (which is in effect one of the major differences compared to the previous data requirements, where efficacy should be demonstrated for single strains).
The necessity to include information on the quantitative composition of the consortium should follow from the efficacy and risk assessment and is not a default prerequisite. As for all microbial active substances, which data requirements are relevant should be determined by for example the identity and ecology of the strains, whether the micro-organisms are sufficiently well-known, and from the proposed use (e.g., seed treatment versus post-harvest treatment of fruits).

FORESEEABLE RISK
(Regulation (EU) No 283/2013, Annex I, Introduction, point 1.1)

The introduction of the data requirements state that a submitted dossier should contain information which is sufficient to evaluate the *foreseeable* risks which the active substance or PPP may entail (point 1.1). Furthermore, this point states that at least the information and results should be submitted which are referred to in the data requirements themselves, but not when this information is not needed due to the nature of the PPP or the proposed use, or when it is technically not possible to supply (see point 1.5 of the introduction to Annex I of Regulation (EU) No 283/2013).
In effect, this means that all information should be submitted to be able to conclude that the use of a PPP is sufficiently effective and does not have harmful effects on human health and has no unacceptable effects on the environment, whether or not inclusion of this information in the dossier was triggered by a data requirement. It also means that information should not be required if – due to the properties of the substance or the use – the information is not necessary to evaluate foreseeable risks. Taken together, this leads to the question: what are these foreseeable risks for which information is required?
In general, a risk is the likelihood of a hazard causing harm. In turn, a hazard is something that has the potential to harm you (EFSA, 2016[1]). Risk therefore depends on hazard and the exposure to this hazard. In turn, a foreseeable risk is a risk which is not far-fetched and can be expected to occur. Due to the inherent differences between chemical and microbial PPP, there are also inherent differences in how the concept of foreseeable risk can be applied in the risk assessment. While for conventional chemical substances a quantitative approach regarding foreseeable risks can be used, for living micro-organisms including their metabolites such a quantitative threshold is often not applicable.
For example, consider the breakdown products of conventional chemical active substance which may cause a risk to aquatic organisms due to toxicity. The data requirements for chemical active substances ask for information on the route of degradation in soil and aquatic systems. All breakdown products should be identified if they occur above a certain percentage of the amount of the active substance applied (e.g., more than 10% of the amount of the active

[1] https://www.efsa.europa.eu/en/discover/infographics/hazard-vs-risk

substance). These 'major metabolites' (major breakdown products) are to be included in the residue definition relevant for the risk assessment and ecotoxicological information for these compounds should be included in the dossier. Therefore, toxicity from these major metabolites is in principle considered as a foreseeable risk, while toxicity from minor metabolites in principle is not.
For microbial active substances, this quantitative threshold as a first step in the risk assessment of metabolites is not possible: there is no quantitative limit below which microbial metabolites are considered as in principle not leading to a foreseeable risk. Instead, a qualitative approach is used for microbial metabolites. Based on the guidance on the assessment of microbial metabolites (SANCO/2020/12258), metabolites are identified which entail a foreseeable risk (metabolites of concern).
Where possible, information on what is considered to be a foreseeable risk has been included in the amended implementing Regulations. For example, while prior to the amendment information on genetic stability was required for all micro-organisms 'where appropriate', the amended implementing Regulation indicates that this information is only needed for non-virulent variants of plant pathogenic viruses. Far-fetched risks such as the risk of a micro-organism which is not closely related to human pathogens suddenly mutating into a human pathogen upon application are therefore excluded as foreseeable risk based on the text of the data requirement.
For those sections of the risk assessment where such information on what is considered to be a foreseeable risk is not included in the requirements or principles, expert judgment is needed to determine what should be and what should not be considered to be a foreseeable risk. For this expert judgment, knowledge on normal microbial ecology (without the use of the microbial PPP) and the body of knowledge on the particular microbial species is highly relevant.

CASES WHERE INFORMATION IS NOT REQUIRED: JUSTIFICATIONS FOR WAIVING
(Regulation (EU) No 283/2013, Annex I, point 1.5)

Microbial diversity is vast; it includes the non-living viruses, bacteria and Archaea inhabiting environments ranging from hydrothermal vents to clouds, yeast and fungi – the latter of which may very well include the largest organisms in the world. Furthermore, the hazards which may apply to the use of a micro-organism are diverse: they do not only include toxicity of metabolites produced by the micro-organism, but also pathogenicity and the possibility to transfer genetic information to human pathogens that renders them resistant to antibiotics. As a result, the risk assessment of a microbial PPP should be able to deal with this diversity of micro-organisms and their potential hazards.

The EU regulatory framework aims to address this diversity by setting requirements to cover for all potential hazards of all micro-organisms. As a result, the data requirements trigger the provision of the data necessary to assess this diversity of potential hazards. At the same time, however, because data requirements are set to cover this full range of diversity, not all data requirements will be relevant for the micro-organism under assessment. The fact that not all data requirements are applicable for each micro-organism is acknowledged by the regulatory framework. Three different elaborations of this principle are used in the data requirement:

- Conditional data requirement for which the text of the data requirement clearly indicates for which micro-organisms the data requirement is relevant. An example is data requirement 5.1.1 of Regulation (EU) No 283/2013: '*For micro-organisms excluding viruses*, …'. In this case, it is clear that no information is required in case the micro-organism is a virus – a statement to this extent suffices.
- Conditional data requirements for which the text of the data requirements does not indicate for which micro-organisms the data requirement is relevant. An example of this

type of conditionality is data requirement 4.2 of Regulation (EU) No 283/2013: '*Where relevant, methods for post-approval monitoring shall be described*.' While this data requirement acknowledged the fact that this data is only needed in certain cases, the text of the requirement does not specify when this data is considered relevant. In this case, a more elaborate statement should be included in the dossier, for example to justify that methods for post-approval are not relevant for the micro-organisms as no metabolites of concern have been identified (including references to the sections of the dossier where metabolites of concern are excluded).

- All data requirements where the requested information is not necessary '*owing to the nature of the plant protection product or its proposed uses, or it is not scientifically necessary, or it is technically not possible to supply*' (point 1.5 of the introduction to Annex I of Regulation (EU) No 283/2013). Also in this case, a justification should be provided to demonstrate the fact that information is not needed or not possible to supply. An example of the latter is when the micro-organism cannot be assigned to a described species (as it is not sufficiently closely related to a described species) – in this case it is not possible to provide the information requested under point 1.3 (ii) of the Annex II, Part B of Regulation (EU) No 283/2013.

Please note that in all cases a justification is needed as to why certain information or studies are not included in the dossier. Only including a statement that a data requirement is not relevant for the micro-organisms without further information cannot be accepted.

LOW-RISK STATUS
(Regulation (EU) No 283/2013, Annex I, point 1.11(z))

The conditions under which an active substance that is a micro-organism may not be considered a low-risk active substrance are given in Point 5.2 of Annex II to Regulation (EC) No 1107/2009 (see Article 22 of Regulation (EC) No 1107/2009). A PPP shall be authorized as a low-risk PPP when all the active substances contained in the PPP are low-risk active substances and no specific risk mitigation measures are needed following a risk assessment (see Article 47 of Regulation (EC) No 1107/2009). Please note that the specification that personal protective equipment (e.g., masks) shall be worn for micro-organisms which are regarded as potential sensitisers due to the unavailability of validated test methods is considered to be a non-specific risk mitigation measure (see Point 2.5.1.4 of Part B of the Annex of Regulation (EU) No 546/2011).

GOOD LABORATORY PRACTICE
(Regulation (EU) No 283/2013, Annex I, point 3)

Studies within the scope of Directive 2004/10/EC must in principle be performed by a GLP-compliant performing laboratory with an area of expertise that is relevant to the study topic. However, as stated in point 3.2 of the introduction of Annex I of Regulation (EU) No 283/2013, a derogation is in place for active substances that are micro-organisms. For these substances, tests and analyses performed to obtain data for other aspects than human health may be conducted by non-GLP compliant official or officially recognised facilities. Please note that all studies used for the assessment of the effects on human health should be GLP-compliant, irrespective of the section of the dossier for which the studies are submitted. For example, analyses for the assessment of antimicrobial resistance genes (see A.2.9) shall be GLP-compliant.
For GLP-compliant studies, compliance of the report is evaluated according to the systematic described in OECD Series on principles of good laboratory practice and compliance

monitoring No. 20.

SPECIFICATION DATA ON TEST BATCHES
(Regulation (EU) No 283/2013, Annex I, point 4, and Annex II, point (vi))

According to (EU) No 283/2013 and 284/2013, ANNEX I, Point 4, the test material used in any study included in a dossier must be fully characterized in analogy with the corresponding Reference specification, i.e., it must include data on all defined constituents (see A.1.4). The information also needs to cover batch number, the weight and/or volume of the batch, the manufacturing date, the site where the batch has been manufactured, and the scale of the process (i.e., commercial or pilot).
As most tests are being conducted prior to the assessment, batches may lack full compliance with the Reference specification as it is ultimately established. In these cases, evidence needs to be submitted that the deviation is not critical to the purposes of the test in which the batch has been used.

GENETIC MODIFICATION
(Regulation (EU) No 283/2013, Annex, point (vii))

As highlighted in (EU) No 1107/2009, Art. 48, any biological entity capable of replication or genetic transfer that is present in a PPP shall comply with EU Directive 2001/18/EC. Organisms modified through mutagenesis are exempt from the Directive, as well as organisms that are incapable of replication or transfer of genetic material. Furthermore, GMO that do not end up in the product are not considered within the 2001/18/EC-framework.

WHOLE GENOME SEQUENCE DATA
Whole genome sequence (WGS) data can be highly effective to inform the risk assessment. However, this effectiveness stands or falls by the availability of correctly annotated sequence information. Although annotation may be performed using publicly available databases, the information in these databases is often not curated and as a result often erroneous. The use of WGS data as a screening step in hazard identification is therefore often problematic.

In contrast, targeted inquiries of the WGS data in case the sequence data of a specific property of the micro-organisms is known are appropriate. For bacteria, this is the case for the assessment of anti-microbial resistance (AMR), where the hazard is due to the presence of a known AMR gene in the genome (see A.2.9). Other cases where WGS data may be usesful is for the exclusion of the presence of certain virulence factors including the production of metabolites. When using WGS data in the risk assessment, the EFSA statement on the requirements for while genome sequence analysis of micro-organisms intentionally used in the food chain should be taken into consideration (EFSA Journal 2021; 19(7):6506). If WGS data is included in the dossier, confidentiality of this data may be requested (see Article 63 of Regulation (EC) No 1107/2009.

Please note that when WGS data is used for the assessment of human health, the analytical phase should be GLP-compliant.

IUCLID

Active substance dossiers should be submitted using the software application IUCLID (International Uniform ChemicaL Information Database). To aid this process, a crosswalks document is available for the table of content in the IUCLID versions for dossiers based on the Regulations before and after the amendment (i.e., the Regulations as they stood before being amended by Regulation (EU) 2022/1439 and Regulation (EU) 2022/1440 versus the Regulations as amended by Regulation (EU) 2022/1439 and Regulation (EU) 2022/1440).

FUTURE DEVELOPMENTS

The requirements and criteria for the risk assessment acknowledge the importance of the body of knowledge on the species or higher taxon of a micro-organism for the assessment of individual strains within this taxon. As a result, the same body of knowledge on a taxon should be included and assessed for each strain within a taxon. The risk assessment for a micro-organisms could be performed more efficiently while maintaining the same level of protection if the body of knowledge would not need to be assessed as part of the assessment of each strain within the assessment. However, at the time of writing this Evaluation Manual (December 2022), no procedure is in place to circumvent the re-assessment of the body of knowledge for each new dossier within a taxon. The EU Commission acknowledges such a procedure as a way to make the assessment procedure more efficient. Currently (December 2022), work is ongoing at OECD on consensus documents on microbial species used in plant protection. In case a consensus document is available for the micro-organisms under assessment, the way the consensus document can be used for the risk assessment will depend on the section of the risk assessment (e.g., human health, biological properties, metabolites) and the body of knowledge of the taxonomical group:

For some sections a reference to the consensus document can fully addresses the data requirements or assessment. For these sections of the dossier, the risk assessment of strains of micro-organisms can be concluded on based on the body of knowledge on the taxonomical group. For example, based on the body of knowledge of *B. amyloliquefaciens*, it can be concluded that *B. amyloliquefaciens* strains are not pathogenic to humans (as is reflected in the inclusion of this taxonomical unit in the QPS list). The data requirements and the assessment of the pathogenicity to humans can therefore be addressed by referring to the conclusion in the consensus document. Other areas of dossier which may be fully addressed by the consensus document are for example the history of use, relationship to known pathogens and effects on certain non-target organisms.

For other sections, focused, strain-level information may be needed as indicated by the consensus document. For these sections of the dossier the risk assessment of strains cannot be concluded on based on the body of knowledge on the taxonomical group, but the body of knowledge can be used to focus which data is needed for individual strains within this taxonomical group. An example would be the identity of the micro-organism (i.e., the unequivocal identification of a certain strain as belonging to a certain species): while information at strain level is always needed for this section of the dossier, the body of knowledge as presented in the consensus document can provide information on which analyses are appropriate to determine if a strain belongs to the taxonomical group. For example, for *B. amyloliquefaciens* the relevant genes needed for identification at species level can be indicated, including references to studies describing the methods and results (e.g., which primers, which criteria). In the dossier, strain-specific experimental data can be provided which was generated based on the methods selected based on the information in the consensus document.

Other areas where the information from a consensus document can be used to focus the information needed in the dossier are for example the production of metabolites (e.g., by

indicating for which metabolites information at strain level is needed – thereby circumventing the need to perform a full metabolite assessment for strains within the taxonomical group), virulence factors or the delineation of the host range of pathogenic micro-organisms.

Other sections of the risk assessment cannot be addressed by the body of knowledge: for these areas strain-level information is needed. This applies to obvious datapoints such as the deposition number of the strain, but also for antimicrobial resistance genes for bacterial strains. To which sections of the dossier this applies will vary between taxonomical groups. For example, while strain-level information on the effects on non-target organisms may be needed for a dossier of a *Metarhizium* strain, for bacteriophage dossier no non-target information may be needed.

A.1 IDENTITY OF THE APPLICANT, IDENTITY OF THE ACTIVE SUBSTANCE AND MANUFACTURING INFORMATION

A.1.1 Applicant

Corresponding data requirement:	(EU) No 283/2013, Annex, Part B, 1.1
Relevant evaluation criterion:	-
Relevant decision making criterion:	-
GLP-compliance:	Not relevant

Purpose of this point:
The applicant is the approval holder and must, as such, be identified as entity addressing all issues relating to the active substance, either directly or through a notified representative.

Conditional / waiving
Not relevant.

Confidentiality
No confidentiality can be claimed for the identity of the applicant.

A.1.2 Producer

Corresponding data requirement:	(EU) No 283/2013, Annex, Part B, 1.2
Relevant evaluation criterion:	-
Relevant decision making criterion:	-
GLP-compliance:	Not relevant

Purpose of this point:
The producer acts as contact point with regard to manufacturing. Furthermore, producer and corresponding plant locations are fundamental identifiers for the manufacturing process.

Conditional / waiving
Not relevant.

Confidentiality
Confidentiality can be claimed for the identity of the producer and the manufacturing location, as this information complies with the criteria in (EC) No 1107/2009, Art. 63.

A.1.3 Identity, taxonomy and phylogeny of the micro-organism

Corresponding data requirement:	(EU) No 283/2013, Annex, Part B, 1.3
Relevant evaluation criterion:	(EU) No 546/2011, Annex, Part B, 1.1.1
Relevant decision making criterion:	(EU) No 546/2011, Annex, Part B, 2.1.4
Criteria for approval	(EC) No 1107/2009, ANNEX II, (2), point 3.4.3

(i) Deposition in culture collection

Purpose of this point: Through the deposition of the micro-organism before the time of

dossier submission, a sample of the micro-organism is preserved for future reference. Furthermore, the unique deposition number can be useful for the evaluation of scientific literature.

Assessment principle:
To be able to verify the status of the culture collection and the deposition of the strain, the official documents relevant for the deposition of the micro-organisms should be included in the dossier.

(ii) Species to which the micro-organism belongs

Purpose of this point: The micro-organism needs to be identified as unambiguously belonging to a certain species, based on up-to-date methodologies and current knowledge. The identification of the correct species is of crucial importance, as the assessment of a micro-organism may be largely based on the body of knowledge on the species to which the micro-organism is assigned. Please note that the methods used to unequivocally classifiy the micro-organism to a certain microbial species (this data point) are not the same methods which are needed to determine if a microbial sample contains the micro-organism under assessment (the latter are the methods included in the dossier to be able to identify the micro-organism at strain level, see A.4.1).

Assessment principle:
To determine whether the micro-organism is correctly identified at species level, both the relevance of the methods used for this classification and the results are evaluated. Which methods are appropriate for a certain micro-organism is determined based on scientific literature describing the most appropriate method(s) for the specific species. Therefore, this information and a justification for the methods used to identify the micro-organism at species level should be included in the dossier. Note that the method itself should also be included under analytical methods (see A.4.1)

Nowadays DNA sequencing is in principle considered the most appropriate method. For example, sequence analysis can be performed on (several) genes that are conserved within the genus to which the micro-organism belongs. Data from Whole Genome Sequencing (WGS) of the micro-organism can be used.

In the EFSA “Guidance on the characterisation of micro-organisms used as feed additives or as production organisms (EFSA Journal 2018; 16(3): 5206, page 6) is stated:

- Bacteria: Whole genome sequence (WGS) analysis is required for the characterisation of bacteria (Section 2.1.1). Therefore, data from WGS should be used for identification of the micro-organism. This can be achieved by computational approach for taxonomic assignments (e.g. phylogenomics or average nucleotide identity (ANI)), or by comparing the sequences commonly used for taxonomic identification (e.g. 16S rRNA gene), or other characteristic genes (e.g. housekeeping genes) to relevant databases.
- Yeasts: As for bacteria, WGS is also required for the characterisation of yeasts (Section 2.1.1). Therefore, data from WGS analysis should be used for identification of the micro-organism. This should be done by phylogenomic analysis (e.g. using a concatenation of several conserved genes to produce a phylogeny against available related genomes).
- Filamentous fungi: When WGS is available, identification should be made by a phylogenomic analysis comparing the genome against available related genomes. If no WGS is available, identification should be made by comparing the 18S rRNA gene

and/or ITS regions and other characteristic genes (e.g. tubulin) with sequences deposited in databases.

These methods are also recommended for micro-organisms used as active substances under Regulation (EC) No 1107/2009. However, WGS is in principle not a requirement for bacteria and yeasts, but is more or less indispensable for investigation of resistance to antimicrobials of clinical relevance and may be useful for the assessment of potential production of known secondary metabolites.

Viruses are classified based on morphology, chemical composition, and mode of replication. Even though viruses differ in classification, all viruses are similar in structure and contain a nucleic acid (genome made up of DNA or RNA) enclosed in a protein coat (capsid).

In case WGS data of the micro-organism is provided, the ”EFSA statement on the requirements for while genome sequence analysis of micro-organisms intentionally used in the food chain” should be taken into consideration (EFSA Journal 2021; 19(7):6506, 14 pp.). This document provides recommendations to applicants on how to describe the analysis and results of WGS data, including quality criteria/thresholds that should be provided/reached (e.g. sequence depth, number of contigs). In addition, several examples are provided of how WGS-based data can be used for the identification of the micro-organism. For bacteria for instance digital DNA-DNA hybridization (dDDH), average nucleotide identity (ANI), or phylogenomic methods are proposed (e.g. Multi Locus Sequence Testing, MLST). While the first two methods compare sequences genome-to-genome, the latter focusses on sequence similarities of conserved genes within a species/genus. For fungi phylogenomic analysis or alignment to a complete reference genome from the same species is proposed.

Examples of databases than can be helpful for identification of the micro-organism are provided by (but not limited to): the International Commission on *Trichoderma* taxonomy (ICTT), the *Bacillus subtilis* MLST Database (PubMLST), the International Committee on Taxonomy of Viruses (ICTV), and the National Center for Biotechnology Information (NCBI).

Interpretation of the framework in specific cases

Micro-organism belongs to undescribed taxon
In case a micro-organism does not belong to a formally described and named species, it is not possible to identify the micro-organism at species level. How this situation may be dealt with in a regulatory context is described in the Guidance on the characterization of micro-organisms used as feed additives or as production organisms (EFSA Journal 2018; 16(3): 5206). This guidance provides the following information regarding this situation: “In the case that the data do not allow the assignment of the strain under assessment to a known microbial species, its phylogenetic position with respect to the closest relatives should be provided”.
The fact that the micro-organism belongs to an undescribes species will have implications for the dossier, as by definition the body of knowledge on this undescribes species is non-existant. Although the body of knowledge on related described species can (and should) be used for the dossier, more information at strain level may be required (see for example the approach described for less well-known species in the guidance on the risk assessment of metabolites produced by micro-organisms used as plant protection active substances (SANCO/2020/12258).

(iii) Synonymous, alternative, and superseded names

Purpose of this point:
All synonymous, alternative and superseded names are needed as these names may be used in scientific literature or other reports. To facilitate the interpretation of literature and reports in case a different name is used for the micro-organism, information on the relevance of these names for the micro-organism should be provided. This means for example that in addition to listing the superseded names, it should be explained why the name of the species has changed (e.g., reclassification of specific micro-organism or revision of microbial classification), when the name was changed and how the superseded names of the micro-organisms and closely related micro-organisms should be interpreted in the context of the risk assessment.

Assessment principle:
The synonymous, alternative and superseded names should be correctly listed, and this information should be incorported accordingly in the remainder of the dossier. Superseded names should for example be included in literature searches: According to the "Future guidance on performing and presenting the literature search", an appendix to the EFSA Guidance on the submission on scientific peer-reviewed open literature (EFSA Journal 2011; 9(2): 2092), if in the previous 10 years the strain had been ascribed to a different species, the name of that other species also needs to have been included in the search terms to ensure a comprehensive search is carried out.

(iv) Phylogenetic tree

Purpose of this point:
Information on the relationship of the micro-organisms to closely related strains, species or higher taxonomical units is needed to support the risk assessment in several ways. The phylogenetic tree provides information on the possible relationship to human pathogens and to pathogens to non-target organisms (see also A.2.6). In addition, the phylogenetic tree can be used to support the justification for read across between the micro-organism and closely related micro-organisms. However, please note that a close relationship in itself is not sufficient to justify the use of read across as information should always be provided on the applicability of read across for the property or trait for which information is needed.

Also, a phylogenetic tree will provide supporting evidence in case of a (future) change of taxonomy, as the phylogenetic tree will provide information on the relevance of the change in taxonomy for the risk assessment of the micro-organism (e.g., are the search terms used in the literature searches still appropriate considering the changes in taxonomy?).

Assessment principle:
The choice for the micro-organisms included in the phylogenic tree and the methods to build the tree should be adequately justified. The method itself should be submitted under analytical methods (see A.4.1.)

(v) Wild type, mutant or genetically modified micro-organism

Purpose of this point: Whether a micro-organisms is a wild type or differs from the wild type is relevant for the interpretation of natural exposure of humans and the environment to related micro-organisms. In addition, for genetically modified organisms, additional regulation applies (see Directive 2001/18/EC on the deliberate release into the environment of GMOs).

Assessment principle:
If the micro-organism is a mutant or genetically modified the differences between the parental strain and the mutant should be explained. This does not only refer to (epi)genetic differences, but also to the effect the (epi)genetic differences may have on the biological properties of the micro-organism, such as persistence, phenotypic difference in host range of a pathogenic micro-organism or the levels of metabolite production under certain conditions. In addition, methods to differentiate the mutant strain from the parental wild type strain should be provided, in accordance to A.4.1(d).

A.1.4 Specification of the microbial pest control agent as manufactured

Corresponding data requirement:	(EU) No 283/2013, Annex, Part B, 1.4
Relevant evaluation criterion:	(EU) No 546/2011, Annex, Part B, 1.1.1
Relevant decision making criterion:	(EU) No 546/2011, Annex, Part B, 2.1.2
GLP-compliance:	5-BA data on relevant contaminating micro-organisms, metabolites of concern, and relevant impurities shall be produced under GLP

Purpose of this point:
The specification established for the MPCA-AM provides an acceptable range for the MPCA itself and possible claimed active metabolites, and furthermore for any additives, metabolites of concern, relevant impurities and relevant contaminating micro-organisms. Its main purpose is to ensure consistency in the manufacturing output in terms of safety and efficacy.

Conditional / waiving
From a strictly pragmatic perspective, establishing an MPCA-AM specification is not necessary as long as a 5-BA-based specification is available for the MPCP. In some cases, the MPCA-AM specification would not even be as meaningful as its MPCP-level counterpart, e.g. (i) when MPCA-viability is significantly modified during the formulation process causing the MPCA-limits established for the MPCA-AM to be less representative, or (ii) when the MPCA-content is derived from a bioassay that needs to be performed with the MPCP anyway.
Moreover, in cases where the MPCA-AM represents a non-isolated intermediate (or 'hypothetical phase'), the MPCP-level specification is simply the only one available.
Regardless of the nature of the case, requests for waiving must be adequately substantiated.

N.B. A major disadvantage of lacking an MPCA-AM specification presents itself when modifying the production process. Logical interpretation of A.1.5.1, 'Suggestions on dealing with non-standard manufacturing in the regulatory context', Principle 1, implies that establishing a specification is needed to define an MPCA-AM, and that definition of an MPCA-AM marks the separation between the manufacturing and formulation processes. When this has not been done, like when there is only an MPCP-specification, such a separation is deemed non-existent, and the process preceding the genesis of the MPCP is by default considered 'continuous'. As a result, any change to the MPCP would be interpreted as a change to the manufacturing process, which triggers evaluation of technical equivalence according to SANCO/12823/2012 – rev.4, albeit in a somewhat stripped-down format; all changes must be described in detail, upon which the Competent Authority decides whether an updated MPCP-specification can be simply derived from the existing one (often the case when the change only affects the co-formulants), or whether a wholly new 5-BA may be required (that corresponds with the existing specification in terms of elements).

Confidentiality
Confidentiality can only be claimed for additives.
Data relating to the 5-BA may be placed in the confidential part of the DAR / RAR, but the specified results must appear in the respective non-confidential sections.

Evaluation principle
A.1.4.1 Content of the active substance

Primarily, a specification must provide clear information on the representative range of the content of the MPCA and that of claimed active metabolites (see 'Defining a specification', directly below on representativeness). For Part B active substances, the present framework does not consider any active substance categories beyond 'MPCA' and 'claimed active metabolite'. Fundamental characteristics of the MPCA and claimed active metabolites are that they (i) are present in the MPCA-AM (and in the MPCP[2]), (ii) are sufficiently stable throughout a practical shelf-life (*N.B. Stability is addressed at the product-level*), and (iii) are quantifiable by conventional microbiological, molecular, or analytical methods.

MPCA
For the purpose of defining a specification, the conceptualization of what is actually causing the plant protection action is necessarily simplified. After all, in reality a micro-organism's mode of action is the resultant of a complex orchestration of effects against a target organism, many of which rely on untraceable, short-lived chemicals that are produced under specific circumstances *in situ*.
For regulatory purposes, characterization of the micro-organism itself is in most cases considered to cover this complexity.
The MPCA shall always be included in the specification because for as long as it is capable of (host-mediated) replication and – depending on its type – gene transfer, the micro-organism is assumed to either directly or indirectly contribute to the overall plant protection action. Even in cases where its direct plant protection action appears to be marginal compared with that of any co-contributing secondary metabolites, it is assumed that a minimal content is necessary to support the main activity, e.g., either to support functionality as vector or as 'sustained releaser' (already discussed under 'Selection of the appropriate assessment type (ANNEX I)'). Furthermore, the MPCA-content range is required as input for the risk assessment.

CLAIMED ACTIVE METABOLITES
Secondary metabolites[3] are additionally included in the specification as 'claimed active metabolites' when they are claimed to be relevant for the plant protection action and are at the same time present in the MPCA-AM / MPCP in quantities that are indispensible to the overall plant protection action.
To gauge the factuality of a claim, the MoA of the claimed active metabolite must therefore first be investigated and described to decide whether the metabolite's effect is aligned with the function of the active substance.
Next, it must be established that the plant protection action caused by the metabolite-quantity that is present in the MPCA-AM / MPCP may not just as well be generated by the amount of the same metabolite that is produced *in situ*. In other words: *"Would a version of the product in*

[2] To maintain consistency between the substance -and product-level risk assessments, the MPCA-AM -and MPCP-specification must always be equivalent in terms of defined elements and how they are expressed. *N.B. This only applies when both specification levels are relevant to the dossier* (see also A.1.5.1, 'Suggestions on dealing with non-standard manufacturing in the regulatory context', Principle 2).
[3] Primary metabolites are wholly exluded from consideration, as they are by definition not employed by the MPCA for any purpose beside maintenance. Even if these substances may add to the plant protection action (as is likely the case for dead micro-organisms), identification is not required due to (i) their reasonably assumed trivial nature, (ii) their short half-lives outside the microbial cell, or (iii) their unidentifiable contribution to the MoA.

which the metabolite has been magically removed, achieve the same efficacy as an unaltered version (…as the removal is compensated anyway by in situ *production of the respective metabolite)?"*

The distinction between claimed active metabolites that are thus 'critically present' in the MPCA-AM / MPCP, and other metabolites that may contribute to the plant protection action is relevant; the quantity of claimed active metabolites in an MPCA-AM / MPCP-batch directly relates to the quality of that batch and should for that reason be included in the specification. including metabolites for which the quantity in the MPCA-AM / MPCP is not especially important to the overall action on the other hand, is meaningless.
To actually distinguish between the two, it is considered that claimed active metabolites are either predominantly produced during manufacturing or have accumulated in the MPCA-AM to a degree that cannot be achieved by *in situ* production upon proposed use. Other efficacy-supporting metabolites are either continually (or ambiently) generated at a relatively constant rate throughout the MPCA's life, or are mainly produced *in situ*. Categorizing metabolites in either group may be difficult, but a practical approach should be sufficient. Actual metabolite levels in the MPCA-AM / MPCP could unambiguously identify a claimed active metabolite, but stability is also a good indicator. After all, build-up to critical levels is not considered likely when the metabolites are short-lived.

Please note that the act of defining a claimed active metabolite for the specification has relatively limited repercussions for the overall assessment: the metabolite exclusively needs to be included in the 5-BA to establish a performance-assuring specified range to its content. Unjustly ignoring the active status of a metabolite will not affect the (more acutely relevant) assignment of a correct risk profile, as the metabolite will inevitably have been correctly examined in the course of the assessment via SANCO/2020/12258 anyway.
Putting this into perspective as such is helpful in cases where a claimed active metabolite (that is NOT a MoC) is, due to technical aspects of its analysis or limited commercial availability as a standard, disproportionately difficult to quantify in a 5-BA context.

A.1.4.2 Identity and quantification of additives, relevant contaminating micro-organisms and relevant impurities

A.1.4.2.1 Identity and quantification of additives

Additives are specifically added to increase the MPCA's stability and/or to facilitate handling. In that sense, they relate to the MPCA-AM in effectively the same way as co-formulants do to the MPCP. For regulatory purposes, it is therefore appropriate to treat them equally insofar this is possible given their dinstinct contexts;

- Like for co-formulants, the choice of the additive and of its content must be proportionally related to its intended function. Additives may neither significantly enhance nor mitigate the overall efficacy of the MPCA and any claimed active metabolites. In case an additive may reasonably be suspected of such behavior, dedicated field trials can be requested for verification. This restriction is not limited to substances that have already been approved as 1107/2009-active substances, but covers all chemical substances.
- Like co-formulants, additives are intentionally added under controlled circumstances. Their content is not affected by spontaneous variation, other than weighing error, and does therefore not need to be determined in the context of a 5-BA. Additives are defined in the specification in terms of chemical identity, content range (min. and max., whenever the content requires batch-specific adaptation to ensure functionality), and function.
- As for co-formulants, the identity of additives is considered confidential by default (see

A.1.4, 'Confidentiality' for the concise considerations that apply with regard to confidentiality and MPCA-AM specifications).

There are also a few fundamental differences between additives and co-formulants;

- Changes that affect the identity and/or content of co-formulants are evaluated in accordance with 'Formulation change GD' SANCO/12638/2011 – rev.2, whereas such alterations to the MPCA-AM's additives would trigger an equivalence assessment according to 'Technical equivalence GD' SANCO/12823/2012 – rev.4.
- Unlike for co-formulants, dedicated analytical methods are required for the determination of additives in the MPCA-AM (see A.4.1, 'Quantitative methods').

A.1.4.2.2 Identity and content of relevant contaminating micro-organisms

It must be shown that the level and nature of contaminating micro-organisms are within the acceptable limits as stated in the OECD issue paper on microbial contaminant limits for microbial pest control products (SANCO/12116/2012 – rev.0).
In case of indications for the presence of a relevant contaminating micro-organism that is not covered by the set proposed by OECD, it shall nevertheless be included in the routine screening – after all, its presence incurs a hazard. The levels of such 'non-standard species' in the representative manufacturing output must be evidenced to remain below a context-derived limit, using certified screening methodology (see A.4.1, 'Quantitative methods' for additional details). It is advisable to consult with the Competent Authority on a consensus limit prior to data generation.

A.1.4.2.3 Identity and quantification of relevant impurities

Like for Part A active substances, relevant impurities are chemicals that are of concern to humans, animals or the environment, and that may unintentionally end up in production batches during manufacturing. In A.1.5.1, 'The essential process checkup; Potential sources of relevant impurities', likely sources of such impurities are discussed, in order to provide a starting point for effective identification. Note that an unfocused inventory of all components present in quantities of 1 g/kg or more and typically up to analytical coverage of at least 980 g/kg, a.k.a. 'SM/RFing', as per (EU) 283/2013, Part A, 1.11, is considered an inappropriate method to identify relevant impurities in the MPCA-context.
Metabolites of concern are identified following the procedure described under A.2.8.

A.1.4.3 Analytical profile of batches

REPRESENTATIVENESS

An analytical profile of batches is established based on the 5-BA. Representativeness is key in this analysis; the five batches[4] that are tested are pragmatically considered to indicate the variation in the output of the relevant manufacturing process[5], thus ensuring that the assessment relates to the actually produced material. To this end, the examined batches...

- …are produced within five years before dossier submission (as evidenced by manufacturing dates on the respective CoAs) ;
- …are produced within a time window that is sufficiently representative of the manufacturing calendar (again, as evidenced by manufacturing dates on the respective CoAs – if needed, amended by a confirmation on the yearly window of operation of the

[4] For micro-organisms, five batches may not suffice in a statistical sense to allow derivation of a truly representative range. On the other hand, the number holds a middle ground that allows obtaining a meaningful indication while maintaining a reasonable amount of regulatory burdening.
[5] Here, 'relevant manufacturing process' is defined as the actual process employed in the manufacture of the MPCA that will eventually end up in products to be marketed in the EU (see also A.1.5.1, 'The essential process checkup; Relevance for EU-context and fundamental process characteristics').

relevant manufacturing plant);
- …are produced according to the relevant process (as evidenced by statement).

EXPRESSION OF CONTENTS

The 5-BA data must present the contents of the specification elements in a meaningful way; the content of the MPCA and that of any claimed active metabolites shall be expressed in a way that most accurately reflects plant protection action.
Although the MPCA is frequently presented in terms of CFUs, this is not always appropriate. For fungi for instance, spores with a potential to germinate (i.e., 'viable spores') often cause the actually intended effect before they can be considered a colony.
When the content of the MPCA does not directly relate to efficacy, a less apparent, indirect association is assumed, and inclusion of the MPCA in the specification is still required – although the accuracy of expression may be less critical.
When plant protection action is expressed in terms of biopotency, which is essentially a parameter that is defined by the conditions set in the appending bioassay, further speciation may be warranted. An especially relevant condition that directly relates to the GAP is the choice of test species. In these cases, the specified biopotency range must therefore be clearly linked to the target species that has been investigated. The choice of species needs to be justified, mostly with respect to sensitivity. Biopotency should only be established for the product.
Claimed active metabolites are generally expressed in gravimetric terms, although other terms appropriate to their nature may be considered (e.g., mol per g or mL). As this mode of expression is also the most effective in capturing a substance's toxicity, the same applies for relevant impurities and MoCs.
For contaminating micro-organisms, it must simply be demonstrated that their content remains below the corresponding OECD threshold.

ESTABLISHING RANGES

The specification range for the MPCA and any claimed active metabolites serves to establish a reference quality for production of the MPCA-AM; it must not be too broad, in order to ensure that batches at either extreme of the range will perform equally with regard to efficacy. At the same time, the range must not be too narrow so that it allows for the variation inherent in the manufacturing process and post-manufacturing productivity of the MPCA – for this reason, the MPCA-content range is preferably not directly derived from the 5-BA, as batches often tend to have very similar contents.
For the MPCA, the minimum of the specified range is therefore primarily proposed by the applicant based on knowledge of the minimal effective dose (MED), supported by specification data of the batches used in the field trials in which minimal effectivity has been observed. As is generally accepted in the field of microbiology, the range maximum is established by simply multiplying the minimum content with a factor of ten (i.e., by 'adding' one log unit). This maximum needs to be covered in the risk assessment.
Whether the proposal is appropriate in terms of representativeness is subsequently verified with results from the 5-BA, from which a minimum is derived by subtracting three standard deviations from the 5-result average, and a maximum by adding three standard deviations to the average[6]. When the 5-BA range reasonably coincides with the 'one log unit range' based on minimal effectiveness, the latter is considered to be sufficiently appropriate to serve as specification range for the MPCA.
Establishing a range that exceeds the one log unit broadness is not desirable, as this would at some point result in non-trivial performance differences between minimally and maximally specified batches. Still, when necessitated by unavoidable variation, a broader range will be

[6] Although the sample set may be too small, and the contents not purely normally distributed, this practice should reasonably approximate the situation in which about 99 % of all produced batches fall within the established range.

accepted once adequately justified.
When activity is expressed in terms of biopotency, the above-mentioned approach may be less appropriate and another way to define a range may be warranted.

To establish a range for claimed active metabolites, provisional guidance is given at this point: in principle, a minimum is derived by subtracting three standard deviations from the 5-BA result average, and a maximum by adding three standard deviations. For established relevant impurities and MoCs, only a specified maximum content-threshold is relevant. It is also calculated by adding three standard deviations to the 5-batch result average.
MoCs which are considered to be of concern only due to *in situ* production are logically not included in the specification.

A.1.5 Information on manufacturing process and control measures for the active substance

Corresponding data requirement:	(EU) No 283/2013, Annex, Part B, 1.5
Relevant evaluation criterion:	(EU) No 546/2011, Annex, Part B, 1.1.2
Relevant decision making criterion:	(EU) No 546/2011, Annex, Part B, 2.1.3 and 2.1.5
GLP-compliance:	Not relevant

Purpose of this point:
The manufacturing process must (i) be well-controlled, efficient, logical in terms of design and process flows, (ii) adhere to good manufacturing practices, (iii) be conducted under adequate hygienic conditions, and (iv) include a tight, sufficiently sensitive, and fail-safe monitoring system – all to ensure consistent quality in MPCA-AM (and thus MPCP) output that complies with the established specification in terms of identity and content.

Conditional / waiving
Describing the manufacturing process is not eligible for (substantiated) waiving.

Confidentiality
Confidentiality can be claimed for data relating to the manufacturing process, as this information complies with the criteria in (EC) No 1107/2009, Art. 63.

Evaluation principle
A.1.5.1 Production and quality control

THE ESSENTIAL PROCESS CHECKUP
This subsection provides a practical checklist of things that need to be covered in the manufacturing process description to allow drawing a conclusion on process control, good manufacturing practice, hygiene, and monitoring.

Relevance for EU-context and fundamental process characteristics
For any Part B active substance, the framework assumes not more than one reference process[7] per applicant, or task force of applicants, involved in the approval of that substance. All other processes involved in serving the EU are considered additional. Typically, the manufacturing process assessed within the context of substance approval (or Renewal) is designated as reference process. Furthermore, the specification assigned to the material that is being produced by the reference process is considered the reference specification. The

[7] Here, the process is considered, rather than the location. Theoretically, multiple, non-equivalent manufacturing processes of the same substance can be performed at a single site.

reference process retains its special status for the whole substance approval duration, irrespective of any changes made to it.
Additional manufacturing processes relevant for the European market must be assessed against the reference limits so that quality and safety of the material used for manufacturing of formulated products is guaranteed regardless of the manufacturing origin.
For any given manufacturing process, reference included, the three key identifiers, i.e., technical details, location of the respective plant, and scale – pilot or industrial – must be indicated. Changes in any of these three characteristics, or notification of a wholly new process, trigger assessment according to SANCO/12823/2012 – rev.4[8].

Functionality of critical conditions
The manufacturing process may be designed in a way that has serious implications for the course of the assessment. For instance, fermentation conditions may either propagate or inhibit the production of secondary metabolites (that may have been identified as potential MoCs or claimed active metabolites). In rarer cases the manufactured material may be sufficiently dilute to allow filtration, so that undesirable components may be physically excluded. Given their potential relevance, critical conditions and their intended function must be clearly defined and their functionality evaluated in terms of their effect on the test material. The type of data needed depends on the nature of the respective process design feature.

Potential sources of relevant impurities
In rare cases, relevant impurities may be introduced to the MPCA-AM. Of the limited number of conceivable contamination sources, starting materials and additives are the most likely. Adequate descriptions of these ingredients are required, stating e.g., identity, origin, supplier, and purity (whenever relevant). Along with *a priori* knowledge on likely contaminants associated with a given material (e.g., mycotoxins and cereal grains), these data should provide sufficient leads for any further investigation.
The Regulation does not provide any specific information as to how relevant impurities are established analytically. Beside focused routine analyses of the material for components expected in a given context, CoAs issued by adequately certified screening labs may also be accepted. Although this 'Tier I'-type of data needs to be sufficiently reliable, GLP-compliance is not per se required at this stage.
Next, contaminated equipment may be considered as source, but the nature of its contribution is considered to be accidental, and therefore unlikely to be picked up within the (long-term) context of approval dossier evaluation. The description of sanitation measures and how equipment is prepared for the process (e.g., removal of residual cleaning agents) should in general suffice to identify systematic issues.

Quality control
Ultimately, the quality control steps need to ensure that all MPCA-AM- (and thus MPCP-) batches produced by the process concerned comply with the established specification with regard to MPCA-identity and content, and the content of claimed active metabolites, additives, relevant contaminating micro-organisms, relevant impurities, and MoCs.
Commonly, the contents of the specification elements have been established based on results produced by one or more contracted labs that will rarely, if ever, be hired to analyze all batches that will henceforth be produced by the respective manufacturer. Rather, in-house analyses must be capable of accurately identifying incompliant batches.
Contrary to the methods employed by the contracted lab, the in-house counterparts do not

[8] A technical equivalence assessment triggered by changes of an existing process in terms of scale, location and/or technical details, or by the notification of an additional process can be performed within the course of the substance assessment, or at any given moment after approval of the active substance (but before commissioning of the changed/new process for the EU).

need to be validated; pragmatically, the 5-BA is assumed to represent the expected variation among batches and any further deviations should be covered by national authorities charged with PPP-monitoring.
To strengthen this 'safety net', the robustness of the in-house methods – or assay methods for standardization, maintenance, and purity of the product – may be examined on a case-by-case basis[9]. First, the methods must be described and specified (see (EU) No 283/2013, Part B, 1.5.1). To ensure fitness for purpose, the description should at least allow comparison with a typical method (most conveniently, the one employed by the contracted lab) in terms of equipment, materials, conditions, and terms in which the measured contents are expressed. Secondly, equivalence of performance may be assessed by comparing in-house method results (that are expected to be available anyway) with those generated by the contracted lab for the same batches.
Third, for all monitored parameters the test criteria maintained by the manufacturer must be made explicit so that they can be related with corresponding international thresholds (such as for contamination micro-organisms) or thresholds that are established in the course of the assessment. The method's LOQ needs to be stated to check whether the method is sufficiently sensitive.

Ideally, quality control batches are drawn at strategic instances during the process to allow early detection of unintended changes to the material being manufactured. Of course, this is mostly in the interest of process efficiency, and therefore particularly relevant to the manufacturer. In the most abstract sense, regulators are primarily concerned with the quality control steps performed with the starting cultures, the MPCA-AM and MPCP, and will at least demand that these materials are under routine monitoring.
The assay results for the starting cultures must evidence preservation of purity and activity, whereas those for the MPCA-AM and MPCP should be relatable to the respective specification. Often, for the purpose of routine control, the MPCA is characterized in terms of spores (per g or mL), as their quantification does not require a laborious incubation step. In many cases however, the MPCA is specified in terms of CFUs. In these cases, it should be substantiated that checking for spores provides a good surrogate for quantifying CFUs.

Storage and repurposing
In some cases, the MPCA-AM is stored for a prolonged duration prior to formulation. No data are required to show that the specification elements remain within acceptable ranges throughout this period, as (long as) these parameters will be routinely checked further downstream – which is always assumed to be the case, as is discussed above in the context of strategic sampling.
Some batches that are irredeemably outside of the specification range for one or more elements may be repurposed for the sake of waste reduction, e.g. by mixing with other batches. Whether this is feasible depends on the nature of their incompliance. In case of repurposing, the criteria that would make a batch fit for reuse need to be specified.

SUGGESTIONS ON DEALING WITH NON-STANDARD MANUFACTURING IN THE REGULATORY CONTEXT
The manufacturing process is at the basis of the development of new concepts of microbial active substances and of the design of more efficient process flows. To avoid that novel concepts are abandoned due to some seeming mismatch with the framework, a set of fundamental principles are defined that provide a clear understanding of the few things that require compliance in any case, for both regulatory and practical reasons. This small set of principles is presented below.

[9] This is considered most relevant for the methods used to check for microbial contaminants, relevant impurities, and MoCs.

Note that the current information does not pretend to encompass everything that is imaginable today, let alone that which lies beyond. Cases that appear to confuse the principles should not immediately be abandoned. Rather, they should be discussed with the Competent Authority early on in the process to explore possibilities for alignment.

Principle 1 – Defining the MPCA-AM(s) and MPCP(s) in the process flow
It is good to remember that the designation 'MPCA-AM' is mainly a regulatory label that clearly identifies the material for which a specification has been established, for reasons that are discussed in detail under A.1.4. Only one practical insight serves to identify the actual MPCA-AM in any process: the MPCA-AM is the material at the boundary of manufacturing and formulation that directly and without further modification[10] enters the formulation process. Figure A.1.5.1-01 below visualizes the separation between the 'manufacturing-part' of the complete process (depicted in blue), and the 'formulation-part' (red). As the figure implies, multiple MPCA-AMs may exist within one process flow; it could be the material resulting from (i) post-processing (e.g., after drying of the fermentate), (ii) post-post-processing (e.g., after harvesting spores from a solid phase that has been inoculated after the main fermentation process. In this case, inoculation is the post-processing step), (iii) auxiliary manufacturing, or (iv) blending of the materials resulting from (i), (ii), and/or (iii).
Deciding which of these should be considered MPCA-AM is a strategic choice to be taken by the applicant. A pivotal argument in this decision involves planned future amendments to MPCA manufacturing that would trigger equivalence assessment. Any change to the MPCA-AM described in A.1.5.1, 'The essential process checkup; Relevance for EU-context and fundamental process characteristics' necessitates re-evaluation of the equivalence status, whereas simple blending of (unmodified) MPCA-AMs does not.

[10] There can be no 'pre-step' within the formulation process. Any modification to the material that carries the MPCA preceding formulation is automatically considered a manufacturing step. This ensures that consistency between MPCA-AM and MPCP is maintained (see Principle 2).

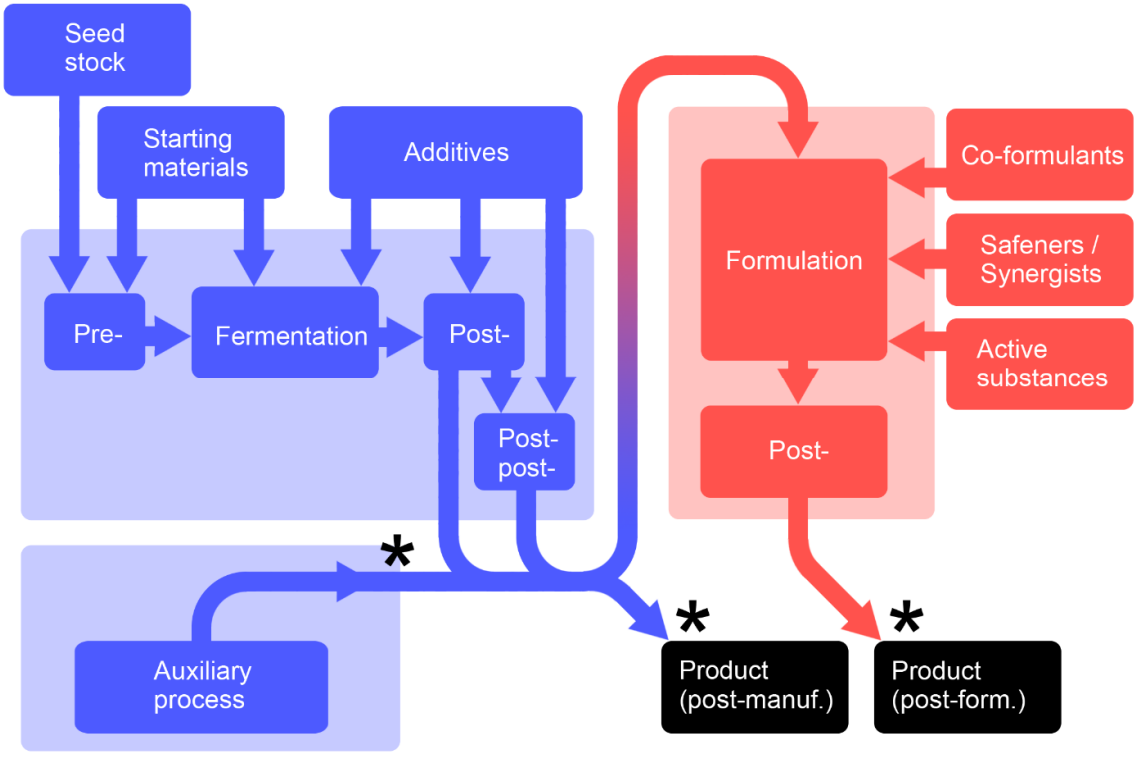


Figure A.1.5.1-01: Graphical representation of a typical manufacturing (blue) / formulation (red) process flow. The asterisks indicate the likely instances where material may be sampled for which a specification may be established. Note that the steps 'pre-', 'post-', and 'post-post-' are designated as such just to save space. They should be considered relative to the main process within their box, i.e., as pre-fermentation, post-formulation, etc.

Principle 2 – Consistency between MPCA-AM and MPCP
In principle, the MPCP-specification should be derivable from the MPCA-AM-specification, by simple multiplication of the concentration of the specification elements in the MPCA-AM, and the concentration of MPCA-AM in the MPCP (see also P.1.4). This relationship between both specification levels requires that the element in the MPCA-AM and its corresponding counterpart in the MPCP cannot be fundamentally different. For example, from a regulatory perspective it is not possible that the MPCA in the MPCA-AM is viable, while it has been deactivated in the MPCP. Any step that involves such a fundamental change to the material is therefore considered part of the 'manufacturing-part' of the process. Further, such steps are excluded during the post-formulation step.
Of course, modifications that are perfectly normal during formulation and post-formulation (e.g., addition of co-formulants, drying) may affect MPCA viability, and thus in a way fundamentally alter the MPCA. As this change is caused by operations that are common for the formulation-part anyway, and rarely affects the consistency between MPCA-AM and MPCP to a significant degree, this is acceptable. In extreme cases where loss of viability would cause a significantly different efficacy, additional actions may be required (e.g., improvement of the formulation process, submission of additional efficacy data and an accompanying 5-BA for the MPCP).

Principle 3 – Consortia
A major feature of the new Data Requirements is the consortium concept (see 'General introduction to micro-organisms' for the essential details). Aside from the fact that consorts

should relate to each other in a meaningful way, they must on an individual level adhere to the criteria of a Part B active substance.
With regard to combining consorts, blending of single-strain/isolate MPCA-AMs, and multi-strain/isolate fermentation are acceptable, although both have their own disadvantages. Blending of single-strain/isolate MPCA-AMs would require separate 5-BAs for each of the materials involved. For fermentation of multiple consorts in one vessel, the process requires sufficient control to ensure reasonably constant quantities of each participating strain/isolate.

Principle 4 – Additives
One of the main functions of an additive is to preserve microbial stability. Substances with such properties often show a broad effectivity against other micro-organisms, which makes them potential efficacy-boosters, depending on the intended function of the active substance. Restrictions on such additives are described in P.6.1.

A.1.5.2 Recommended methods and precautions concerning handling, storage, transport, or fire

No specific interpretation necessary for this point.

A.1.5.3 Procedures for destruction or decontamina

No specific interpretation necessary for this point.

A.2 BIOLOGICAL PROPERTIES OF THE MICRO-ORGANISM

General introduction
According to the uniform principles the biological properties and the mode of action of a micro-organism are the first and crucial step in the evaluation process, because they define which are the aspects and elements on which the evaluation should focus, and also which aspects are not relevant for this specific micro-organism. The information provided in this chapter can be used as (part of) a justification, by following a weight of evidence approach, to address certain points in other sections of the evaulation.

In following section, information is included for each data requirement on how the information can inform the risk assessments conducted in the other sections, e.g. on human health, residue, environmental occurrence and ecotoxicology (see A.5, A.6, A.7 and A.8).

A.2.1 Origin, occurrence and history of use

Corresponding data requirement:	(EU) No 283/2013, Annex, Part B, 2.1
Relevant evaluation criterion:	(EU) No 546/2011, Annex, Part B, 1.2.1.1
Relevant decision making criterion:	-
Criteria for approval	-

Purpose of this point:
In contrast to many conventional chemical active substances, micro-organisms occur naturally. Due to this natural occurrence, humans and the environment may already be exposed to micro-organisms which are closely related to the micro-organism under

assessment. As a result, the body of knowledge on a microbial species can include information on the (absence of) adverse effects due to this natural exposure. Information on the location from where the micro-organism was isolated (geography and habitat) and the natural occurrence of the species provide information on the extent of the natural exposure of humans and the environment.

In addition to this natural exposure, exposure to the micro-organism or closely related micro-organisms may result from (other) uses of these micro-organisms. Therefore, information on the uses of the micro-organism and closely related micro-organisms will provide information on the extent of the exposure of humans and the environment. This information can be used in the risk assessment to better interpret the information on (the absence of) adverse effects.

Besides providing information on the exposure of humans and the environment, the information on the origin, occurrence and history of use provide information on the biological properties of the micro-organism which is relevant for the risk assessment. These properties include for example the habitat in which the micro-organism is expected to occur and its growing conditions.

Required information

2.1.1. Origin and isolation source
In this section a.o. the geographical location and environmental compartment from which the micro-organism was isolated should be given, including the method of isolation and the selection procedure. Information on the method of isolation can provide information on the substrate onto which the strain can grow on, possible host specificity and natural occurrence in an environmental compartment.

Information on the geographical location is especially relevant for pathogenic micro-organisms. As described in A.7.1.2 and the introduction of A.8, the natural occurrence of closely related micro-organisms - and thereby the geographical location from which the micro-organism was isolated - is an important factor in the risk assessment of pathogenic micro-organisms.

2.1.2. Occurrence
The geographical distribution of the micro-organism and environmental compartment in which the micro-organism occurs should be described at a relevant taxonomical level. A special attention should be given to the occurrence of the micro-organisms in EU environments relevant to agriculture. As the populations of micro-organisms can be highly dynamic, information on absence or presence of the micro-organism may be as informative as information on actual population densities.

Which taxonomical level is relevant for this data point may differ per micro-organism as well as per section of the risk assessment. For example, while species-level information will in general be relevant for micro-organisms of which the mode of action (MoA) is competition, for pathogenic micro-organisms the natural occurrence of a specific virulence factor of the species may be more relevant. Similarly, when hazards are identified for a certain toxin produced by the micro-organisms, information on the natural occurrence of micro-organisms producing this toxin may be more relevant than a detailed description of the natural occurrence of the microbial species. Therefore, the selected taxonomical level to provide information on the occurrence should be explained.

The origin of the strain under evaluation itself is already described under 2022/1439; 2.1.1. Please note that by definition a microbial strain does not occur naturally - only upon application

can the strain occur in the environment. See Part B of the Uniform Principles; Commission Regulation (EU) 2022/1441 amending Regulation (EU) No 546/2011 for definitions relevant for micro-organisms.

2.1.3. History of use

Information on all previous and current uses of the micro-organism (and closely related micro-organsims if relevant) can be used in the risk assessment as it may provide information e.g. on the extent of exposure of human and/or the environment. This information may include research, commercial uses (biostimulant, probiotics, bioremediation, etc) and uses evaluated for the list of micro-organisms with the Qualified Presumption of Safety status (Qualified Presumption of Safety (QPS): EFSA Journal (wiley.com). These uses should therefore not be limited to plant protection or agricultural uses. Information provided in assessment under other relevant regulatory frameworks can be useful to better interpret the information on (the absence of) adverse effects. The relevance for the risk assessment of the information on the history of use of closely related micro-organisms such as microbial strains from the same species or closely related species should be explained.

A.2.2 Ecology and life cycle of the micro-organism

Corresponding data requirement:	(EU) No 283/2013, Annex, Part B, 2.2
Relevant evaluation criterion:	(EU) No 546/2011, Annex, Part B, 1.2.1.2
Relevant decision making criterion:	-
Criteria for approval:	-

Purpose of this point:
Information on the ecology of the micro-organism is basic information for any risk assessment of a micro-organism. The ecology of a micro-organism describes how the micro-organisms interacts with its environment including other organisms. Information on the life cycle of the micro-organism also provides general information, such as whether the micro-organism can produce resistant resting stages.

Required information:
The information presented in this section should provide a clear overview of the available information on the ecology and life cycle of the micro-organism. Specific topics which should be addressed are for example:

- Whether the micro-organism is known to be a parasite (e.g., a mycoparasite), a saprophyte, endophyte or pathogen. Regarding endophytes, a distinction can be made between obligate and facultative (passenger) endophytes (see e.g. Scheepmaker 2021[11]). In case the micro-organism is known to be able to live endophytically, information on the plant parts in which the micro-organism occurs may be relevant for the expsosure of humans and non-target organisms.
- Under which conditions can the micro-organism survive or multiply in the environment?
- What is the life cycle of the organism? For example, can the micro-organism form resting structures and if so, which types and under which conditions?

Fungi and bacteria

All forms in which the micro-organism can occur need to be described. For instance, for fungi and bacteria an overview of available information on resting stages, resistance of spores

[11] Scheepmaker 2021. Exploring the necessity of additional data requirements under the pesticide regulation to take into account endophytes. RIVM rapport 2021-0056; http://dx.doi.org/10.21945/RIVM-2021-0056.

against environmental conditions (e.g. UV light, heat or possible chemicals present in the environment), survival time of the spores and conditions for germination of spores needs to be provided. In general, the information presented in this section can be based on publicly available scientific information and information obtained in for example efficacy trials.

Likewise, for fungi and bacteria information should be presented on whether the micro-organism is capable of biofilm formation. Micro-organisms in a biofilm are typically embedded by an extracellular matrix which makes them less vulnerable for adverse environmental conditions (as opposite to single planktonic cells), like for instance desiccation. Biofilm formation can also play an important role in pathogenicity (if relevant) as the micro-organism will be more protected against compounds produced by the immune systems of insects or plants. Moreover, micro-organisms in a biofilm are less susceptible for therapeutic antimicrobials in cases of opportunistic infections.

Bacteriophages
For bacteriophages – viruses which infect bacteria – information should be provided on their lytic and lysogenic properties. During a lytic life cycle (coupled to virulent phages), the entire metabolism of the bacterial host cell is taken over after injection of the genetic phage material to generate phage progeny. Finally, the host cell is lysed for the release of bacteriophages. Typically, the time between infection and progeny release is rather short (hours). In contrast, temperate phages follow a lysogenic life cycle, where the genetic material of the bacteriophage will be incorporated into the host genome (forming a prohage), where it can remain dormant for several generations. As a result, temperate phages are not only less desirable from an efficacy point of view (as the mode of action is the result of progeny release that is accompanied by lysis of the host cell), there may also be a higher probability of horizontal gene transfer.

A.2.3 Mode of action on the target organism and host range

Corresponding data requirement:	(EU) No 283/2013, Annex, Part B, 2.3
Relevant evaluation criterion:	(EU) No 546/2011, Annex, Part B, 1.2.1.2 (EU) No 546/2011, Annex, Part B, 1.2.1.3 (EU) No 546/2011, Annex, Part B, 1.2.1.4
Relevant decision making criterion:	-
Criteria for approval:	-

Purpose of this point:
Information on the mode of action (MoA) on the target organisms is needed, as this not only explains the function of the active substance that is a micro-organism, but is also extremely helpful for the identification of hazards. Hence, special attention should be paid to possible infectivity, pathogenicity, toxicity, and relevant antimicrobial activity in the mode of action against the target organism.

Information regarding the host range of the micro-organism should be given (if applicable), including information on possible population density of host organisms.

Required information:
All available information on mode(s) of action against the target organism(s) need to be provided. Although it is not needed to identify a single mode of action as most important, available information on the relevative contributions to the efficacy should be provided. The MoA supports the understanding of the intended use and function (in other words, it explains

why the product(s) based on the micro-organism(s) will work against the intended target pest species, when applied at the proposed method, timing, and rate proposed for application). As such, the level of detail that is required should be such that it will provide useful information regarding the mechanism of the MoA(s) on the target organism to facilitate the assessment (e.g. to explain why the product will work and what could be the hazards), but for instance a detailed description of the full molecular understanding will not be required in most cases (a concise summary of the available information may suffice).

The mode of action can be based on pathogenicity, parasitism, the production of compounds that are toxic or have an antimicrobial effect on the target pest, competition for nutrients or space, or the induction of plant defences (list not exhaustive).
The efficacy evaluation (addressed in more detail under P.6, Efficacy data) distinguishes direct and indirect MoAs; this influences extrapolation possibilities and the way the risk of possible development of resistance in the target organism(s) is evaluated. When the MoA is direct, the micro-organism will have a direct effect on the target organism(s), e.g. by pathogenicity, infectivity or parasitism or by the production of toxins or antimicrobial compounds. In contrast, during competition for nutrients or space, or the induction of plant defences, the effect of the micro-organism on the target organism is of an indirect nature. During the induction of plant defences, the micro-organism will trigger a systemic resistance in the plant that is (typically) active against a broad range of pathogens. Hence it is not the micro-organism itself that acts against the target organism but host defences of the plant that are induced by the micro-organism.

Regarding extrapolation, with a direct MoA, the claimed crops are considered of less relevance and extrapolation of data between crops may be possible (taking into account crop morphology, cropping system, application technique, feeding are on the plant etc.). With an indirect MoA, the claimed pest is considered as less relevant and extrapolation to other pests may be possible (taking into account life cycle of the pest, feeding bahaviour etc.). This is well explained in EPPO standard PP1/296(1) on “The principles of efficacy evalution for low-risk plant protection products”. In addition, specific guidance is available for certain MoAs. There is a general EPPO standard for plant protection products with a predominant mode of action as plant defence inducers (elicitors), EPPO standard PP1/319(1). For more information regarding the efficacy evaluation is further referred to P.6 (Efficacy data).

Special attention should be paid to possible infectivity, pathogenicity, toxicity, and relevant antimicrobial activity in the MoA against the target organism (note, these are all direct MoAs) to better understand the risks that should be assessed in other chapters.

Infectivity, pathogenicity, parasitism
When the MoA on the target pest is based on infectivity, pathogenicity or parasitism, it is needed to provide information on the site of infection and mode of entry into the target organism(s), infective dose and susceptible stages of the target organism(s). In addition is referred to point A.2.5 on infectivity to the target organism.

Host range
It is needed to list all known host organisms (including also beneficial interactions) and provide information on possible density of these host organisms, as this will support the indication on natural occurrence of the micro-organism and is relevant for the environmental occurrence of the micro-organism upon application. In case of infectivity and pathogenicity the indicated host range may provide information on the capacity of the micro-organism to infect hosts other than the target or vector (possible risk for NTO).

Toxicity/antimicrobial activity
The production of compounds that have a toxic or antimicrobial effect on the target organisms can be part of the MoA. Here, only the toxic or antimicrobial effect on the **target** organisms will be discussed. In this case, information should be provided on the mode of action of the metabolite and the exposure route (e.g. way of uptake) of the secondary metabolite to the target organism. See also the relevant information on metabolites and MoA in the general introduction (under selection of the appropriate assessment type).

Note that the assessment of metabolites (including those that can be part of the MoA) regarding potentional harmful effects on human and animal health and non-target organisms is discussed in section A.2.8.

A.2.4 Growth requirements

Corresponding data requirement:	(EU) No 283/2013, Annex, Part B, 2.4
Relevant evaluation criterion:	(EU) No 546/2011, Annex, Part B, 1.2.1.5
Relevant decision making criterion:	-
Criteria for approval:	-

Purpose of this point:
The information provided in this section should allow defining limiting factors (e.g. UV light, humidity, pH, temperature, and other relevant agro-environmental conditions) influencing the growth of the micro-organism. The growth requirements of the micro-organism may give an understanding of its physiological needs and thus to its potential occurrence (e.g. distribution, viability, persistence) in the environment. This information is also relevant for test protocols, for example for non-target testing. Moreover, the provided information may give insights on preferential conditions of use to ensure maximal efficacy (e.g. the product should be protected from light or preferably applied under conditions of certain humidity).

Required information:
The conditions required for growth and proliferation of the micro-organism needs to be described. It should for instance be stated wich nutrients are required. Or in case when a host organism is required for production (e.g. for viruses), which host organism. Growth limiting factors (e.g. UV light, humidity, pH, temperature, osmotic potential) should also be described. Often information on growth conditions is known from scientific literature on closely related strains. However, if the information is insufficient, small scale in vitro laboratory tests may be performed to determine the growth conditions of the micro-organism.

The minimum, optimum and maximum temperature required for growth and proliferation shall be reported. This may for instance support the exclusion of an infectivity/pathogenicity potential for human and certain terrestrial vertebrates (e.g. mammals and birds), in case growth at body temperature can be ruled out, as may be the case for psychrophilic (cold-loving) micro-organisms. If the growth temperature data is used as justification (along with other relevant information provided for e.g. point A.2.1., A.2.3 and A.2.6 and data provided for point A.5.1) for non-submission of studies to assess the potential infectivity and pathogenicity of the micro-organism to humans (point A.5.2), the growth temperature study should be carried out under GLP.

The generation time under favourable growth conditions shall be reported. This information is for example relevant for the design and interpretation of tests (e.g., regarding infectivity and pathogenicity).

A.2.5 Infectivity to the target organism

Corresponding data requirement:	(EU) No 283/2013, Annex, Part B, 2.5
Relevant evaluation criterion:	(EU) No 546/2011, Annex, Part B, 1.2.1.3
Relevant decision making criterion:	-
Criteria for approval:	-

Purpose of this point:
In case of a pathogenic mode of action (MoA) to the target organism, the factors that enhance the pathogenicity/virulence of a micro-organism and environmental factors affecting them need to be described. This information will justify the conditions of use (e.g. explain how the product should be applied to ensure maximal efficacy). Moreover, the information will be used for the assessment of risks related to potentional infectivity/pathogenicity towards humans or non-target organisms.

Required information:
In case of a pathogenic mode of action on the target organism (see A.2.3), information on known virulence factors and (if applicable) environmental factors affecting them need to be provided. Virulence factors are factors that enhance the pathogenicity/virulence of a micro-organism. Information may be obtained from experimental studies and/or information from existing literature at the relevant taxonomic level. Please note that information on the infectivity to other organisms than the target organism should be included in either the section on human health (see A.5.3) or the section on ecotoxicology (see A.8).

A.2.6 Relationship to known human pathogens and to pathogens to non-target organisms

Corresponding data requirement:	(EU) No 283/2013, Annex, Part B, 2.6
Relevant evaluation criterion:	(EU) No 546/2011, Annex, Part B, 1.2.1.4
Relevant decision making criterion:	-
Criteria for approval:	-

Purpose of this point:
Information on the relationship of the micro-organism to known pathogens to humans, animals and non-target organisms is fundamental information for the hazard identification in chapters A.5 (humans health) and A.8 (ecotoxicological studies). Any available information on the relationship of the micro-organism to known pathogens to humans, animals, plants, and other non-target species should be described at this point, at the most appropriate taxonomic level.

Required information:
In case the micro-organism is related to any known pathogens to humans, animals, crops or other non-target species, these pathogens and type of disease they caused needs to be listed. Known virulence factors of the listed pathogens should be described and (if relevant) compared to known virulence factors belonging to the micro-organism proposed as active substance. The phylogenetic relationship between the micro-organism and the related pathogens needs to be described. Consequently, this data requirement is strongly related to the datapoint described under A.1.3, as the phylogenetic tree provided there should include all relevant known pathogens described for the current datapoint. The chosen taxonomic level to address this point should be explained (e.g. is information provided on genus level or any

other (mono)phyletic clade). Lastly, the way or means to distinguish the active micro-organism from pathogenic strains and species needs to be clearly described.

A.2.7 Genetic stability and factors affecting it

Corresponding data requirement:	(EU) No 283/2013, Annex, Part B, 2.7
Relevant evaluation criterion:	
Relevant decision making criterion:	(EU) No 546/2011, Annex, Part B, 2.2.1
Criteria for approval (low-risk):	Related to non-target plants: (EC) No 1107/2009 Annex II, point 5.2.2.
Eligible for substantiated waiving:	Yes (see text).

Purpose of this point:
If the micro-organism is a non-virulent variation of a plant pathogen virus, the likelihood of regaining virulence through mutation after application under the proposed conditions of use needs to be discussed. This is needed to assess the hazard of regaining virulence.

Conditional/data waiving:
This data requirement is only applicable for non-virulent isolates of plant pathogenic viruses. Hence, data can be waived for all other other types of micro-organisms.

Required information:
This data requirement is only applicable for non-virulent variants of plant pathogenic viruses (a.k.a mild virus isolates). This specific category of micro-organisms may trigger gene silencing in plants. Gene silencing is a plant defence mechanism. This mechanism will also be effective against more agressive (virulent) isolates (the target organisms). As gene silencing is based on sequence similarities between the two virus isolates, the non-virulent and virulent virus isolates will by default be very closely related. Consequently, the possibility may exist that the non-virulant virus isolate will regain virulence through mutation. To assess this hazard, information should be provided for non-virulent virus isolates on the likelihood of regaining virulence through mutation. This can be done for instance by describing the underlying genetic basis that differentiates the non-virulent virus isolate from the virulent virus isolates. If only a single point mutation is underlying the difference between being virulent or non-virulent, the likelihood of (re)gaining virulence is higher than those cases where the difference is based on frameshifts or complete absence of essential virulence genes in the non-virulent isolate. Information regarding possible risk mitigation measures to reduce the likelihood of this to occur should also be provided.

According to Regulation (EU) No 546/2011, Annex, Part B, 2.2.1, no authorization can be granted for non-virulent virus isolates when the likelihood of (re)gaining virulence and causing adverse effects in target and non-target plants is not neglible (even with possible risk mitigation measures in place).

Regarding low risk criteria, (EC) No 1107/2009. Annex II, (12), point 5.2.2 indicates that non-virulent isolates of plant pathogenic virus can be considered as low-risk substances, unless they have demonstrated adverse effects on non-target plants.

For micro-organisms other than non-virulent isolates of plant pathogenic viruses, information on genetic stability upon application is in principle not required for this data requirement. For bacteria, information on the presence of transferable AntiMicrobial Resistance (AMR) genes

should be provided as discussed under point A.2.9. Genetic stability of micro-organisms before application is considered as part of the quality assurance process during manufacturing (see A.4.1)

A.2.8 Information on metabolites of concern

Corresponding data requirement:	(EU) No 283/2013, Annex, Part B, 2.8
Relevant evaluation criterion:	(EU) No 546/2011, Annex, Part B, 1.2.1.7 (evaluation of metabolites of concern) 1.5 (relevant antimicrobial activity)
Relevant decision making criterion:	(EU) No 546/2011, Annex, Part B, 2.5.1 (effects on human health)
Criteria for approval (low-risk):	-

Purpose of this point: For all micro-organisms except for viruses, information is needed on metabolites which can be produced by the micro-organism. The phrasing of data requirement 2.8 is focused on metabolites of concern; however, it should be noted that in order to be able to identify and list the metabolites of concern, also all information to list the metabolites produced by the micro-organisms and the information to exclude or identify metabolites as being of concern is required.

A summary and conclusion on the assessment of metabolites should be included under the current point (for example in the overview table for the metabolite assessment – see text below). As a result, the information submitted for this datapoint functions as a reading guide for the dossier on the subject of metabolites – without this reading guide it may not be clear why certain information on metabolites is included in other sections of the dossier.

The reports of the underlying studies of the metabolite assessment which provide information on potential toxicity of metabolites and exposure to metabolites should be included and evaluated in the respective sections of the dossier (e.g., human health or ecotoxicology sections). In contrast, the underlying studies on relevant antimicrobial properties of metabolites which may be present in the plant protection product (as referred to in Regulation (EU) No 546/2011, Annex, part B, 1.5) should be included under the current point 2.8 along with their summary and conclusion.

Required information and assessment principle:
Guidance for the assessment of metabolites is given in the guidance on the risk assessment of metabolites produced by micro-organisms used as plant protection active substances (SANCO/2020/12258). The aims of this guidance are twofold: to describe how to exclude or identify metabolites of concern produced by the micro-organism and how to perform a risk assessment for metabolites which are of concern.

Two hazards may apply to metabolites produced by micro-organisms: toxicity and relevant antimicrobial activity (for the latter, please see the definition as provided in the introduction of Part B in Annex II of Regulation (EU) No 283/2013). The outcome of the metabolite assessment as presented for this point in the dossier should include an outcome for each metabolite which either excludes the metabolite as being of concern or which identifies the metabolite as being of concern.

To be able to exclude the production of metabolites of concern by the micro-organism or to perform a risk assessment in case the micro-organism does produce a metabolite of concern, the appropriate information should be included in the dossier. The guidance document therefore provides a step-by-step approach which describes which information is needed for the assessment and how this assessment can be performed. Please note that the approach described in the guidance document should not be seen as a fixed route that should be followed for each metabolite of each micro-organism: depending on the specific situation another approach may be more appropriate.

It should be noted that it is expected that in most cases the assessment of metabolites will lead to the conclusion that no metabolites of concern are produced. In those cases where metabolites of concern are identified for a microbial active substance, as a general rule it is expected that these metabolites will be present in the MPCA-AM due to production during the fermentation process.

For the sake of efficiency and harmonisation of the assessment of metabolites, it is highly recommended to use the template for the overview table for metabolites as provided in 'Appendix I to EM Biopesticides Part 1: Microorganisms – Roadmap for SANCO/2020/12258' (separate document).

Relevant antimicrobial activity
The definition of a metabolite of concern as provided in Regulation (EU) No 283/2013 includes 'known relevant antimicrobial activity'. In turn, relevant antimicrobial activity is defined as being caused by relevant antimicrobial agents which are included either in the WHO list of medically important antimicrobials or in an EU list of antimicrobials reserved for the treatment of certain infections in humans. Furthermore, in the Guidance for the assessment of metabolites information is given on when the production of relevant antimicrobial agents by micro-organisms used in plant protection products are considered to be a foreseeable risk: relevant antimicrobial agents are only considered to be a foreseeable risk when they are present in detectable amounts in the formulated product (see page 6 of the introduction of the guidance and Step 14) leading to expected environmental concentrations above the LOQ under realistic conditions of use.

When analyses are performed to exclude the presence of detectable amounts of relevant antimicrobial agents in the product, the relevance of these analyses should be justified based on available information on which antimicrobials may be produced by the micro-organisms .

A.2.9 Presence of transferable antimicrobial resistance genes

Corresponding data requirement:	(EU) No 283/2013, Annex, Part B, 2.9
Relevant evaluation criterion:	(EU) No 546/2011, Annex, Part B, 1.2.1.8
Relevant decision making criterion:	(EU) No 546/2011, Annex, Part B, 2.2.1
Eligible for substantiated waiving:	Yes (see text).

Purpose of this point:
Bacteria may have the potential to transfer anti-microbial resistance genes to bacteria which are pathogenic to humans, potentially affecting the effectiveness of antimicrobials used in human or veterinary medicine. Due to this hazard, bacteria can only be approved if it is concluded that they do not have any known, functional and transferable genes coding for resistance to relevant antimicrobial agents.

Conditional/data waiving:
This data requirement is only applicable for bacteria. Information may also be relevant when a bacterium is used in the manufacturing process of the active substance as manufactured (e.g., in the case of bacteriophages).

Assessment principle:
The assessment of antimicrobial resistance is described in three main steps:
- Whole Genome Sequencing (WGS) data screening
- Phenotypic testing
- Decision making

Whole Genome Sequencing (WGS) data screening
In accordance to the Guidance on the approval and low-risk criteria linked to "antimicrobial resistance" applicable to micro-organisms used for plant protection in accordance with regulation (EC) No 1107/2009 (SANTE/2020/12260), WGS data should be screened for the presence of genetic material known to encode for, or contributing to, resistance to antimicrobials (AMR genes) relevant for use in humans and animals (MIAs). Regarding WGS data generation, the EFSA statement on the requirements for while genome sequence analysis of micro-organisms intentionally used in the food chain should be taken into consideration (EFSA Journal 2021; 19(7):6506, 14 pp.). This document also provides information regarding the percentage of sequence identity and sequence length that can be used as threshold (also see 'Introduction to general concepts and principles of the risk assessment of microbial PPP' for further information regarding the use of WGS data).

According to the guidance document on AMR, screening for AMR genes should be done against at least two up-to-date and curated international databases (see for examples the guidance document itself). If the WGS screening identifies a hit for an AMR gene, this should be phenotypically investigated. In addition, it should be investigated whether this AMR gene is located on a mobile genetic element (MGE), and thus is transferable. This latter may be done by looking at the neighbouring sequences. For instance, if the neighbouring sequence is derived from plasmid DNA, the AMR can be considered transferable (note that this underlines the importance of including plasmid DNA during WGS assembly). Other MGE are described in a review by Partide et al., 2018 (as indicated by the guidance document on AMR): Partide et al., 2018; Clin. Microbiol. Rev. 31 (4): e00088-17. Information regarding the functionality of AMR genes may be gained from frameshifts, deletions or preliminary stop codons, in combination with phenotypic testing.

Phenotypic testing
Information on the micro-organisms resistance or sensitivity to antibiotics or other antimicrobial agents must be provided by performing phenotypic testing based on determination of a minimum inhibitory concentration (MIC) for a selected group of antimicrobials. European Committee on Antimicrobial Susceptibility Testing (EUCAST) and the EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) defined MIC breakpoint values for different micro-organism species based on published data. In case no MIC breakpoint values are available for micro-organisms EUCAST proposes different approaches to determine which breakpoint value can be used for these micro-organisms in the guidance document: Antimicrobial susceptibility tests on groups of organisms or agents for which there are no EUCAST breakpoints (2021)[12].

[12] See EUCAST Guidance 'Antimicrobial susceptibility tests on groups of organisms or agents for which there are no EUCAST breakpoints'.

Phenotypic susceptibility for at least two antimicrobial agents with different modes of action has to be demonstrated for bacteria and fungus to ensure treatment options in any case of opportunistic infection (see A.5.1).

Please note that all experimental data for the assessment for human and animal health should be GLP-compliant as laid down in Annex I of Regulation (EU) No 283/2013; this includes experimental data on phenotypic susceptibility and the analytical phase of WGS analyses.

Interpretation of the framework in specific cases

Bacteriophages
Although the data requirements on the presence of AMR genes only explicitly mention bacteria, information may be needed also in other cases where bacteria are involved in the production of the active substance. This is for example the case for bacteriophages, as the production of bacteriophages depends on using bacterial hosts. Therefore, to rule out the spread of AMR genes by horizontal gene transfer (HGT) by bacteriophages, the genome of the bacterial hosts used in production for AMR genes can be screened. This is also indicated in a recent published OECD guidance document for bacteriophages "Guidance Document for the Regulatory Framework for the Micro-organism Group: Bacteriophages, Series on Pesticides **No. 108,** ENV/CBC/MONO(2022)40."

A.3 FURTHER INFORMATION

The information required in this section mainly concerns efficacy information for the active substance. In addition, the information on the literature search(es) performed for the micro-organism and its metabolites should be included in this section.

A.3.1 Function and target organism

Corresponding data requirement:	(EU) No 2022/1439, ANNEX II, Part B, 3.1
Relevant evaluation criterion:	See for relevant evaluation and decision making criteria P.3.3 where information regarding the target organism(s) is discussed in more detail.
Relevant decision making criterion:	
Criteria for approval	

Purpose of this point:
To provide information on the disease or target organisms against which protection is afforded.

Assessment principle:
(EU) No 283/2013 , ANNEX II, Part B, 3.1 lists the following biological functions:
- control of bacteria,
- control of fungi,
- control of viruses,
- control of insects,
- control of mites,
- control of molluscs,
- control of nematodes,
- control of plants,
- other (needs to be specified)

Under “other” for example micro-organisms that act as defence inducer (a.k.a. elicitors) can be listed. For more information regarding micro-organisms that act as defence inducers, please see A.2.3.

Although the title encompasses both function and target organism, information on the specific target organisms for proposed uses should be included at product level (see (EU) No 283/2013, Annex, Part B, 3.3 (Function, target organisms and plants or plants products to be protected and possible risk mitigation measures).

A.3.2 Field of use envisaged

Corresponding data requirement:	(EU) No 283/2013, Annex, Part B, 3.2
Relevant evaluation criterion:	-
Relevant decision making criterion:	-
Criteria for approval	-

Purpose of this point:
The indication of the field of use of the plant protection is used to assess the relevance of the information on the efficacy for the proposed use and to determine the appropriate exposure scenario for the risk assessments for humans, animals and the environment.

Assessment principle:
The field(s) of use, existing (if relevant) and proposed, for the micro-organism can be specified from among the following:

- agriculture, horticulture, forestry, or viticulture,
- protected crops (e.g. in greenhouses)
- non-cultivated areas,
- home gardening,
- houseplants,
- stored food/feed items,
- seed treatment,
- other (needs to be specified).

If amateur/non-professional use is intended (whether or not in addition to professional use), this should be clearly indicated.

Interpretation of the framework in specific cases

Protected crops
For protected crops the type of protection should be indicated (e.g. greenhouse, walk-in tunnel, shade house). Different types of protected structeres are described in the “EFSA Guidance Document on clustering and ranking of emissions of active substances of plant protection products and transformation products of these active substances from protected crops (greenhouses and crops grown under cover) to relevant environmental compartents” EFSA Journal 2014; 12(3):3651. In addition to the type of protected structure, the growing system should be indicated (soilbound versus soil-less). This information is used to determine the exposure scenarios of humans and the environment for the risk assessment.

A.3.3 Crops or products protected or treated

Corresponding data requirement:	(EU) No 283/2013, Annex, Part B, 3.3
Relevant evaluation criterion:	-
Relevant decision making criterion:	-
Criteria for approval	-

Purpose of this point:
The details of existing or intended use(s) in terms of crops, groups of crops, plants or plant products protected is not only used for the efficacy assessment, but also for the risk assessment as it provides information on the exposure of humans and the environment to the micro-organism.

Assessment principle:
The crops, crop groups, plants or plant products for which protection is claimed should be clearly indicated. This information is needed for the efficacy assessment, but also to determine the correct exposure scenario for risk assessments for human health and the environment. To avoid mis-interprettion of ambigious terms (e.g. ornamentals can encompass different plant groups in different member states) it is advisable to also include the relevant EPPO codes and scientific names.

A.3.4 Information on possible development of resistance in the target organism(s)

Corresponding data requirement:	(EU) No 283/2013, Annex, Part B, 3.4
Relevant evaluation criterion:	Here only the inherent properties of the micro-organism to trigger the development of resistance in the target organism(s) is discussed. For the full resistance risk assessment is referred to P.6.4.
Relevant decision making criterion:	
Criteria for approval	

Purpose of this point:
Information on the possible development of resistance in the target organism(s) is needed to assess whether a lasting efficacy of the micro-organism used in the plant protection product(s) is ensured. Please note that for the current data requirement, only the inherent properties of the micro-organism to trigger the development of resistance in the target organism(s) is discussed; the resistance risk assessment which is performed at product level is described in P.6.4. If there is a risk on development of resistance in the target organism(s), it is essential that the likelihood of resistance developing in target species will be minimised by relevant resistance management strategies. Any relevant resistance management strategies that are deemed appropriate need to be included under this point (if applicable).

Assessment principle:
PPPs based on micro-organisms often have novel modes of action that do not show cross-resistance with existing products. As such they can offer advantages to resistance management. However, pests or pathogens may develop resistance to certain micro-organisms. In these cases, resistance management needs to be addressed. In some cases target organisms may have developed resistance to some strains of a micro-organism, but not to other strains of the same species (e.g. resistance to baculoviruses is isolate specific). This differs from conventional PPPs, where often cross-resistance exists between many active substances. If there are indications of occurrence of resistance against the target organism(s) caused by the strain/isolate of the micro-organism under evaluation, it will be determined,

considering the information provided for the representative product or product to be registered, which resistance management strategies can be used to reduce this risk.

Based on available information from scientific peer-reviewed literature or other reliable sources of information on the possible occurrence of the development of resistance of cross-resistance of the target organism(s), the risk that the inherent properties of the micro-organism will result in the development of resistance in the target organism(s) is assessed. Combined with the information provided for the representative PPP (described under P.6.4), the risk is classified as low, medium or high and if resistance management strategies should be in place. If it is anticipated that resistance management strategies will be deemed necessary, these should be described (where possible).

Resistance risk depends for a large part on the MoA (see also the information provided under A.2.3). Therefore, it is important to clearly describe the MoA. As stated in the EPPO standard PP1/276(1) on the "Principles of efficacy evaluation for microbial plant protection products", micro-organisms with an indirect MoA (e.g. host plant defence induction or competition for nutrients) are often not at risk of inducing resistance development in target organisms. This is because there is no direct selection pressure on the target organism. In such cases this data point may be addressed with a justification. Micro-organisms with a direct MoA on the target organisms (e.g. pathogenicity, parasitism, or the production of toxins or antimicrobial compounds) can be at risk of inducing resistance development in the target organism, and several such cases are known from practice (for instance in the case of baculovirus resistance). In these cases, the EPPO standard PP1/213(4) on "Resistance risk analysis" should be followed during product registration (further discussed under point P.6.4). For the present data point (A.3.4), known cases of resistance in target organisms, preferably with references to scientific literature, can be described (if relevant).

It should be noted that not all micro-organisms are listed yet in the MoA classification systems set up by the Fungicides Resistance Action Committee (FRAC) or Insecticide Resistance Action Commitee (IRAC). Currently the FRAC Code List 2022® lists microbial elicitors (P 06), and several strains of micro-organisms under Biologicals with multiple modes of action: Microbial (consisting of living microbes, extracts or metabolites)(BM 02).

Micro-organisms in IRAC include group 11 (microbial disruptors of insect midgut membranes, e.g. *Bacillus thuringiensis*), group 31 (baculoviruses), and UNB (bacterial agents (excluding Bt) of unknown or uncertain MoA) and UNF (fungal agents of unknown or uncertain MoA).

The Herbicide Resistance Action Committee (HRAC) currently does not include micro-organisms.

A.3.5 Literature data

Corresponding data requirement:	(EU) No 283/2013, Annex, Part B, 3.5
Relevant evaluation criterion:	-
Relevant decision making criterion:	(EU) No 546/2011, Annex, General introduction, 3.10
Criteria for approval	-

Purpose of this point:
Together with the correct identification of the micro-organism at species level, literature data form the basis of the dossier. The information on the literature searches performed to

retrieve the relevant literature data should be included at the current point.

Assessment principle:

The literature search should be carried out in accordance with the EFSA Guidance on the submission of scientific peer-reviewed open literature (EFSA Journal 2011; 9(2): 2092) and the summary of the search included at the current data point. Literature retrieved from this search should be reported in the relevant sections of the dossier (e.g., see A.2.8 for information on metabolites, A.5 Effects on human health and A.8 Ecotoxicological studies).

Additional guidance, including further considerations for literature searches performed for microbial active substances and PPP, is given in the Appendix of the above mentioned guidance 'Further guidance on performing and presenting the literature search'. This document also includes a template for presenting the outcome of the peer-reviewed open literature search in DARs/RARs (see Appendix to Literature GD).

In addition to the species name of the micro-organism, the search terms should include any previous names given in the 10 years prior to dossier submission. Likewise, in case of alternative names for the micro-organisms these should be included (see A.1.3).

As indicated by the Metabolite guidance, additional searches are needed for metabolites of potential concern to determine if these metabolites have known toxic or antimicrobial properties. Please note that these searches should not include the name of micro-organism in the search terms, as information on a specific metabolite produced by a different species should also be retrieved. Please refer to point A.2.8 for more detailed information regarding the literature search for the risk assessment of metabolites produced by the micro-organism.

Should the dossier be making use of read across between different species because of similar biology or other traits / factors, then a systematic search for that other species should in principle be included at least in relation to the property for which read across is proposed. This is needed to ensure all relevant information on this property is included.

Applicants and RMS should also make use of the systematic literature reviews that EFSA procured and published (Mudgal *et al.*, 2013[13], Hackl *et al.*, 2015[14]) ensuring publications identified there have been considered in the dossier. The search strategies reported in these two references may be helpful to determine the appropriate search strategy (including search terms) for the micro-organism.

Please note that with regard to ecotoxicology, the literature search should be conducted encompassing all trophic levels, as listed in the data requirements. For example, the search strategy should include the micro-organism at species level, including infectivity and pathogenicity (and adverse effects), birds, mammals, reptiles, amphibians, fish, daphnia, bees, pollinators, arthropods, biological control. Effects on algae, aquatic and terrestrial plants should be included for the organisms that are closely related to plant pathogens or with known herbicidal mode of action. Please also note that in some situations the search strategy might need to be adapted, for instance to the nature or mode of action of the microorganism or the genus level be included.

Scientific peer-reviewed literature which is relied on for the dossier, should be presented in the dossier at the relevant sections using the format indicated in Appendix E of EFSA's Administrative Guidance.

[13] Mudgal, S; De Toni, A; Tostivint, C; Hokkanen, H; Chandler, D. EFSA Supporting Publications 2013:EN-518.
[14] Hackl, E; Pacher-Zavisin, M; Sedman L.; Arthaber, S; Bernkopf, U.; Brader G; Gorfer, M; Mitter, B; Mitropoulou, A; Schmoll, M; Van Hoesel, W; Wischnitzky, E; Sessitsch, A. EFSA Supporting Publication 2015:EN-801.

1. Information on the study

Data point	xxxx
Report author	xxxx
Report year	xxxx
Report title	xxxx
Report No	xxxx
Document No	xxxx
Guidelines followed in study	xxxx
Deviations from current test guideline	xxxx
Previous evaluation	xxxx
GLP/Officially recognised testing facilities	xxxx
Acceptability/Reliability:	xxxx

2. Full summary of the study according to OECD format

Abstract: xxxx

3. Assessment and conclusion

Assessment and conclusion by RMS:

xxxx

A.4 ANALYTICAL METHODS

A.4.1 Methods for the analysis of the MPCA as manufactured

Corresponding data requirement:	(EU) No 283/2013, Annex, Part B, 4.1
Relevant evaluation criterion:	(EU) No 546/2011, Annex, Part B, 1.4.1
Relevant decision making criterion:	(EU) No 546/2011, Annex, Part B, 2.4.1
GLP-compliance:	Not required for method validation

Purpose of this point:
Methods for analysis of the MPCA-AM, used (i) to verify the identity of the micro-organism as unequivocally belonging to a certain species, (ii) to distinguish the micro-organism from other strains / isolates, (iii) to check any genetic variability of the micro-organism and its seed stock, (iv) to determine the content of the micro-organism, claimed active metabolites, and any MoCs and relevant impurities established for the MPCA-AM, and (v) to detect possible contaminating micro-organisms, must be evidenced to be sufficiently specific, linear, accurate, and precise – whichever criterion is relevant for the respective method – to serve their purpose.

Conditional / waiving
Not relevant.

Confidentiality
Confidentiality can be claimed for methods that allow identification and detection of the MPCA at strain level. Furthermore, the WGS-data relating to the MPCA may be confidential.

Evaluation principle

MPCA IDENTIFICATION METHODS

(a) Methods for the characterisation of the micro-organism
The method which is used for characterisation of the micro-organism at species level shall be described (see A.1.3 (ii)). As a rule, this method is not the same method used to determine if a microbial sample contains the micro-organism under assessment. Additionally, the analytical methods used for building the phylogenetic tree (see A.1.3 (iv)) shall be described.
The provided methods must be evidenced to be capable of verifying the results obtained for the identification of the micro-organism at species level and for establishing the position in the submitted phylogenetic tree.

(b) Methods for unequivocal identification of the micro-organism
A method shall be provided for identification at strain level, based on unique genotypic or phenotypic markers or a combination thereof to distinguish the strain from other strains belonging to the same species.

(c) Methods for providing information on possible variability of seed stock / MPCA and its storability
The data detailing the manufacturing process must include a full description of quality assurance measures, regarding e.g., validation, maintanance and storage conditions of the seed stock, drawing from the seed stock to initiate manufacturing, viability, and contamination checks during manufacturing. Taken together, the precautionary steps must reasonably suffice to maintain purity of the produce.

To limit variability, for micro-organisms it is often essential to generate sufficient aliquots of the master seed stock, stored in such a way that, while remaining viable, the micro-organism will not multiply. Frequent subcultering may result in genetic or epigentic changes which may lead to loss of activity (e.g. due a reduced production of virulence factors).

Here, storability is interpreted as the ability of a microbial active substance to maintain its viability over a longer period at which it is stored in certain packaging at a practical temperature. The required analytical methodology is the same as that described under A.4.1, ‘Quantitative methods to determine the content of specification elements in the MPCA-AM’. The context of storage stability testing is furthermore described in detail under P.2.6.2.

(d) Methods to differentiate a spontaneous or induced mutant from the parent wild strain
In case the micro-organism is a mutant (either spontaneous or induced) it is essential that the mutant strain can be distinguished from its original parental wild type strain. A method should be provided for this.

This point is only relevant when the micro-organism is a mutant. This can either be a spontaneuous mutant (e.g. picked up in the laboratory during subculturing) or an artificially induced mutation (e.g. by exposure to radiation or a chemical mutagen). Lastly, the mutant may be genetically modified (in which case Directive 2001/18/EC should be considered, as discussied previously under point A.1.3).

This point is not related to the one above that considers possible variability of seed stock. Whereas possible variability of seed stock is considered unintentionally, the difference between the mutant micro-organism and the parential wild type strain is purposefully provoked. The mutant may for instance have slightly different biological properties compared

to the wild type strain, making the mutant more suitable for the use as PPP. According to A.1.3, both the genetic and biological differences between the mutant and the parental strain should be explained. The method provided here should be able to differentiate the mutant strain from the parental wild type strain. While a molecular method based on (any of the) genetic difference may be the most obvious method, alternative methods may be acceptable. But note that under A.1.3, it will be still required to list all known genetic differences between the mutant and the wild type strain.

(e) Methods for the establishment of purity of seed stock
Please refer to point *(c)*.

QUANTITATIVE METHODS

(f) Methods to determine the content of the MPCA and methods to detect relevant contaminating micro-organisms
The choice of method to quantify the MPCA depends on how its activity is best expressed. Below, the two main approaches to quantify the content of the MPCA and/or its activity are presented. Other methodologies for MPCA-quantification exist (e.g., qPCR), but have, to our knowledge, not yet been employed within the context of active substance approval. Therefore, no framework-dedicated validation criteria have yet been established for such methods. This point concludes on screening methods for relevant contaminating micro-organisms.

MPCA enumeration methods – Bacterial and fungal spores, and virus particles[15] are generally counted in a counting chamber (hemocytometer).
Colony-forming MPCAs whose activity relies on their viability can be enumerated by plating on an appropriate type of nutrient agar, and subsequent incubation and colony enumeration. Conversely, bacteriophages are counted by the purged areas, or plaques, that they leave when incubated on a plate colonized by their target bacterium.
Currently, there is no formal guidance on validation criteria for these methods. Regulation (EU) No 283/2013, Part B, Section 4 states the universal validation parameters, i.e., specificity, linearity, accuracy, and precision, but leaves the actual acceptance thresholds undefined. Methods that have been validated according to SANCO/3030/99, at least for linearity and precision, are commonly encountered. The document is however intended for evaluation of analytical chemistry methods, and is less suitable for the microbiological methods discussed here. Nevertheless, as the SANCO/3030/99-criteria are on the strict side for the microbial context, compliance automatically means acceptability for enumeration methods, again, at least with regard to linearity and precision.
To provide a degree of systemization, the following pragmatic rules may be considered until a micro-organism-dedicated guideline has been adopted:

- *Specificity:* the morphological characteristics based on which the MPCA-colonies are identified during counting must be described. These characteristics must be sufficiently distinctive to recognize the MPCA among any consorts, whenever relevant.
  For the plaque-forming bacteriophages, that are approved as consortium by definition, isolate-by-isolate differentiation may not be possible. These MPCAs are preferably enumerated in single-isolate solutions;
- *Linearity:* the hemocytometer -and plate count range of a single sample roughly covers a factor of 10 (typically 30 – 300 per (plate) area). Given this limited broadness,

[15] Often, expressing the MPCA in terms of spores or virus particles per g or L of matrix may not be the most accurate way in relation to activity. Still the spore content may be a useful metric in the context of quality control (see A.1.5.1, 'The essential process checkup' for a note on this). Moreover, especially for viruses, the virus particle content is commonly required for a meaningful expression of dosing levels (e.g. in virus particles per g of diet). See 'Bioassays' in this subsection for more details.

triplicate counts at three dilution levels (typically a factor of three apart) are advised. A linearity plot and regression equation must be presented, along with the coefficient of determination r^2. Acceptability is assessed based on fit for purposeness;

- *Accuracy:* a possibly critical feature affecting the method's accuracy is the dilution chain. As enumeration procedures often include five to seven subsequent dilution steps, the cumulative error introduced by inhomogeneous distribution of the micro-organism in the increasingly diluted matrix could be substantial. To gauge the extent of this error, mostly for MPCA-AMs that are expected to suffer from inhomogeneity based on their physical appearance, it may be useful to prepare a final dilution by consistently drawing material from the lower tenth of the vessel in which the dilution series is prepared, whereas the other is produced by sampling the upper tenth during every step. Both synchronous measurements should be performed three times.
- *Precision:* Precision data must include at least 5 independent determinations performed at the same dilution. The mean, %RSD, and number of determinations must be reported. Precision criteria may be adopted from ISO -or EN-standards that are appropriate with regard to species and matrix. If none are available, acceptability is assessed based on fit for purposeness.

MPCA biopotency assays – Limited by practicality, specifications can do little more than capture a rough abstraction of the multifaceted reality of an MPCA's efficacy. Bioassays provide a middle ground between the oversimplification inherent in the expression of virus particles or colony formers per matrix quantity and the complexity surrounding their actual activity in the field.
Similar to dose-effect testing for toxins, a bioassay includes exposure of test organisms to a range of MPCA levels, plotting of response against dose, and subsequent derivation of a median lethal dose (LD_{50}). Currently, tests are far from being standardized, which limits the evaluation efficiency. Furthermore, test outcomes are reported in various ways, often non-intuitive and difficult to untangle. To promote standardization of the evaluation, and the derivation of better-referenced and more communicable metrics, the following points should be considered:

- First, it is important to have the test batch characterized in a way that is meaningfully related to the observed effect. Based on this information, subsequent exposure concentrations can be expressed in terms of the actual component causing lethality in the test organism per unit of feeding medium (e.g., as 'mg of δ-endotoxin' or 'virus particles', instead of the unnecessarily inaccurate 'mL of product', per gram of exposure medium).
- The amount of dosing matrix (e.g., diet material, water) to which the organism is actually exposed must be a non-negligible fraction of the total of prepared matrix, in order to minimize bias due to the invariably inhomogeneous distribution of the MPCA in the matrix.
- Next, the test species should be justified. Ideally, it is the species for which a biopotency minimum has been established in the specification. The tests must be performed with healthy individuals.
- The test must at least include five separate dosing groups, with a concentration difference of about 0.5 log units between neighbouring groups. A sixth group will be the control and receives unspiked exposure medium. The number of individuals per group should account for the overall variability in test performance, and needs to be justifiable from a statistical point of view.
  Ideally, the LD_{50} coincides with the group in the middle, mortality in the lowest and highest dose groups, and the control group is about 15, 90, and 10 %, respectively. Preliminary range finding experiments should help optimizing the test design.
- The test report should present the raw data, and sufficient details of the data analysis.

Probit analysis could be regarded as default, but other statistical operations may be warranted. The median LD_{50} and the 99 % confidence interval limits must be reported. By rule of thumb, a lower limit of 0.5 x LD_{50}, and an upper limit of twice the LD_{50} is amply acceptable, whereas a factor of > 9 difference between the upper and lower limit suggests poor data quality.

- As an internal performance check, the test item is preferably compared with a reference item – often a benchmark batch of the microbial active substance itself – that undergoes synchronous testing. In these cases, resulting biopotency, reflected by the LD_{50}, is commonly presented as *relative* biopotency, i.e., LD_{50} (reference item) / LD_{50} (test item). An important criterion for a reference item is that, under well-controlled circumstances, it presents as little variation in performance as possible. To evidence this, supporting data should be made available that show a workable degree of consistency in the reference item's LD_{50} over multiple standard test runs, if possible over a timespan of several years.

Contaminating micro-organism screening methods – Beside safe limits and context-dependent information on relevant contaminating species, SANCO/12116/2012 – rev.0 provides guidance on recommended methodology. Having drawn its inspiration from food/feed-legislation, the document typically advises use of internationally standardized reference methods (e.g. FDA BAM, USDA MLG, AOAC, and ISO), commonly employed in screening of food and feed. Whereas the recommended methods still only include the more traditional plating methods that were the norm at the time of drafting, the EU food/feed-framework has evolved in the meantime to allow the use of more innovative, alternative methods – mainly through translational standard ISO 16140-2, that validates alternative methods against reference methods.
To be able to benefit from more advanced methodology within the PPP-context as well, alternative methods that are ISO 16140-2 -or AOAC-certified[16] are acceptable. Of course, internationally recognized reference and alternative methods require no further validation within the context of an approval dossier.
Relatively recently, the Competent Authority has seen initiatives for setting up screening methods that are distinctly PPP-dedicated and therefore explicitly depart from the existing food law-related certification context. Though there is a solid rationale to encourage such developments, safe implementation of such 'non-certified alternative methods' requires PPP-specific reinterpretation of ISO 16140-2 criteria to ensure fitness for purpose in terms of e.g., test design, matrix preparation, inclusivity, and sensitivity[17].
By definition, validation of such methods is extensive and typically takes place outside of the dossier context. As such, validation of contaminating micro-organism screening methods is not covered by the assessment systematic described in this EM.

(g) Methods for the determination of relevant impurities, metabolites of concern, and additives
Below, the approaches to quantify specification elements with a chemical nature are presented.

Chromatographic methods – When claimed active metabolites, additives, MoCs, and relevant impurities are compatible with conventional chromatographic methods, validation must be compliant with the criteria set out in SANCO/3030/99 – rev.5.
An issue that may be especially problematic for MoCs, is the potential unavailability of

[16] Within the EU food framework, non-standard screening techniques are validated against translational criteria (such as those in ISO 16140-2) and, in case of successful validation, certified by designated normalization bodies (e.g., Afnor, AOAC, or NordVal).
[17] Definition of PPP-dedicated criteria is currently in progress.

analytical standards. Since purification or synthesis of the MoCs are not deemed realistic due to the disproportionate investments involved, alternative approaches are considered by default. Often, the use of structurally similar chemicals is advised in these cases – if suitable candidates may be found in the first place given the complex molecular of most secondary metabolites). This approach is however debatable, as the representativeness of a substitute standard does not depend on its structural similarity, but rather on the agreement between its RRF[18] and that of the actual metabolite. The availability of reliable RRFs for substances for which no analytical standards are obtainable depends heavily on how intensively the substances have been studied. Custom *in silico* methods have shown promising results in specific contexts, but their success in dealing with complex molecular structures and their applicability for the purpose of dossier drafting may (yet) be limited.
In summary, finding a substitute that may perform well enough is likely to present a challenge due to the highly specialized nature of the investigation involved.
To conclude on a pragmatic note, the metabolite assessment process (see Appendix I to EM Biopesticides Part 1: Microorganisms – Roadmap for SANCO/2020/12258' (separate document)) requires quantitative data at a stage in which it has already been largely established whether a given metabolite will be of concern or not. Based on the context presently available, only a small minority of metabolites is expected to be assigned an MoC-status. In the majority of cases, quantification of metabolites will therefore not be required in the first place. For the extreme cases where a MoC has been established for which no analytical standards are available, method accuracy may be deemed secondary to method conservativeness. In other words, a substitute standard must simply have an RRF that is lower than that of the MoC (for monitoring purposes) or higher (for (eco)tox-testing) – which should be easier to address than seeking substances with matching RRFs.

Other methods – Chromatographic methods may not be compatible with any conceivable specification element with a chemical nature, like e.g., relatively large proteins that rather necessitate the use of other methods, such as SDS-PAGE. As no dedicated guidelines are yet in place, the method evaluation will focus on the universal quality criteria, i.e., specificity, linearity, accuracy, and repeatability, stated in (EU) No 283/2013, Part B, Section 4.

A.4.2 Methods to determine the density of the micro-organism and quantify residues

Corresponding data requirement:	(EU) No 283/2013, Annex, Part B, 4.2
Relevant evaluation criterion:	(EU) No 546/2011, Annex, Part B, 1.4.2
Relevant decision making criterion:	(EU) No 546/2011, Annex, Part B, 2.4.2
GLP-compliance:	Not required for method validation

Purpose of this point:
The method used to determine and quantify the density of the MPCA is required for human toxicology and ecotoxicology studies. Methods for analysis of residues may be required for risk assessment of the MPCA and/or MoCs in relevant crops, foodstuffs, feeding stuffs, animal and human tissues and fluids, and environmental matrices. Any monitoring methods that may be required for MoCs must be sufficiently simple, cheap, robust, and sensitive.

Conditional / waiving
Not relevant.

[18] The RRF (relative response factor) of a substance is the ratio between the abundance of that substance (i.e., its peak area or height) and its concentration in a respective sample. The factor is mainly a resultant of ionization efficiency, and to a lesser degree of matrix effects and ion transport.

Confidentiality
Not relevant.

Evaluation principle

METHODS TO QUANTIFY THE DENSITY OF THE MICRO-ORGANISM IN RELEVANT ENVIRONMENTAL COMPARTMENTS
In case experimental data is required for the risk assessment under Point 7.1.4 of the Annex Part B of Regulation (EU) No 283/2013 or to provide information on the density of the micro-organism to support the estimation of exposure to residues (see Point 6.1 of the Annex Part B of Regulation (EU) No 283/2013) a method to quantify the density of the micro-organism in the relevant environmental compartments (e.g., edible part of crop, soil, plant surfaces) is needed. A description of these methods (including for example sampling strategy, extraction of nucleic acids, PCR-protocols) should be provided.
Methods for post-approval monitoring of the density of the micro-organism (viable residues) are in principle not needed. Indeed, for none of the currently approved microbial active substances monitoring definition has been set (nor for viable residues, nor for metabolites of concern). If methods to quantify viable residues would be required, no guidance is available. Until such guidance is available, methods will be evaluated on a case-by-case basis.

METHODS TO QUANTIFY RESIDUES OF METABOLITES OF CONCERN
When pre- or post-approval methods are required to quantify metabolites of concern, criteria for method validation are available (see SANTE/2020/12830 – rev.1).

A.5 EFFECTS ON HUMAN HEALTH

Scope
As mentioned in Regulation (EU) No 283/2013, the information provided by the applicant should be sufficient to:

'— Permit a decision to be made as to whether or not the micro-organism is to be approved,
— specify appropriate conditions or restrictions to be associated with the approval,
— specify risk and safety phrases for the protection of human and animal health and the environment to be included on packaging (containers),
— identify relevant first aid measures as well as appropriate diagnostic and therapeutic measures to be followed in the event of infection or another adverse effect in humans.'

The hazards related to the use of micro-organisms in plant protection products are different to those of chemicals. In addition to the potential hazard related to the toxicity of metabolites produced by micro-organisms, micro-organisms may have the potential to cause infection or pathogenicity in humans, which must be carefully assessed and excluded. They may also have the potential to cause sensitising reactions and non-specific effects such as an inflammatory response after exposure via inhalation. To assess these hazards of a micro-organism the scientific knowledge on the biology of micro-organisms should be taken into account.

According to the amended uniform principles (Regulation (EU) No 546/2011, Annex, part B, 1.5., SANTE/ 10716/2021) the most important aspects that shall be assessed are:

'— infectivity and pathogenicity;

— toxicity of metabolites of concern, safeners, synergists, and relevant impurities;

— relevant antimicrobial activity of metabolites present in the plant protection product;

— susceptibility to relevant antimicrobial agents to ensure the availability of sufficient treatment options in case of an opportunistic infection.

These aspects comprise a complex set of interactions between micro-organisms and the hosts, and need to be assessed in an integrated way and applying a weight of evidence approach.

An assessment of infectivity and pathogenicity is always necessary.'

This assessment of infectivity and pathogenicity is described in the current chapter (A.5). Information on the other effects on human health are either included in the current chapter, or in other chapters as indicated below. The susceptibility to relevant antimicrobial agents to ensure the availability of sufficient treatment options in case of an opportunistic infection is described in A.5.1 and A.2.9. The assessment of infectivity and pathogenicity is described in A.5.2 to A.5.4 and toxicity of metabolites and whether they are of (potential) concern is described in A.5.5. The quantitative exposure assessment for metabolites of concern is described in chapter A.6 and P.7. Identification of metabolites of potential concern produced by the micro-organism and the assessment of relevant antimicrobial activity of metabolites present in the plant protection product is described in A.2.8. The information on toxicity of co-formulants as e.g. safeners, synergists and impurities is described in chapter P.7.6.

Literature search
According to the Annex I Introduction to Regulation (EU) No 283/2013, all available relevant data from the scientific peer reviewed and open literature on the micro-organism should be provided. Please refer to A.3.5 for further information on the literature search.
The literature search on metabolites relevant for human health is discussed in A.5.5 and should be based on the 'Guidance on the risk assessment of metabolites produced by micro-organisms used as plant protection active substances, SANCO/2020/12258'.

Hazard testing
Although it is stated that an assessment of infectivity and pathogenicity is always necessary, it is important to realise that a weight of evidence approach can be sufficient to address infectivity and pathogenicity as explained further in the text under point 1.5.1.2 of Regulation (EU) No 546/2011 and data requirement 5.2 of Regulation (EU) No 283/2013. This approach corresponds to the approach used to assess if a micro-organism can be included in the QPS list[19]. The explicit mentioning of the weight of evidence approach is an important update in the revised data requirements and supports the 3-R principle for replacement, reduction and refinement of animal use. Moreover, due to the host range of the micro-organism and differences in the immune system of humans and test animals, the relevance of animal tests to assess the pathogenicity of micro-organisms to humans is not a priori clear. Based on the body of knowledge on the micro-organism, further specific studies may be required, as indicated in point 5.3.1 and 5.4 of Part B of the Annex to Regulation (EU) No 283/2013 and explained further in the text under point 1.5.1.2 of Regulation (EU) No 546/2011. These test may for example involve inquiring WGS data for virulence factors or non-animal methods such as *in vitro* testing with cell lines.

The typical OECD test guidelines are not tailored towards micro-organisms. This is acknowledged by the ongoing activities initiated at the 2022 OECD Conference on Innovating

[19] https://www.efsa.europa.eu/en/topics/topic/qualified-presumption-safety-qps.

Microbial Pesticide Testing. In case experimental data is necessary for the assessment of infectivity and pathogenicity to humans, and pending the acceptance of specific guidelines at international level, it is recommended to reach agreement with the competent authority on the test guidelines that may be used for the specific micro-organism (e.g. US EPA's microbial pesticide test guidelines[20], please refer to the Commission Communication concerning Part B of the Annex to (EU) No 283/2013 (Official Journal of the European Union, 2023/C 202/03)[21]. This document provides a list of test methods and guidance documents relevant to the implementation of (EU) 283/2013. The document lists OECD guidelines, US Environmental Protection Agency (US EPA) OPPTS 885 test guidelines and relevant EFSA/ECHA/European Commission guidance documents. It is important to note that there are fundamental differences between chemical and micro-organism based active substances. Micro-organisms are living organisms, and thus a specific approach is required when conducting toxicological studies. This fundamental difference should be reflected in testing by assessing the infectivity and pathogenicity of the organism in question. Therefore, testing a micro-organism -based active substance by using an OECD test guideline generally will not adequately address the potential for infectivity and pathogenicity. Where appropriate, in case no US EPA test guideline is available, test guidelines as described in Part A of Regulation (EU) No 283/2013 may be adapted in such a way that they are appropriate for micro-organisms.

When testing is required, the scope for replacement, reduction and refinement of animal tests should be taken into account, which is strongly promoted in Regulation (EU) No 283/2013 and Regulation (EU) No 1107/2009.

Furthermore, point 4.2 of ANNEX I to Regulation (EU) No 283/2013 emphasizes that the active substance as manufactured should be used in studies (i.e., the MPCA-AM). When different test material (e.g. active substance manufactured in the laboratory or in a pilot plant production system) is used, a justification should be provided that the test material is essentially the same for toxicological testing and assessment.

Good laboratory practice (GLP)
All experimental data for the assessment for human and animal health should be GLP-compliant, as laid down in Annex I of Regulation (EU) No 283/2013. Please note that this also includes information submitted in other sections of the dossier, but used for the assessment of human and animal health, such as antimicrobial resistance or growth temperature of the micro-organism.

Classification
The provisions of the CLP Regulation (Regulation (EC) No 1272/2008) are not applicable to micro-organisms and thus the micro-organism cannot be classified or labelled under the current classification and labelling system.

Data waiving
Please note that not submitting data for a particular data requirement is not acceptable without further justification.

[20] https://www.epa.gov/test-guidelines-pesticides-and-toxic-substances/series-885-microbial-pesticide-test-guidelines
[21]. Communication from the Commission concerning Part B of the Annex to (EU) No 283/2013 setting out the data requirements for active substances in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market (Official Journal of the European Union, 2023/C 202/03).

A.5.1 Medical data

Corresponding data requirement:	(EU) No 283/2013, Annex, Part B, 5.1
Relevant evaluation criterion:	(EU) No 546/2011, Annex, Part B, 1.5.1
Relevant decision making criterion:	(EC) No 1107/2009, ANNEX II, point 3.6.6 (EU) No 546/2011, Annex, Part B, 2.5.1
Eligible for substantiated waiving:	No

Purpose of this point:
Information related to (the absence of) symptoms of infection or pathogenicity caused by the microbial active substance that may be available from medical reports or from case reports should be reported. Information on the effectiveness of first aid and therapeutic measures should be submitted as well.

Conditional/data waiving: Listing antimicrobial agents with effectiveness against the micro-organism is not required for viruses.

Required information:

Therapeutic and first aid measures

In addition to therapeutic and first aid measures a list shall be provided with antimicrobial agents with effectiveness against the micro-organism to ensure the availability of sufficient therapeutic measures in the event of opportunistic infections. For further guidance, please refer to data requirement 2.9 and the Guidance on the approval and low-risk criteria linked to antimicrobial resistance (SANTE/2020/12260). Furthermore, where relevant, antagonists should be listed in case of identification of metabolite(s) of concern in 2.8.

Information on the production of 'relevant antimicrobials agents', i.e., antimicrobials which are also used as therapeutic and first aid measures in infections should be provided under data requirement 2.8 (see 'Guidance on the risk assessment of metabolites produced by micro-organisms used as plant protection active substances', SANCO/2020/12258).

Information on antimicrobial resistance of the micro-organism should be provided under data requirement 2.9.

Medical surveillance

Reports on occupational health surveillance programmes should include detailed information on the design of the programme as well as on frequency, level and duration of exposure to the micro-organism. Preferably, these reports must include data from persons exposed in manufacturing plants or after application of the micro-organism (e.g. in efficacy trials). Available information on (the absence of) the sensitisation and allergenic response from workers, e.g. in the manufacturing plants, agricultural and research workers, must be provided as well. These records provide useful information, particularly as there are no validated methods for testing of sensitisation in animals.

Information on sensitisation and allergenicity

In compliance with Regulation (EU) No 283/2013 and the Uniform Principles from Regulation (EU) No 546/2011, all micro-organisms shall be regarded as potential sensitisers until validated tests for investigating sensitization are available. The precautionary warning phrase 'Micro-organisms may have the potential to provoke sensitising reactions' is included on MPCP-labels for all micro-organisms in the product. Consequently it is considered as a general precautionary measure and not as the result of a risk assessment. Therefore, this sentence does not preclude micro-organisms being considered as 'low-risk' substances (see

excerpt[22] from the 'Background document for the purpose of a possible amendment of the current low-risk criteria', SANTE/11953/2015 – rev.5).

In case there is clear evidence in literature that a component (e.g. protein) from the microbial active substance is a respiratory sensitiser conventional classification applies instead of the precautionary warning phrase, consequently the H-statement H334 (May cause allergy or asthma symptoms or breathing difficulties if inhaled) should be assigned.

Dermal sensitisation by micro-organisms is considered unlikely, as the skin is an effective barrier for micro-organisms. Micro-organisms will not penetrate the intact skin, thus external skin exposure will not lead to systemic exposure. There are currently no validated methods to evaluate sensitisation potential of micro-organisms. If a study report is retrieved from e.g. the literature search, the results of this study, either positive or negative, should be interpreted with caution since the current sensitisation studies are not validated for micro-organisms.

Direct observations
Clinical case reports and epidemiological studies of the micro-organism and related micro-organisms should be considered for the assessment of infectivity and pathogenicity in humans. In case related micro-organisms are pathogenic or infective, information should be provided in the dossier to exclude these properties for the micro-organism. This information may include information on the biological properties of the micro-organism such as growth requirements and the absence of known virulence factors in the micro-organism.

A.5.2 Assessment on potential infectivity and pathogenicity of the micro-organism to humans

Corresponding data requirement:	(EU) No 283/2013, Annex, Part B, 5.2
Relevant evaluation criterion:	(EU) No 546/2011, Annex, Part B, 1.5.1
Relevant decision making criterion:	(EC) No 1107/2009, Annex II, point 3.6.6 (EU) No 546/2011, Annex, Part B, 2.5.1
Eligible for substantiated waiving:	No

Purpose of this point:
The outcome of the weight of evidence approach provided for this point is used to determine which information should be included under data requirements 5.3 and 5.4. To this end, available information on infectivity and pathogenicity should be combined in a weight of evidence approach to provide a robust conclusion to either exclude infectivity and pathogenicity of the micro-organism or to provide information on (specific) data needed to conclude on the assessment of infectivity and pathogenicity.

Assessment principle:
A weight of evidence approach shall be applied in order to evaluate whether the possible non-submission of certain studies required in points 5.3.1 and 5.4 of Part B of the Annex II to Regulation (EU) No 283/2013 is justified. Information such as provided under points 2.1, 2.3, 2.4, 2.6 and 5.1, public literature and Qualified Presumption of Safety should be used in a

[22] SANTE/11953/2015 – rev.5 states the following: '*In compliance with the Uniform Principles from Regulation (EU) No 546/2011, all micro-organisms shall be regarded as potential sensitizers in the absence of validated test for investigating sensitisation. The warning sentence "Micro-organisms may have the potential to provoke sensitising reactions" is included for all micro-organisms in the label of plant protection products containing micro-organisms. Consequently it is considered as a general precautionary measure and not as the result of a risk assessment. Therefore, this sentence does not preclude micro-organisms being considered as 'low-risk' substances'.*

weight of evidence approach to demonstrate absence of infectivity and pathogenicity to humans. The body of knowledge should be sufficient to provide a robust conclusion. The evaluation of the body of knowledge and whether it is sufficient to demonstrate absence of infectivity and pathogenicity of the micro-organism will be based on expert judgement case-by-case.

Considerations:

- As indicated in Regulation (EU) No 546/2011: *'Replication temperatures may be different from mammalian body temperature, possibly indicating low likelihood of persistence and multiplication in the host. However, temperature adaptation may occur, and this parameter alone shall not be considered sufficient to conclude on persistence and multiplication of the micro-organism in the host.'* Furthermore, growth temperature data is less relevant for e.g. eye and skin infections. When data on growth temperature is used in the weight of evidence approach under this point please note that the experimental data should be GLP-compliant.

- Suitability of the test model: For micro-organisms, infectivity and pathogenicity tests on animals may not be suitable for extrapolation to humans due to differences between humans and test animals (e.g. immune system, microbiome). Furthermore, micro-organisms might have a narrow host range, hence it cannot always be assumed that a micro-organism that does not cause disease in the animals tested has the same result in humans for example. Please provide adequate justification for the suitability of the test model.

A.5.3 Infectivity and pathogenicity studies on the micro-organism

Corresponding data requirement:	(EU) No 283/2013, Annex, Part B,
Relevant evaluation criterion:	(EU) No 546/2011, Annex, Part B, 1.5.1
Relevant decision making criterion:	(EC) No 1107/2009, Annex II, point 3.6.6 (EU) No 546/2011, Annex, Part B, 2.5.1
Eligible for substantiated waiving:	Yes (see text)

Purpose of this point:
The information on experimental infectivity and pathogenicity studies are only needed in case infectivity and pathogenicity of the micro-organism to humans cannot be excluded based on the body of knowledge on the micro-organism.

Conditional/Waiving: Infectivity and pathogenicity studies with the micro-organisms are only needed when infectivity and pathogenicity of the micro-organism to humans cannot be excluded based on the body of knowledge on the micro-organism (see point A.5.2). Please note that also when experimental studies are needed, the body of knowledge should be used as a starting point to determine which studies are relevant for the micro-organism. Especially for those micro-organisms for which there are indications of pathogenicity and infectivity based on their relationship to known pathogens, information on these related pathogens is needed to determine the approach to exclude pathogenicity and infectivity in the micro-organism under assessment. This approach may be based on in silico methods (e.g., excluding the presence of known virulence factors – see point A.2.6), in vitro methods (e.g., cell culture studies, see A.5.3.2 and A.5.4) or in vivo methods (A.5.3.1).

5.3.1 Infectivity and pathogenicity

If testing is required, then consider Commission Communication, section 5.3.1 (see footnote 21 on p. 58), the recommendations specified under the section “hazard testing” in the introduction of A.5 and the following points:

- Suitability of the test model
  For micro-organisms, infectivity and pathogenicity tests on animals may not be suitable for extrapolation to humans due to differences between humans and test animals (e.g. immune system, microbiome, host range; see section 5.2). Please provide adequate justification for the suitability of the test model.

- Observation period and clearance
  Please consider an observation period that is suitable for the micro-organism to be sure clearance (or reduction of CFUs) in the host can been observed. The choice of appropriate timing of the observational period may be based on available information such as biological properties of the micro-organism or other relevant available information. Slow clearance is known for some species (for example *Bacillus thuringiensis*) and the given observation period of 21 days in the test guidelines might not be sufficient to observe reduction of CFUs. For these species a longer observation period is appropriate.

- Dose level
  According to OPPTS guidelines (see Commission Communication, section 5.3.1 (see footnote 21 on p. 58)), a single dose level of at least 10^8 CFU of the MPCA per test animal should be used for oral and intratracheal studies, and 10^7 CFU for injection studies. If the minimum dose level is not used, a justification must be provided.

- Exposure route
  The most appropriate exposure route for infectivity and pathogenicity studies should be determined based on the body of knowledge of the micro-organism and relevant exposure routes due to intended uses. The choice for the exposure route used for testing should be justified accordingly.

- Intratracheal/ intranasal infectivity and pathogenicity
  Intratracheal/ intranasal infectivity and pathogenicity can be tested either through inhalation or intratracheal exposure. While intratracheal exposure ensures high exposure of the test animal to the micro-organism, the exposure due to inhalation often is too low due to a low concentration of micro-organisms in the atmosphere and a large particle size. Furthermore, the viability of the micro-organism can be affected by nebulization and should therefore be quantified as part of the experimental test. Due to these considerations inhalation exposure is normally not recommended for micro-organisms and an intratracheal study is preferred.
  In intratracheal studies unspecific effects can occur which are caused by the administration of a material directly to the lungs. Therefore it is important to include a suitable negative control in the study, e.g. inactived (e.g., autoclaved) material.

- Intravenous, intraperitoneal or subcutaneous single exposure
  In addition to the oral and intratracheal study, an intravenous, intraperitoneal or subcutaneous injection study can be considered. The subcutaneous injection may be preferred if the maximum growth temperature is lower than 37 °C as the micro-organism may in this case be more likely to cause infections in the skin rather than deep tissue. Intravenous and intraperitoneal injection studies are unrealistic exposure routes and should only be performed if justified, e.g. if unexpected adverse effects occur in the acute oral or intratracheal study.

5.3.2 Cell culture study

The data requirements state that for intracellular replicating micro-organisms, such as viruses and viroids, or in some cases for bacteria and protozoa, a cell culture study should be carried out. A cell culture study gives information on the ability of a micro-organism to infect, replicate in, transform or cause toxicity in human cells. A virus which is infective to humans under any circumstances cannot be approved.

The selection for cell or tissue cultures of a specific organ should be based on the expected target organ upon infection. If human cell or tissue cultures of the specific organ are not available, other mammalian cell and tissue cultures can be used.

A.5.4 Specific infectivity and pathogenicity studies on the micro-organism

Corresponding data requirement:	(EU) No 283/2013, Annex, Part B,
Relevant evaluation criterion:	(EU) No 546/2011, Annex, Part B, 1.5.1
Relevant decision making criterion:	(EC) No 1107/2009, ANNEX II, point 3.6.6 (EU) No 546/2011, Annex, Part B, 2.5.1
Eligible for substantiated waiving:	Yes (see text)

Purpose of this point:

Provide further information on infectivity and pathogenicity of the micro-organism to humans if there are indications of infectivity, pathogenicity or any other adverse effect.

Conditional/waiving: If infectivity and pathogenicity of the micro-organism to humans is excluded based on the information provided under point 5.1, 5.2 and 5.3 further testing is not required.

Testing: if testing is required, then consider Commission Communication, section 5 (see footnote 21 on p. 58). However, in many cases test guidelines may not be available. Before performing such studies it is highly recommended that the applicant shall seek the agreement of the competent authority on the approach including type of study.

Assessment principle: The evaluation of specific infectivity and pathogenicity studies on the micro-organism will be based on expert judgement case-by-case.

An example of a specific infectivity and pathogenicity study on the micro-organism and to be included in this section is a cell culture study conducted with the micro-organism (e.g. bacteria) to assess the germination behavior of spores upon exposure to intestinal cells so that vegetative cells start to grow and produce harmful metabolites.

A.5.5 Information and toxicity studies on metabolites

Corresponding data requirement:	(EU) No 283/2013, Annex, Part B, 5.5
Relevant evaluation criterion:	(EU) No 546/2011, Annex, Part B, 1.5.1
Relevant decision making criterion:	(EU) No 546/2011, Annex, Part B, 2.5.1
Eligible for substantiated waiving:	No

Purpose of this point:

Provide all the information on toxicity of metabolites produced by the micro-organism to

humans which is used for point 2.8 of Regulation (EU) No 283/2013 to identify or exclude metabolites as being of concern.

5.5.1 Information on metabolites

While the information submitted for point 2.8 of Regulation (EU) No 283/2013 should consist of a summary and conclusion of the assessment of metabolites produced by the micro-organism, for the current point all underlying information for the hazard identification and characterisation of metabolites which are relevant specifically for the assessment of the effects on human and animal health should be included. This is reflected by the text in the data requirements (i.e., point 5.5.1 of Regulation (EU) No 283/2013): *'Information (e.g. scientific literature, studies results) on the toxicological characterization of the metabolites and the related identified hazards to human and animal health, collected or generated with the aim to identify the metabolites of concern, or to exclude them as being of concern…'.*

The information included in the dossier for point 2.8 related to human health should therefore be based upon the information included in the current section. Please refer to point A.2.8 of this Evaluation Manual for information on the assessment of metabolites produced by the micro-organism according to the 'Guidance on the risk assessment of metabolites produced by micro-organisms used as plant protection active substances, SANCO/2020/12258', including a template for an overview table for microbial metabolites.

For those metabolites produced by the micro-organism for which a hazard to human or animal health is identified, information on human exposure should be provided as described under points A.6 (residues in or on treated products, food and feed) and A.7.2 (fate and behaviour of metabolite(s) of concern).

5.5.2 Additional toxicity studies on metabolites of concern

For extensively studied micro-organisms, in this section information is only needed in case a metabolite of concern which causes a hazard to humans or animals has been identified and reference values for toxicity cannot be set based on already available information (including TTC values) or need further investigation. Studies shall be performed based on a case-by-case approach (for example short-term toxicity studies and genotoxicity studies) and using the requirements set out in Part A for the specific type of study using relevant fractions of the MPCA-AM. It is highly recommended to reach agreement on these tests with the competent authority beforehand.

For organisms which have not been extensively studied, the absence of indications for metabolites of concern in scientific literature is not sufficient to conclude on the absence of a foreseeable risk to human health due to metabolites produced by the micro-organism. Therefore, for these less studied micro-organisms more experimental data is needed. A repeated-dose toxicity study is required based on relevant fractions of the MPCA-AM and further studies may be needed based on the outcome of these studies. Also in this case, It is highly recommended to reach agreement on these tests with the competent authority beforehand.

Testing: if testing is required, then consider Commission Communication, section 5 (see footnote 21 on p. 58).

Considerations related to testing: In addition to the recommendations specified under the section "hazard testing", it is highly recommended to:

- Genotoxicity
  For metabolites suspected to be of genotoxic concern from the scientific literature and

following (Q)SAR prediction and read-across, and when their exposure is exceeding 0.0025 µg/kg[23] bw per day, it seems appropriate to conduct the testing battery which should include as a minimum two *in vitro* tests, covering all three genetic endpoints, i.e. gene mutations, structural and numerical chromosomal aberrations. The specific metabolite could be tested in purified form using the same test methods as for chemical active substances. However, since micro-organisms may produce a large array of metabolites, testing of a crude extract (i.e. the chemical constituents of the MPCA-AM with cell walls etc., removed) could be considered when micro-organisms have not been extensively studied, as indicated in 'Guidance on the risk assessment of metabolites produced by micro-organisms used as plant protection active substances', SANCO/2020/12258 and Regulation (EU) No 283/2013. In such a test, the study design needs to be carefully considered as the concentrations of each component can be expected to be low and a component with a low genotoxic potential would thus not be detected in the test.
When performing genotoxicity studies with a crude extract it is important to avoid interference by constituents in the test samples such as provision of nutrients by lysates (e.g. histidine), growth factors that may produce abnormal growth, growth inhibition of DNA synthesis, enzymatic activity that could mimic endogenous activity in the test organism (e.g. kinase or phosphokinase activity in the TK+/- or HPRT assays), the occurrence of potentially active constituents as bound or complexed forms, or intracellular molecules with nuclease or proteolytic activity from *in vitro* lysates that would not normally have access to mammalian cell *in vivo* (MacGregor, 2005)[24].

If a positive result has been obtained with an *in vitro* study an *in vivo* genotoxicity study is required. When any results of an *in vivo* in somatic cells is positive, in vivo testing for germ cell effect may be justified. The recommended methods are the same as for chemicals, please refer to Commission Communication 2013/C 95/01 Part A section 5.4.

- Cytotoxicity studies conducted with for example the fermentation broth of the MCPA-AM are not considered sufficient to exclude the toxicity of metabolites of (potential) concern identified in 2.8. As these metabolites may not be formed during the laboratory test or in very low quantity and therefore the possible adverse effects of the metabolites may not be reliably covered by *in vitro* laboratory studies. In addition, when an effect on viability of cells is observed in the study it is not clear which metabolite is responsible for the response.

A.6 RESIDUES IN OR ON TREATED PRODUCTS, FOOD AND FEED

As micro-organisms which are pathogenic to humans cannot be approved, consumer exposure to the micro-organism itself is not relevant for the risk assessment. This chapter therefore focuses on consumer exposure to metabolites of (potential) concern. Any adverse effect to humans caused by the micro-organism itself should be addressed in section 5: Effects on human health.

While the information submitted for point 2.8 of Regulation (EU) No 283/2013 should consist of a summary and conclusion of the assessment of metabolites produced by the micro-organism, for the current point all underlying information for the consumer exposure assessment for

[23] TTC-value relevant to such substances.
[24] MacGregor, JT. Genetic Toxicity Assessment of Microbial Pesticides: Needs and Recommended approaches. Report to OECD. December 2005.

metabolites which are relevant specifically for the assessment of the effects on human and animal health should be included. Qualitative or semi-quantitative information on consumer exposure should be included under point 6.1, while quantitative information should be included under point 6.2, please refer to the Commission Communication concerning Part B of the Annex to (EU) No 283/2013 (Official Journal of the European Union, 2023/C 202/03)[25].

Please note that while consumer exposure to the micro-organism itself is not considered relevant, information on the absence or density of the micro-organism on edible parts of treated crops can be used to support the assessment.

Literature search
According to the Annex I Introduction to Regulation (EU) No 283/2013, all available relevant data from the scientific peer reviewed and open literature on the micro-organism should be provided. The literature search should be carried out in accordance with the Literature GD. Literature retrieved from this search should be reported in the relevant sections of the dossier. When a literature search is conducted it is important to correspondingly consider previous/alternate taxonomic names for the organism in question which may have been used in past publications. The search strategy reported by Hackl et al. (2015)[26] and Mudgal (2013)[27] might be helpful for consideration of search terms in the literature search.

Data waiving
Please note that not submitting data for a particular data requirement is not acceptable without further justification.

A.6.1 Estimation of consumer exposure to residues

Corresponding data requirement:	(EU) No 283/2013, Annex, Part B, 6.1
Relevant evaluation criterion:	(EU) No 546/2011, Annex, Part B, 1.5.2
Relevant decision making criterion:	(EC) No 1107/2009, ANNEX II, point 3.1 (EU) No 546/2011, Annex, Part B, 2.5.2
Eligible for substantiated waiving:	Yes (see text)

Purpose of this point:
Qualitative or semi-quantitative information on consumer exposure to residues of metabolite of potential concern is used to determine that there is no harmful effect to human or animal health arising from residues. In this way, metabolites of potential concern for human or animal health are either determined to be not of concern (no further assessment needed) or of concern (in which case a quantitative assessment is needed; see A.6.2).

Conditional/waiving: If there are no metabolites of potential concern (no hazard) for human and animal health identified in 2.8 and 5.5 no further information than a justification for waiving is required for this section.

Assessment principle:

[25]. Communication from the Commission concerning Part B of the Annex to (EU) No 283/2013 setting out the data requirements for active substances in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market (Official Journal of the European Union, 2023/C 202/03).
[26] Hackl, E; Pacher-Zavisin, M; Sedman L.; Arthaber, S; Bernkopf, U.; Brader G; Gorfer, M; Mitter, B; Mitropoulou, A; Schmoll, M; Van Hoesel, W; Wischnitzky, E; Sessitsch, A. EFSA Supporting Publication 2015:EN-801.
[27] Mudgal, S; De Toni, A; Tostivint, C; Hokkanen, H; Chandler, D. EFSA Supporting Publications 2013:EN-518.

Information should be provided for metabolites of potential concern for human or animal health (identified based on information provided in 5.5.1 and 2.8) to be able to perform an indicative consumer risk assessment (i.e., a qualitative or semi-quantitative assessment). Regulation (EU) No 283/2013 provides multiple methods to estimate the exposure to metabolites, for which a hazard to human or animal health was identified, considering the intended use:

- *'…a calculation of the expected residue levels of these metabolites on edible parts of treated crops using worst-case estimates, taking into account the critical good agricultural practice(s), ecology of the micro-organism, such as its lifestyle (e. g. saprophytic, parasitic, endophytic), host range, life cycle, population growth requirements and the conditions which trigger the production and the properties of the metabolite for which a hazard to human health was identified.'*

  When an endophytic lifestyle has been demonstrated for the micro-organism the report written by Scheepmaker (2021)[28] on metabolite production by endophytes can be included in the weight of evidence approach. This report indicates that many MPCAs can grow endophytically and that this lifestyle does not constitute a hazard in itself as population densities and metabolite concentrations for endophytic micro-organisms are commonly low.

- *'…direct measurements of the metabolite, e.g. to show the absence of the metabolite on edible parts at time of harvest. When determining the need for direct measurements, the possibility and relevance of exposure to the metabolite produced after application on the edible parts (in-situ production) shall be taken into consideration. This may include a comparison between the background level of the metabolite and the elevated level of it due to treatment with the plant protection product containing the active substance.'*

- *'…direct measurements of the density of the micro-organism on edible parts of treated crops, e.g. if it cannot be adequately justified that in-situ production of the metabolite is not relevant for the consumers. Such measurements shall be performed under normal conditions of use and in accordance with good agricultural practice.'*

  In case experimental data to demonstrate the absence of the micro-organism on edible crops is used to demonstrate the absence of consumer exposure to the metabolite, it is needed to do so for all growth stages of the edible part – not only at the time of harvest. Especially if plating methods are used as detection method, the absence of live micro-organisms is not sufficient to demonstrate the absence of the metabolite, as the metabolite may have been produced at an earlier growth stage and remained on the edible part.

- Where relevant, adequate justification for read-across shall be provided.

When using information on the natural background levels of the metabolite or the microbial species, please note that natural occurrence in itself is not sufficient to determine on the absence of harmful effects, as the natural presence of a metabolite may result in harmful effects. Therefore, information on natural occurrence should always be used in combination with information on the (absence of) harmful effects.

[28] Scheepmaker, J. (2021) Exploring the necessity of additional data requirements under the pesticide regulation to take into account endophytes. RIVM letter report 2021-0056.

If the metabolite of potential concern is present in the MCPA-AM, a consumer risk assessment should be provided based on the maximum level (mean value found in the batch analysis+ three times standard deviation) at which the metabolite may be present in the product (see also P.1.4, 'Specification of the microbial pest control agent as manufactured'). As described in SANCO/2020/12258 (Stage 3, Step 14) for hazards arising from human dietary exposure, a worst-case theoretical estimate of the residue can be made by assuming that, upon application, the entire product-borne amount of the metabolite of concern will end up on the edible parts. With data on crop yields, a theoretical estimate of the residue can be calculated, by taking the lowest mean crop yield for the EU in the last five years (a low level of crop yield from a possible range should be used to give a worst case estimate of the residue, since the aim should be to assess the highest likely residues that could arise following the intended use). Together with the application rate (CFU/kg per ha) and the metabolite concentration (in mg/ha), the maximal residue of the metabolite in µg/kg crop can be calculated. With this worst-case approach, dietary uptake from a given crop can be compared with available health-based reference values, such as the Acceptable Daily Intake (ADI) and Acute Reference Dose (ARfD), with natural exposure levels, or with the Threshold of Toxicological Concern (TTC) when no other reference values are available. Furthermore, the expected consumer exposure to these residues can be estimated using EFSA's Pesticide Residue Intake Model (PRIMo).

A.6.2 Data generation on residues

Corresponding data requirement:	(EU) No 283/2013, Annex, Part B, 6.2
Relevant evaluation criterion:	(EU) No 546/2011, Annex, Part B, 1.5.2
Relevant decision making criterion:	(EC) No 1107/2009, ANNEX II, point 3.1 (EU) No 546/2011, Annex, Part B, 2.5.2
Eligible for substantiated waiving:	Yes (see text)

Purpose of this point:
Provide data on residues of metabolites of concern for which a hazard to humans or animals has been identified in case where the substantiated estimation in 6.1 does not demonstrate an acceptable risk to consumers in step 14 . (SANCO/2020/12258 (Stage 4, Step 16)

Conditional/waiving: As described in the introduction of section 6 in Regulation (EU) No 283/2013: *'Data on residues as required in point 6.2 shall be provided, unless:*

— based on a weight of evidence approach concerning the information submitted in accordance with Sections 2, 3, 5 and 7, it can be justified that possible metabolites of concern identified (see point 2.8) are not hazardous to humans as a result of the intended use,

— it is possible to conclude, through estimation of consumer exposure to residues of metabolites for which a hazard to human health was identified (see point 5.5.1) that the risk for consumers is acceptable, or

— the micro-organism is a virus.'

Testing: if testing is required, then consider Commission Communication 2013/C 95/01 Part A section 6.

Assessment principle:
Full residue data, as required for chemicals, are rarely needed because in general sufficient information is available to address the concerns. However, if significant quantities of the metabolite of concern are foreseen (for example due to high concentrations in the MPCA-AM)

and risk to humans and animals cannot be excluded based on information provided in 2.8, 5.5.1 and 6.1, relevant studies of a data package on residues as provided in Section 6 of Part A may be required.

To determine concentrations of metabolites, edible parts that have been treated with the MPCP in accordance with representative use can be chemically analysed. By determining the concentration of metabolites of concern in this way, both the exposure resulting from the presence of the metabolite in the product and from *in situ* production are covered. The expected consumer exposure to these residues can be estimated using EFSA's Pesticide Residue Intake Model (PRIMo) and this can then be compared with the health-based reference values mentioned above.

For further guidance, please refer to Annex II of the 'Guidance on the risk assessment of metabolites produced by micro-organisms used as plant protection active substances, SANCO/2020/12258.

A.7 ENVIRONMENTAL OCCURRENCE OF THE MICRO-ORGANISM, INCLUDING FATE AND BEHAVIOUR OF METABOLITES OF CONCERN

The aim of this Section 7 is to provide the information on the occurrence of the micro-organism in the relevant environmental compartments and to assess the potential exposure of humans and non-target organisms to the micro-organism, and where relevant to metabolites of concern. Please note that while this chapter addresses the environmental occurrence of the micro-organism itself (*i.e.*, the strain/isolate under evaluation), information on the natural occurrence of related organisms (*e.g.*, at species level) should be provided under point 2.1.2.

Information on the fate and behaviour of metabolites may be needed either to exclude metabolites as being of concern, or to perform a risk assessment for metabolites of concern. The method by which environmental concentrations are determined depends on whether the metabolite is present in the product, or produced *in situ* upon application. For metabolites which are present in the product and for which *in situ* production is not relevant, calculation models can be used (point 7.2.1). When *in situ* production may be relevant, calculation models may not be relevant and a tiered approach to assess exposure of humans, non-target organisms and the environment is followed. First, a qualitative exposure assessment is performed based on the available information on the ecology of the micro-organisms and information on the metabolite (point 7.2.2). If both the calculation of environmental concentrations using calculation models and the qualitative assessment are not sufficient to conclude that exposure to this metabolite is not of concern, a quantitative assessment for the metabolite is needed (point 7.2.3). As calculation models are not appropriate for metabolites of concern at this stage of the assessment (see point 7.2.1), experimental data on concentration of the metabolite in relevant environmental compartments is needed.

Please note that while the information submitted for point 2.8 of Regulation (EU) 283/2013 should consist of a summary and conclusion of the assessment of metabolites produced by the micro-organism, for the chapter point all underlying information for the environmental exposure assessment of metabolites should be included.

A.7.1 Environmental occurrence of the micro-organism

Corresponding Annex point:	(EU) No 283/2013, Annex, Part B, 7.1
Relevant evaluation criterion:	(EU) No 546/2011, Annex, Part B, 1.6.1

Purpose of this point:
The purpose of this point is to provide information on the environmental occurrence of the micro-organism to be able to assess the potential exposure of humans and non-target organisms to the micro-organism in the environment.

In principle, information on the environmental occurrence of the micro-organism is only needed in case a hazard for humans or non-target organisms for this micro-organism has been identified. In case ecotoxicological testing is performed, Predicted Environmental Densities (PEDs) calculated based on the proposed use (points 7.1.1.1 and 7.1.1.2; also see chapter 8) are needed to perform the ecotoxicological risk assessment. In case further information on the environmental occurrence of the strain is needed when a hazard has been identified for humans or the environment, this chapter follows a tiered approach. As a first step, qualitative information on the environmental occurrence of the micro-organism is used (point 7.1.3). If this information is not sufficient to conclude the risk assessment, quantitative information on the population densities of the micro-organism is needed (point 7.1.4). As calculation models are not appropriate to predict the environmental population densities of micro-organisms, this experimental data should be provided.

In this chapter, specific information is required for micro-organisms which are pathogenic to target or non-target organisms (point 7.1.2). This is because pathogenic micro-organisms may multiply in their host organism. In contrast for non-pathogenic micro-organisms, calculated PED values may not be a conservative estimation of exposure of NTOs if NTOs are exposed to infected host organisms. Therefore, the exposure assessment for pathogenic micro-organisms differs on two main points from the assessment for non-pathogenic organisms. Firstly, for pathogenic micro-organisms exposure can in principle not be excluded based on the proposed use. This means that for example also in case of a use in a permanent greenhouse exposure of NTOs such as plants, birds and mammals is assumed. As the release of a single micro-organism can in principle cause disease in populations of NTOs, for these pathogenic micro-organisms there is in principle always a possibility of exposure of NTOs. Secondly, as the exposure of NTOs to the micro-organism may be highest due to exposure to infected host organisms, information on this level of exposure is needed.

A.7.1.1 Predicted environmental density

Assessment principle:
In case a hazard for NTOs cannot be excluded based on the body of knowledge on the micro-organism (see chapter A.8), PED values should be determined for the environmental compartments soil and water. For groundwater, no PED values for the micro-organism are needed, as micro-organisms cannot be approved if they are pathogenic to humans.

In contrast to qualitative (A.7.1.3) and quantitative exposure assessments (A.7.1.4), PED calculation does not follow a targeted approach, but is always performed for the environmental compartments soil and surface water.

PED values are calculated using the formula or models provided below based on the proposed use. The exposure of soil and surface water differs for field and protected crops. Therefore, the Guidance on protected crops should be used to determine the appropriate exposure scenario. In general, for non-permanent greenhouses the same approach should be taken as for field uses. Please note that the calculation methods described in this guidance document do not apply to micro-organisms; only the information to determine if the proposed use should

be determined as a field or protected use is relevant.

Background information on the nature of the assumptions and methods used for the PED calculations are provided in OECD guidance No. 67, sections 3.1.2 and 3.2.1 and the PRAPeR expert meeting M2 of February 16-18, 2009. It should be noted that these calculations provide an unrealistic worst-case initial predicted density when multiple applications are considered and especially in case of multiple crop cycles per year; these calculation do not take into account unfavourable conditions that will most likely rapidly and negatively impact the population density for most micro-organisms (*e.g.,* temperature, lack of nutrients, competition).

A.7.1.1.1 PEDSOIL

The method to calculate the PED in soil is based on a worst-case scenario in which all applications of a crop cycle (in case of multiple crop cycles per year) or year (in case of permanent crops such as fruit trees) are summed and no decline of the population density upon application is assumed. The application rate used in PED calculations is calculated based on the use rate of the product (*e.g.*, L/ha) and the maximum content of the micro-organism in the product based on the specification (*i.e.*, the highest concentration of the range of values).

With the introduction of the Commission Communications for the implementation of Part B of the Annex to Regulation (EU) No. 283/2013 the methodology for the estimation of PED_{SOIL} follows the suggestions provided in EFSA Journal 2017;15(10:4982) section 2.7 and the use of the OECD 67 guidance. The EFSA guidance provides a tiered assessment using the PERSAM tool. It should be noted that both guidances have been approved in the Commission Communications and that these provide different default values for *e.g.* soil density, the applicant should in any case provide the most conservative value. The first tier assessment is based on a default DT_{50} of 1000 days, K_{OC} of 2000 mL/g without interception and at a soil depth of only 5 cm. The modelling in PERSAM should thus be set as a perennial application, as this always provides a PED_{SOIL} at a depth of 5 cm, not considering annual tillage. As a tiered assessment is possible, the decline of the population and interception by the crop can be refined using values found in either experimental data, or extrapolated to a surrogate crop interception value from the Generic Guidance for Tier 1 FOCUS Ground Water Assessments (2014). This second tier approach can only be used when reliable experimental data is available at strain-level or on closely related strains if justified.

The concept of accumulation in soil as for persistent chemical substances does not apply to micro-organisms. Therefore, only the initial PED values in soil as described above are relevant for the risk assessment.

For uses in permanent greenhouses no PED_{SOIL} is required as greenhouse soils are not considered to be natural soils. Similarly, no PED_{SOIL} is required for indoor uses.

A.7.1.1.2 PED_{SW}

As for the calculation of the PED in soil, the method to calculate the PED for surface waters is based on a worst-case scenario. Note that for field uses run-off, drainage and aerial deposition are in principle not considered.

$$\mathrm{PED_{SW}\ as}\ \frac{\mathrm{CFU}}{\mathrm{L}} = \frac{\mathrm{Application\ rate} \cdot\ n\ \cdot (\frac{\mathrm{D}}{100})}{10000 \cdot \mathrm{Vd}}$$

Where:

- the application rate is the unit of product applied per application multiplied by the maximum concentration of the micro-organism in the product (as given in the specification)
- *n* is the number of applications per crop cycle/year
- D is the percentage of drift (field uses) or emission (protected uses)
- 10 000 as the conversion factor from hectare to m^2
- Vd as the volume of the standard ditch per surface area (L/m^2)

The BBA drift[29] values in combination with the volumetry of the FOCUS standard ditch should be used (*i.e.*, 300 L/m^2) for field uses including uses in non-permanent greenhouses.
For permanent greenhouse uses of micro-organisms, an emission percentage of 0.1% should be used. This emission value for greenhouse uses is considered to cover all emission routes of microbial active substances and was agreed upon during pesticide peer review expert meeting 25 on micro-organisms (March 2020). As an exception to this rule, for granular soil-incorporated applications of micro-organisms in permanent greenhouses, no emission to surface water is assumed (as proposed by EFSA as part of the peer review of *Metarhizium brunneum* BIPESCO 5/F52).

A.7.1.2 Exposure to micro-organisms known to be pathogenic either for plants or for other organisms.

Assessment principle:
While for non-pathogenic micro-organisms the PED values can be used as a conservative estimation of the environmental occurrence of the micro-organism upon application, this assumption may not hold for pathogenic micro-organisms not native to Europe. These pathogenic micro-organisms may proliferate in their host organisms resulting in highly localised (*i.e.*, in their host) higher population densities of the micro-organism. Therefore, in addition to providing information on PED values in soil and surface water, information is needed on the likelihood and level of exposure of NTOs to the micro-organism via infected host organisms. This information may be provided based on biological properties of the active substance or relevant literature data or studies (from *e.g.* section 2 or 8). For example, if the micro-organism is an entomopathogen which can infect larvae of a certain species of beetle, this information may be required for the risk assessment for insectivorous NTOs.

Please note that for pathogenic micro-organisms, exposure to NTOs is in principle assumed regardless of the proposed use. This means that exposure is also assumed when based on the default calculation method for PED values in soil and surface water the PED value equals zero.

A.7.1.3 Qualitative exposure assessment

Information on the environmental occurrence of the micro-organism upon application is only needed if a hazard has been identified for humans or non-target organisms. This hazard can consist of adverse effects on NTOs due to the micro-organinism itself (pathogenicity and infectivity) or to humans and NTOs due to *in situ* production of toxic metabolites. In the latter case, the qualitative exposure assessment to the micro-organism is used to inform the

[29] Ganzelmeier H, Rautmann D, Drift values according to the BBA (Federal Biological Agency of Agriculture and Forestry, Germany) 2000: Bekanntmachung des Verzeichnisses risikomindernder Anwendungsbedingungen für Nichtzielorganismen. Bundesanzeiger 100: 9878-9880.

qualitative exposure assessment to the metabolite (A.7.2.2).

Assessment principle:
In contrast to the calculation of PED values, which are calculated for the environmental compartments soil and surface water, the qualitative exposure assessment should follow a targeted approach. For example, if a hazard has been identified due to pathogenicity of the micro-organism to tree-dwelling caterpillars, information on the population density of the micro-organism in soil or surface water may be irrelevant. In contrast, information on the population density on the leaves on which the caterpillar feeds may be relevant. As such, the first step to provide information for the qualitative exposure assessment is to identify the exposure routes of the humans or NTOs to which the hazard applies. Next, the environmental compartments relevant for this exposure route should be identified. Please note that these compartments may be highly specific, such as infected insects, flowers or the rhizosphere.

As indicated in the data requirements, the weight of evidence approach for the qualitative exposure assessment as a rule draws heavily on information on the biological properties of the micro-organism. In addition, in certain cases a semi-quantitative approach can be followed using experimental data, for example by using information generated during efficacy trials. In this way and where relevant, it may for example be possible to demonstrate the absence of the micro-organism in edible parts of the plant for micro-organisms which are applied as seed or soil treatment or as a foliar application during early growth stages.

In addition to information on the ecology of the micro-organism itself, information on the natural occurrence of closely related micro-organisms can be included. When using information of closely related micro-organisms, a justification should be provided as to why this information is relevant for the micro-organism – a close phylogenetic relationship in itself is not sufficient as justification. For example, when a hazard has been identified for a NTO due to pathogenicity, information on the comparability of the virulence traits (*e.g.*, host range) is needed when information on the natural occurrence of closely related micro-organisms is used for the risk assessment.

A.7.1.4 Experimental exposure assessment

Experimental (quantitative) data on the exposure of humans or NTOs is needed in case the information considered under points 7.1.1 to 7.1.3 and 7.2 is not sufficient to conclude on the risk caused by the identified hazard. As for the qualitative exposure assessment described in A.7.1.3, this hazard can consist of adverse effects on NTOs due to the micro-organinism itself (pathogenicity and infectivity) or to humans and NTOs due to *in situ* production of toxic metabolites. In the latter case, the quantitative exposure assessment to the micro-organism is used to inform the exposure assessment to the metabolite (A.7.2.2 and A.7.2.3).

Assessment principle:
The quantitative exposure assessment should follow the same targeted approach as described in A.7.1.3. For the relevant environmental compartments, experimental data on the population density of the micro-organism should be provided in a time course including pre-application (*i.e.,* not the natural background of CRS) and immediately post-application. The length of the time course should be set so as to be able to assess the potential decline of the population density upon application.

The relevance of the experimental conditions for the risk assessment should be justified. This justification may include information on the choice of crop, soil and climatic region. For post-harvest application information on storage conditions may be relevant. Furthermore, information on relevant environmental parameters should be provided, such as humidity, pH,

temperature, salinity, as these parameters may have a large effect on the population dynamics of the micro-organism. In case the experimental data are extrapolated to other uses of the micro-organism, a justification for this read-across should be provided.

A.7.2 Fate and behaviour of metabolite(s) of concern

Corresponding Annex point:	(EU) No 283/2013, Annex, Part B, 7.2
Relevant evaluation criterion:	(EU) No 546/2011, Annex, Part B, 1.6.2
Relevant decision making criterion:	(EU) No 546/2011, Annex, Part B, 2.6.1 to 2.6.3

Purpose of this point:
The purpose of this point is to provide information on the exposure of humans and the environment to metabolites of (potential) concern. As described in the 'Guidance on the risk assessment of metabolites produced by micro-organisms used as plant protection active substances' (the 'metabolite guidance'; SANCO/2020/12258), this information on the fate and behaviour of metabolite(s) is used to determine if the metabolite is not of concern (in which case no further assessment is needed) or to perform a quantitative risk assessment for metabolite(s) of concern.

For metabolites of concern to which surface water or groundwater is exposed, it should be demonstrated that the level of contamination of surface water and groundwater does not exceed the concentrations relevant for the water framework directive and the drinking water directive.

A.7.2.1 Predicted environmental concentration
The need for PEC values of metabolites present in the product is triggered by the approach described in the metabolite guidance. Please note that this approach to calculate PEC values cannot be used for metabolites which are produced *in situ* upon application. To provide information on the exposure to metabolites which are produced *in situ*, a qualitative or quantitative exposure assessment is needed, as described in A.7.2.2 and A.7.2.3, respectively.

Assessment principle:
As a first step, the environmental compartments which are relevant for the exposure to the metabolite of either humans or the NTO(s) for which a hazard has been identified should be determined. In case the metabolite is a medically important antimicrobial, all environmental compartments (soil, surface water and groundwater) are considered to be relevant (see Step 14 of the metabolite guidance).

For metabolites present in the product, the pesticide fate models developed for chemical active substances (FOCUS DG SANTE[30]) should be used. If data on the physical-chemical parameters that are required for the models are lacking, conservative default values may be used. These are described in their respective guidance documents. Aside from the EFSA guidances, ECHA guidances may also be used (e.g., the Guidance on information requirements and chemical safety assessment, Chapter R.16) but keep in mind that these values are normalised for 12°C.

Irrespective of the NTO (including humans) for which a hazard has been identified, for metabolites of concern which are present in the product, it should be demonstrated that the

level of contamination of surface water and groundwater does not exceed the concentrations relevant for the water framework directive and the drinking water directive. Please note that this information is only required for metabolites of concern; if the metabolite for which a hazard has been identified (a metabolite of potential concern) is demonstrated not to be of concern based on a qualitative risk assessment, this information is not needed.

A.7.2.2 Qualitative exposure assessment

Purpose of this point:
Information on the environmental concentrations of a metabolite is only needed if a hazard (toxicity) for this metabolite has been identified for humans or non-target organisms. Based on the qualitative assessment, the metabolite can either be demonstrated not to be of concern, or to be of concern. In the latter case, a quantitative assessment is needed for this metabolite of concern (see A.7.2.3). For metabolites which are also present in the product at the time of application, the qualitative assessment is used to determine if *in situ* production of the metabolite is relevant for the risk assessment.

The qualitative exposure assessment of metabolites follows the same targeted approach as described for the qualitative exposure assessment to the micro-organism (see A.7.1.3). Please note that the environmental compartments which are relevant for the assessment may differ for the micro-organism and its metabolite, as metabolites may be mobile in the environment upon production.

Assessment principle:
For the qualitative exposure assessment for a metabolite, the information on the environmental occurrence of the micro-organism is used (see A.7.1). In addition, available information on the levels at which the metabolite can be produced by the micro-organism and the environmental conditions needed for this production should be included (see A.2.8). Furthermore, available information on the fate and behaviour of the metabolite itself should be used. This includes information on the stability and the adsorption of the metabolite.

As for the qualitative exposure assessment for the micro-organism, the qualitative exposure assessment for metabolites may include information on the natural background levels of the metabolite. As the same metabolite may also be produced by other micro-organisms (which need not be closely related), information on the natural occurrence of other producers of the metabolite may also be included. Please note that an exposure at or below the natural background levels in itself does not demonstrate safety, as also natural background levels can have adverse effects on humans on the environment. Therefore, the natural background concentrations should be used in a weight of evidence approach in which also information on the (absence of) effects due to the natural exposure is included.

A.7.2.3 Experimental exposure assessment

Purpose of this point:
Experimental (quantitative) data on the exposure of humans or NTOs to the metabolite of concern is needed in case the information provided under points 7.2.1 and 7.2.2 is not sufficient to conclude on the risk caused by the identified hazard.

Assessment principle:
As mentioned for the qualitative exposure assessment for metabolites, this experimental exposure assessment should follow a targeted approach (*i.e.*, addressing those environmental compartments which are relevant for the exposure route of humans or NTOs for which a hazard was identified for this metabolite of concern). In case the relevant environmental

compartment is soil, surface water or groundwater, the study should be conducted in accordance with the provisions for this study as described in Part A of the data requirements (*i.e.*, the environmental fate and behaviour of chemical substances). For those cases where the environmental compartment which is relevant for the exposure to the metabolite is the same environmental compartment in which the micro-organism is present, information on the population density of the micro-organism should be provided in accordance with point 7.1.4.

Similar to the experimental exposure assessment for the micro-organisms, the relevance of the experimental conditions for the risk assessment should be justified. This justification may include information on the choice of crop, soil and climatic region. For post-harvest application information on storage conditions may be relevant. Furthermore, information on relevant environmental parameters should be provided, such as humidity, pH, temperature, salinity, as these parameters may have a large effect on the population dynamics of the micro-organism. In case the experimental data are extrapolated to other uses of the micro-organism, a justification for this read-across should be provided.

Please note that for all metabolites of concern it should be demonstrated that the level of contamination of surface water and groundwater does not exceed the concentrations relevant for the water framework directive and the drinking water directive. However, while for metabolites of concern for which *in situ* production is not relevant the approach for chemical substances can be followed, a different approach is needed for metabolites which are produced *in situ*. It is expected that these uniform principles are mainly relevant in case the metabolite of concern is present in relevant quantities in the product, not for *in situ* produced metabolites. However, a justification should be provided and in certain cases agreement with the competent authority on the approach may be sought prior to dossier submission.

A.8 EFFECTS ON NON-TARGET ORGANISMS

Scope

As mentioned in (EU) No 283/2012, the information provided by the applicant should be sufficient to:

- *"decide whether or not the micro-organism can be approved,*
- *specify appropriate conditions or restrictions to be associated with any approval,*
- *permit an evaluation of short- and long-term risks for non-target species - populations, communities, and processes, as appropriate, and*
- *specify any precautions deemed necessary for the protection of non-target species*".

According to (EU) No 283/2012, "*special attention shall be paid to microbial species which are not known to occur in the relevant European environments. The information provided shall be sufficient to determine the physiological and ecological host range (in conjunction with the analysis of key biological traits of the micro-organisms) in order to assess impacts on non-target organisms"*.

As a result of the risk assessment conducted in the ecotoxicology section, a safe use should be concluded for the products placed on the market and thus their application does not result in unacceptable effects to non-target organisms. In order to ensure the safety of the product for which authorization is sought by the applicant, the Member States should use the Uniform Principles for evaluation and authorization of plant protection products.

Data waiving
Please note that not submitting data (guideline studies) for a particular data requirement is not acceptable without adequate justification (i.e., all data requirements must be addressed).

The updated Uniform Principles and Data Requirements follow the risk principle (i.e., risk = hazard × exposure) and allow for waiving either exposure-related data requirements or hazard-related data requirements, if the absence of the other can be concluded. According to section 7.1 of (EU) 283/2013, the predicted environmental density shall be estimated, unless the applicant justifies the absence of hazard. In other words in absence of exposure, no hazard data need to be generated (can be waived) and in absence of hazard the specific exposure data may be waived. Thus, the updated Uniform Principles and data requirements aim to only require 'need to know' information. Therefore, data on the environmental occurrence of the micro-organism upon application (see Section 7 of the data requirements) is only needed if the use of the micro-organism causes a hazard for humans or non-target organisms. Similarly, when the body of knowledge on a micro-organism is sufficient to conclude the absence of a hazard, no additional ecotoxicological data needs to be generated and data required to quantify specific environmental levels following application is not needed for the risk assessment.

If it is not possible to conclude on the absence of a hazard to non-target organisms, ecotoxicological tests can be performed using a maximum hazard approach (i.e., MHD/MHC, maximum hazard dose/maximum hazard concentration). The MHD and MHC are defined in the US EPA OPPTS 885.4000 guideline[31] and in the Canadian Guidance document on testing new microbial substances (Canadian GD)[32]. Please note that both documents are referred to in the the Commission Communication concerning Part B of the Annex to (EU) No 283/2013 (Official Journal of the European Union, 2023/C 202/03).

Please note that while certain justifications for absence of exposure may be appropriate for non-pathogenic micro-organisms (e.g., only applied in permanent greenhouses), for pathogenic micro-organisms the phrasing of the uniform criterion '*where the possibility of being exposed cannot be excluded*' should be taken literal. For example, a plant-pathogenic micro-organism for which approval is only sought for greenhouse uses, a waiver of data requirements for non-target plants based on negligible exposure will not be acceptable, as any release of the plant-pathogen into the environment (e.g., ventilation of greenhouses) may lead to unacceptable effects on non-target plants.

If effects are observed in the maximum hazard tests, further information on exposure and hazard characterization is needed for the risk assessment.

Justifications for waiving of ecotoxicological testing/data requirements:

a) Testing can be waived if, based on the available data at the most relevant taxonomic level in the public and peer-reviewed literature (n.b., including the risk assessment in other regulations outside EU, the use of the micro-organism in feed, etc), and/or information on the biological properties of the micro-organism (e.g., mode of action and host range, growth temperature, natural occurrence of the species, ecology and life-cycle, fate and behaviour for qualitative exposure estimations (see Fate section 7.1.3), it can be concluded that no hazard to specific non-target organisms is expected.

[31] https://www.epa.gov/test-guidelines-pesticides-and-toxic-substances/series-885-microbial-pesticide-test-guidelines
[32] Guidance document for testing the pathogenicity and toxicity of new microbial substances to aquatic and terrestrial organisms .: En49-7/1-44-2016E-PDF - Government of Canada Publications - Canada.ca

b) When it can be determined that there will be no (or negligible) exposure from the proposed use(s) there is no need to provide data on potential hazards. Commonly, it may be argued that there is no exposure of a certain organism based upon the type of proposed use (e.g., only in greenhouses). The EFSA Guidance Document on Protected Crops[33] (EFSA, 2014) provided definitions for different types of protected crops and as well guidance on deriving exposure estimations for different types of environmental compartments. Following the publication of this guidance, it was considered necessary to address the ecotoxicological risk assessment for organisms for which the exposure is not covered by the Guidance on protected crops. Therefore, this topic was discussed in the general ecotoxicology meeting, Pesticide Peer Review Meeting 133 in September 2015 [34].

When justifying no exposure to specific organisms (as in the greenhouse example above), the following must be considered:

According to section 7.1.2 of (EU) 283/2013 "*For micro-organisms not occurring in the relevant European environments at the relevant highest taxonomic level and which are known to be pathogenic either for plants or for other organisms (see points 2.2 and 2.3), the host organisms in which proliferation of the micro-organism is expected shall be indicated. If non-target organisms indicated under Section 8 may be exposed to the host organisms colonised by the pathogen, information on the likelihood and, if applicable, level of exposure shall be provided".*

Hence, for non-native pathogenic micro-organisms data cannot be waived directly based on negligible exposure, as for these cases negligible exposure cannot be assumed. Please note that '*the relevant highest taxonomic level'* is meant to refer to either the strain, species or genus level, depending on the 'similarity' of the micro-organism strain with regard to the naturally occurring strains/ species or genera in the EU. Information on closely related micro-organisms can be addressed via identity, e.g. (phylo)genetic/molecular) similarity analyses and their biological properties, including the comparability of the virulence traits (*e.g.*, host range; see Section 1, 2 and Section 7).

Hazard testing

When discussing hazard testing for a micro-organism as an active substance, it is important to clearly understand what this encompasses. According to the definition provided in (EU) 283/2013, "

Microbial Pest Control Agent as manufactured*' ('**MPCA-MA**') means the outcome of the manufacturing process of the micro-organism(s) intended to be used as active substance in plant protection products, consisting of the micro-organism(s) and any additives, metabolites (including metabolites of concern), chemical impurities (including relevant impurities), contaminating micro-organisms (including relevant contaminating micro-organisms) and the spent medium/rest fraction resulting from the manufacturing process or, in case of a continuous manufacturing processes where a strict separation between the manufacturing of the micro-organism(s) and the production process of the plant protection product is not possible, a non-isolated intermediate*". The MPCA-AM may thus be a complex mixture of a living organism and chemicals, including the metabolites produced by the micro-organism.

[33] EFSA Journal 2014;12(3):3615 EFSA Guidance Document on clustering and ranking of emissions of active substances of plant protection products and transformation products of these active substances from protected crops (greenhouses and crops grown under cover) to relevant environmental compartments

[34] EFSA Supporting publication 2015:EN-924, Outcome of pesticides peer review meeting on recurring issues in ecotoxicology

Where there is a predicted exposure to non-target organisms from the intended use of the micro-organism, its metabolites and impurities , as mentioned in the Annex I, Introduction to (EU) No 283/2013, the information provided by the applicant should be sufficient to assess the foreseeable risk to non-target organisms from exposure to the micro-organism and relevant associated metabolites of concern.

According to the Annex I Introduction to Regulation (EU) 283/2013, all available relevant data from the scientific peer reviewed and open literature on the micro-organism should be provided. The literature search should be carried out in accordance with the Literature GD. See point A.3.5 for more information. Literature retrieved from this search should be reported in the relevant sections of the ecotoxicological dossier.

If the applicant has submitted a dossier to another regulatory agency or an authorization was granted in a country outside the EU, this information should be submitted to the EU Member State. Additionally, if the organism was assessed and approved under other regulations (e.g., micro-organism used as probiotic in feed) this information should also be submitted (n.b. information on waivers is included in each section, if applicable).

If no information could be retrieved from the peer-reviewed and open literature, the applicant should consider conducting the relevant tests (see the sections below for more specific information on testing).

With regard to the test material, point 4.2 of ANNEX I to Regulation (EU) No 283/2013 emphasizes that the active substance as manufactured should be used in studies (i.e., the MPCA-AM). When different test material (e.g. active substance manufactured in the laboratory or in a pilot plant production system) is used, a justification for equivalence of the MPCA-AM (as in full scale production) and the lab or pilot batches tested in ecotoxicological studies and used for the environmental assessment. For this the Guidance document on the assessment of the equivalence of technical materials of substances regulated under Regulation (EC) No 1107/2009 (SANCO/10597/2003 – rev 10.1, July 2012) can be used..
In general, GLP studies are preferred, but other scientifically sound studies can also be accepted. In section 3.2 of Commission Regulation (EU) No 283/2013, it is stated that by way of derogation from point 3.1 (i.e. conducting tests in accordance with the principles laid down in Directive 2004/10/EC) for a.s consisting of micro-organisms, tests done to obtain data on safety with respect to aspects other than human health may be conducted by official or officially recognised testing facilities or organisations which satisfy at least the requirements under points 3.2 and 3.3 of Introduction of the Annex to (EU) 284/2013. In order to avoid conducting extra vertebrate studies, studies that are not fully compliant with GLP or current test methods shall be considered in the data package if they were conducted in accordance to the test guidelines in place at the moment when the studies were conducted, however, when conducting new studies it is recommended to follow GLP.

The Commission Communication concerning Part B of the Annex to (EU) No 283/2013 (Official Journal of the European Union, 2023/C 202/03) provides a list of test methods and guidance documents relevant to the implementation of (EU) 283/2013. The document lists OECD guidelines, US Environmental Protection Agency (US EPA) OCSPP 885 test guidelines and the approach used by Canada's Pest Management Regulatory Agency (PMRA). The PMRA recommendations are, in fact, a combination of PMRA's microbial registration guidelines, US EPA test guidelines and detailed study descriptions of OECD test guidelines. It is important to note that there are fundamental differences between chemical and micro-organism based active substances. Micro-organisms are living organisms, and thus a specific approach is required when conducting ecotoxicological studies. This fundamental difference

should be reflected in testing by assessing the infectivity and pathogenicity of the organism in question. Therefore, testing a micro-organism -based active substance by using an OECD test guideline generally will not adequately address the potential for infectivity and pathogenicity. On the other hand, the US EPA OCSPP guidelines were written to test a variety of micro-organisms at very high level of exposure (i.e., maximum hazard concentration, MHC) intented to account for the potential field exposure and thus include the possible threshold for infection of test organism. Testing at these high levels, however, can result in challenges to testing, for example due to hydrophobicity, which complicates the interpretations of the study results.

Micro-organisms which are infectious can invade, evade the immune system of a host, persist in a viable state in the host or even subsequently multiply in tissues and organs over an extended period of time, with or without causing a disease.

A complete definition of pathogenicity is given in the PMRA Guideline, namely "*Pathogenicity refers to the ability of a micro-organism to infect a host (e.g., a test organism), establish itself and multiply there, and subsequently inflict injury or damage that might or might not lead to death. The effect on the host might be sublethal or lethal, and depends on the virulence of the pathogen (i.e., the micro-organism) as well as on host resistance or susceptibility*".[…] *Pathogenic and toxic substances are both capable of causing gross and microscopic anomalies (i.e., damage to tissues or organs, as observed by necropsy or histological examination). These substances can also cause sublethal effects such as growth retardation or impaired reproductive success, which are common biological endpoints in sublethal toxicity tests. Both pathogenic and toxic substances can cause the death of host organisms. Additionally, certain microorganisms produce toxins that can affect the host (test) organisms by way of a toxic response (i.e., toxigenicity the capacity of an organism to produce a toxin)".*

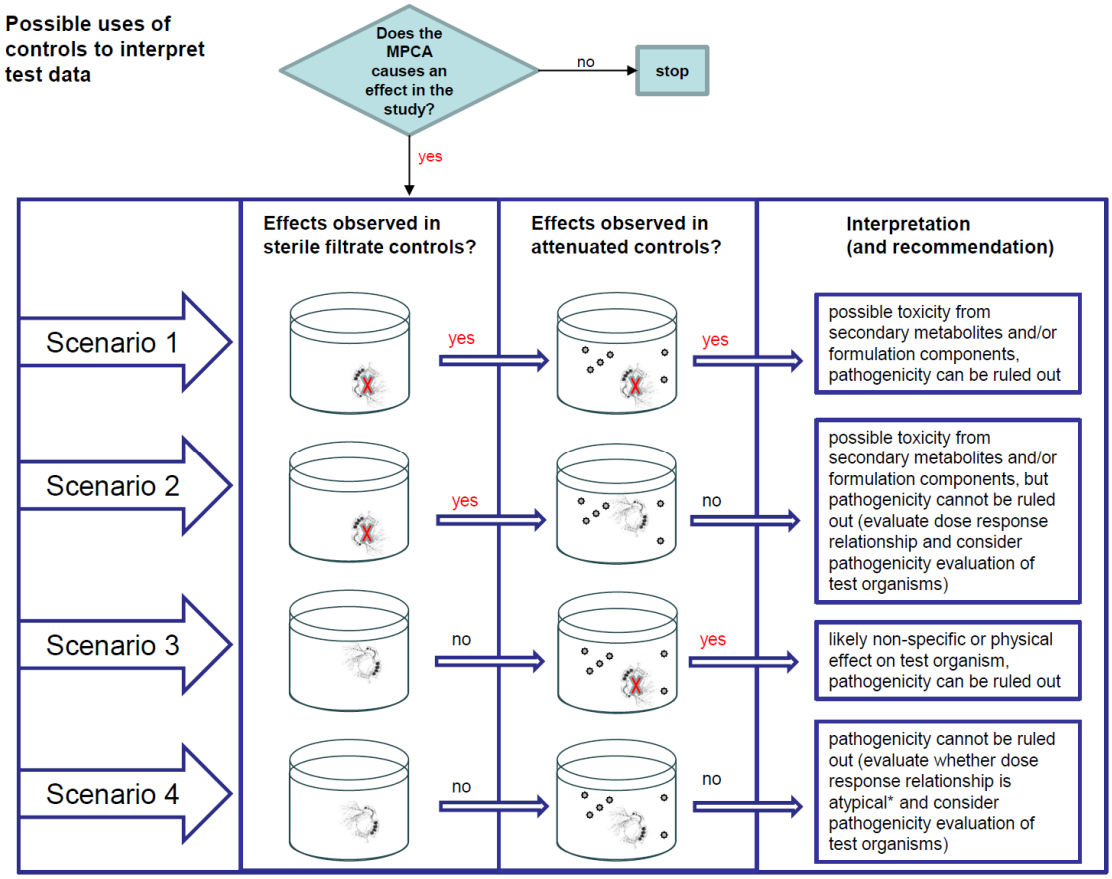
In order to ascertain whether the effects seen in tests are due to pathogenicity or due to toxicity, appropriate controls (i.e., sterile filtrate and non-infectious, attenuated controls) should always be included.

An attenuated control consists of the MHC of the micro-organism whose cell integrity was preserved, but which was inactivated by heating. The micro-organism has thus lost its viability and the capacity to infect a non-target organism and potentially cause pathogencity (i.e., disease).

A sterile filtrate control consists of the MHC of the micro-organism which was inactivated and consequently filtered to remove all the suspended solids (i.e., suspended particles associated with the inactivated micro-organism and any other particles from the test materials) from the sample. This control determines whether the soluble metabolites initially produced by the micro-organism prior to inactivation, and any other chemicals that are heat stable, are responsible for the effects seen in the test.

Please note that the heating procedure often used in attenuated ('autoclaved') controls may alter the physical nature and ecotoxicological properties of the test item, which complicates interpretation of test data (Karaoglan B, 2022[35]) (as shown in the figure below).

[35] Karaoglan B. (2022) Aquatic Safety Studies with Microbial Pesticides – Retrospective analysis and recent advancements, OECD Conference on Innovating Microbial Pesticide Testing.



* Note: Pathogenic responses are not expected to yield typical dose-response relationships as compared to a toxic response

As opposed to toxicity, pathogenicity does not follow a log dose-response curve and it is not particularly dependent upon the initial introduced concentration of the test material, in this case the micro-organism. While a chemical can be diluted to less harmful concentrations, a micro-organism cannot be so diluted. If a micro-organism is a pathogen, the initial concentration is not paramount, as the organism will multiply in the host and cause sub-lethal or lethal effects over time. Considering this, it is important to modify (e.g., increase study duration, include appropriate controls) the available test guidelines so that these effects can be better captured.

The choice of the appropriate non-target test organism is another important aspect when conducting tests with micro-organisms. Some of the standard test organisms were selected based on their sensitivity to chemicals (i.e., tier 1 NTAs), and also on the usefulness in the agriculture (i.e., honey bees, NTAs) and are considered representative for certain taxonomic groups. In the case of micro-organisms, however, biological characteristics (e.g., enthomopathogens) can already be a trigger for which taxonomic groups can be expected to be possibly impacted by the application of the micro-organism in the plant protection framework. Therefore, it is important to determine the host range as well as the most important route of exposure (e.g., contact for enthomopathogenic bacteria and fungi).

A.8.1 Effects on terrestrial vertebrates

Corresponding data requirement:	(EU) No 283/2013, Annex, Part B, 8.1
Relevant evaluation criterion:	(EU) No 546/2011, Annex, Part B, 1.7.1
Relevant decision making criterion:	(EU) No 546/2011, Annex, Part B, 2.7.1

Eligible for substantiated waiving: Yes (see the section above on data waiving)

Purpose of this point:
Provide information on the infectivity and pathogenicity of the micro-organism, its metabolites and impurities to birds, mammals, amphibians and reptiles. Please note that this point can be addressed with the information available in the peer-reviewed and public literature. In the context of the 3Rs, the vertebrate testing should be avoided, when possible.

Testing: if testing is required, then consider Commission Communication concerning Part B of the Annex to (EU) No 283/2013 (Official Journal of the European Union, 2023/C 202/03) section 8.1.
Note: Please note the OECD test with amphibians, were validated for investigation of thyroid active chemicals (e.g. OECD 248 XETA assay), substances active within hypothalamic-pituitary-thyroid (HTP) axis (e.g. OECD 231 AMA assay), and adverse effects on endocrine-relevant endpoints (e.g. OECD 241 LAGDA assay). Please note that these tests are not per se suitable to assess infectivity and pathogenicity in terrestrial amphibians. There are currently no test guidelines validated for reptiles. Nevertheless, should there be a concern for amphibians or reptiles (i.e., based on the m.o. in question and/or indicative literature data), the applicant is encouraged to discuss the options for testing and risk assessment with the Ctgb.

Considerations related to testing: In addition to the recommendations specified under the section “hazard testing”, it is highly recommended to:
- Perform the gross necropsy
- For pathogenic micro-organisms or viruses (e.g., entomopathogens) that are expected to multiply in the environment following an application according to the GAP, the oral dose administered in the studies should be at least the concentration/density possible in the field, e.g., taking into account the numbers of maximally infected insects that the terrestrial vertebrates may ingest on a daily basis in case of acute exposure. The oral dose might be justified based on the information submitted under fate section, 7.1.1. and 7.1.2.

A.8.2 Effects on aquatic organisms

Corresponding data requirement: (EU) No 283/2013, Annex, Part B, 8.2
Relevant evaluation criterion: (EU) No 546/2011, Annex, Part B, 1.7.2
Relevant decision making criterion: (EU) No 546/2011, Annex, Part B, 2.7.2
Eligible for substantiated waiving: Yes (see the section above on data waiving)

Purpose of this point:
Provide information on the infectivity and pathogenicity of the micro-organism, its metabolites and impurities to fish, aquatic invertebrates, algae and aquatic macrophytes. Please note that the data requirement for fish can be addressed with the information available in the peer-reviewed and public literature. In the context of the 3Rs, the vertebrate testing should be avoided, when possible.

Testing: if testing is required, then consider Commission Communication concerning Part B of the Annex to (EU) No 283/2013 (Official Journal of the European Union, 2023/C 202/03) section 8.2.

Considerations related to testing: In addition to the recommendations specified under the section “hazard testing”, it is highly recommended to:
- Perform gross necropsy in fish

- Studies with algae and macrophytes are required in cases where the micro-organism is known to have an herbicidal mode of action or to be closely related to a plant pathogen.
- In order to ensure that the test organisms are sufficiently exposed, the test item concentration shall be verified throughout the study period.
- Testing at maximum hazard concentration (MHC) as recommended in the US EPA OCSPP guideline can result in turbidy of the aqueous medium. The turbity can cause oxygen depletion in the test systen and as well physical effects on test organisms. These effects are unrelated to the infectivity and pathogenicity of the micro-organism. Before conducting these test, it is recommended to consult the Environment and Climate Change Canada (2016) Guidance document for testing the pathogenicity and toxicity of new microbial substances to aquatic and terrestrial organisms (EPS1/RM/44)[36] for additional guidance on testing.

A.8.3 Effects on bees

Corresponding data requirement:	(EU) No 283/2013, Annex, Part B, 8.3
Relevant evaluation criterion:	(EU) No 546/2011, Annex, Part B, 1.7.3
Relevant decision making criterion:	(EU) No 546/2011, Annex, Part B, 2.7.3
Eligible for substantiated waiving:	Yes (see the section above on data waiving)

Purpose of this point:
Provide information on the infectivity and pathogenicity of the micro-organism, its metabolites and impurities to bees including adult and larval stages

Testing: if testing is required, then consider Commission Communication concerning Part B of the Annex to (EU) No 283/2013 (Official Journal of the European Union, 2023/C 202/03) section 8.3.
Please note that for the uses in permanent greenhouses, exposure of pollinators introduced as part- of IPM programmes is considered relevant.

Considerations related to testing: In addition to the recommendations specified under the section “hazard testing”, it is highly recommended to:

- Conduct the studies at the maximum recommended application rate
- Verify the exposure. For oral honey bee larva studies the need for providing royal jelly in the diet might present a challenge as royal jelly is known to have antimicrobial effects and the exposure is hence expected to be lower. As the presence of royal jelly is a realistic scenario this phenomenon is not to be avoided. The ‘stability’ of the microorganims in the diet may be characterized with appropriate pre-testing analytical work (e.g., qPCR and/or plating techniques).. This will allow a more quantitative exposure estimate.

A.8.4 Effects on non-target arthropods other than bees

Corresponding data requirement:	(EU) No 283/2013, Annex, Part B, 8.4
Relevant evaluation criterion:	(EU) No 546/2011, Annex, Part B, 1.7.4
Relevant decision making criterion:	(EU) No 546/2011, Annex, Part B, 2.7.4
Eligible for substantiated waiving:	Yes (see the section above on data waiving)

Purpose of this point:

[36] https://publications.gc.ca/site/eng/9.827958/publication.html.

Provide information on the infectivity and pathogenicity of the micro-organism, its metabolites and impurities to non-target arthropods other than bees.

Testing: if testing is required, then consider Commission Communication concerning Part B of the Annex to (EU) No 283/2013 (Official Journal of the European Union, 2023/C 202/03) section 8.4.
Please note that for the uses in permanent greenhouses, exposure of natural enemies (of insect pests) introduced as part- of IPM programmes is considered relevant.

According to (EU) No 283/2013, Annex, Part B, 8.4, "*If studies are required, they shall be performed on two arthropod species other than bees playing a role in biological control and comprising different taxonomic groups (orders), where possible, for which agreed testing protocols are available, and the applicant shall provide a justification for number and taxonomy of the tested species. Moreover, these tests may require conditions affecting growth or viability of the micro-organism.*
Where adverse effects are observed in such studies, further relevant studies (e.g. extended laboratory tests or field studies under representative conditions in accordance with the proposed conditions of use) shall be performed".

Considerations related to testing: In addition to the recommendations specified under the section "hazard testing", it is highly recommended to:

- Conduct the studies at the maximum recommended application rate
- Verify the exposure rate
- In the case of entomopathogenic fungi and bacteria, it is important to consider the contact and oral route, respectively
- Consider the life-cycle of the non-target organism and whether it makes sense to use the organism in testig for pathogenicity.

A.8.5 Effects on non-target meso- and macro-organisms in soil

Corresponding data requirement:	(EU) No 283/2013, Annex, Part B, 8.5
Relevant evaluation criterion:	(EU) No 546/2011, Annex, Part B, 1.7.5
Relevant decision making criterion:	(EU) No 546/2011, Annex, Part B, 2.7.5
Eligible for substantiated waiving:	Yes (see the section above on data waiving)

Purpose of this point:
Provide information on the infectivity and pathogenicity of the micro-organism, its metabolites and impurities to non-target meso- and macro-organisms in the soil

Testing: if testing is required, then consider Commission Communication concerning Part B of the Annex to (EU) No 283/2013 (Official Journal of the European Union, 2023/C 202/03) section 8.5.

According to (EU) No 283/2013, Annex, Part B, 8.5, "*If studies are required, they shall be performed on two non-target meso- and macro-organisms species chosen based on the biological properties of the micro-organism under evaluation, where possible, for which agreed testing protocols are available.*
Where adverse effects are observed in such studies, further relevant studies (e.g. under representative conditions in accordance with the proposed conditions of use) shall be performed".

Considerations related to testing: In addition to the recommendations specified under the section “hazard testing”, it is highly recommended to:

- Conduct the studies at the maximum recommended application rate
- Verify the exposure rate

A.8.6 Effects on non-target terrestrial plants

Corresponding data requirement:	(EU) No 283/2013, Annex, Part B, 8.6
Relevant evaluation criterion:	(EU) No 546/2011, Annex, Part B, 1.7.6
Relevant decision making criterion:	(EU) No 546/2011, Annex, Part B, 2.7.6
Eligible for substantiated waiving:	Yes (see the section above on data waiving)

Purpose of this point:
Provide information on the infectivity and pathogenicity of the micro-organism, its metabolites and impurities to non-target terrestrial plants. These effects should be addressed if the MPCA-AM has a herbicidal mode of action or is known to be closely related to a plant pathogen.

Testing: if testing is required, then consider Commission Communication concerning Part B of the Annex to (EU) No 283/2013 (Official Journal of the European Union, 2023/C 202/03) section 8.6.

Considerations related to testing: In addition to the recommendations specified under the section “hazard testing”, it is highly recommended to:

- Conduct the studies at the maximum recommended application rate for the spray application and 10^8 CFU/g soil (dw), or 1000 times the expected concentration in the soil

A.8.7 Additional studies on the micro-organism

Corresponding data requirement:	(EU) No 283/2013, Annex, Part B, 8.7
Relevant evaluation criterion:	(EU) No 546/2011, Annex, Part B, 1.7.1-1.7.6
Relevant decision making criterion:	(EU) No 546/2011, Annex, Part B, 2.7.1-2.7.6
Eligible for substantiated waiving:	Not applicable

Purpose of this point:
Provide information on the infectivity and pathogenicity of the micro-organism, its metabolites and impurities to non-target organisms different from the species under 8.1-8.6. These studies are submitted under section 2 (for example host range, growth requirements, relationship to pathogens to non-target organisms, information on metabolites of concern), section 3 (for example function and target organisms, literature data), section 5 (for example, infectivity and pathogenicity studies in mammals, metabolites toxicity studies conducted in mammals), and section 7 (environmental exposure data). Information from approval under other regulations outside the EU can be submitted under this data point. Additional infectivity and pathogenicity studies can be submitted if effects were seen in points 8.1-8.6.

A.8.8 Information and toxicity studies on metabolites

Corresponding data requirement:	(EU) No 283/2013, Annex, Part B, 8.8
Relevant evaluation criterion:	(EU) No 546/2011, Annex, Part A, 1.5.2.1-1.5.2.6
Relevant decision making criterion:	(EU) No 546/2011, Annex, Part A, 2.5.2.1-2.5.2.6
Eligible for substantiated waiving:	Not applicable

Purpose of this point:
Identify or exclude the metabolites of concern.
According to the (EU) No 283/2013, Annex, Part B, 8.8: "*Information (e.g. scientific literature, studies results) on the toxicological characterization of the metabolites and the related identified hazards relevant to non-target organisms, collected or generated with the aim to identify the metabolites of concern , or to exclude them as being of concern, shall be submitted. […]*
For metabolite(s) of concern, identified based on information provided on hazard to (see point 8.8.1) and exposure of (see points 7.2.1 and 7.2.2) non-target organisms and listed under point 2.8, further information on their toxicity to the non-target organisms which are relevant (e.g. based on exposure and indication of toxicity) among those described in points 8.1 to 8.6, shall be provided. In case it is necessary to generate experimental data, relevant studies on ecotoxicology as provided for in Section 8 of Part A shall be submitted.'

Assessment principles – Product

P.1 IDENTITY OF THE APPLICANT, IDENTITY OF THE PLANT PROTECTION PRODUCT AND MANUFACTURING INFORMATION

P.1.1 Applicant

Corresponding data requirement:	(EU) No 284/2013, Annex, Part B, 1.1
Relevant evaluation criterion:	-
Relevant decision making criterion:	-
GLP-compliance:	Not relevant

Purpose of this point:
The applicant is the approval holder and must, as such, be identified as entity addressing all issues relating to the active substance, either directly or through a notified representative.

Conditional / waiving
Not relevant.

Confidentiality
No confidentiality can be claimed for the identity of the applicant.

P.1.2 Producer of the preparation and the micro-organism(s)

Corresponding data requirement:	(EU) No 284/2013, Annex, Part B, 1.2
Relevant evaluation criterion:	-
Relevant decision making criterion:	-
GLP-compliance:	Not relevant

Purpose of this point:
The producer acts as contact point with regard to the production of the preparation.

Conditional / waiving
Not relevant.

Confidentiality
Confidentiality can be claimed for the identity of the producer and the location of the plant where the preparation is produced, as this information complies with the criteria in Regulation (EC) No 1107/2009, Art. 63.

P.1.3 Trade name or proposed trade name, and producer's development code number of the preparation if appropriate

Corresponding data requirement:	(EU) No 284/2013, Annex, Part B, 1.3
Relevant evaluation criterion:	-
Relevant decision making criterion:	-
GLP-compliance:	Not relevant

Purpose of this point:
The trade name provides a unique identifier relating to the product's authorization. The development code number is associated with a specific compositional version of the product, and is required to keep track of any formulation changes thoughout the dossier history.

Conditional / waiving
Not relevant.

Confidentiality
Not relevant.

P.1.4 Detailed quantitative and qualitative information on the composition of the preparation

Corresponding data requirement:	(EU) No 284/2013, Annex, Part B, 1.4
Relevant evaluation criterion:	(EU) No 546/2011, Annex, Part B, 1.1.3
Relevant decision making criterion:	(EU) No 546/2011, Annex, Part B, 2.1.2
GLP-compliance:	5-BA data on contaminating micro-organisms, metabolites of concern, and relevant impurities shall be produced under GLP. *N.B. Product-level 5-BA data are only needed when an MPCA-AM specification is not available*

Purpose of this point:
The information on the composition of the preparation includes the MPCP-specification (derived or newly established) and a detailed description of components that have been added during the formulation process (co-formulants, other active substances, and any safeners / synergists). These data include all compositional parameters of the MPCP that are necessary to unambiguously identify the product, and that are furthermore critical to the multiple purposes of the product-level assessment.

Conditional / waiving
Not relevant.

Confidentiality
The same applies as for A.1.4; confidentiality can only be claimed for additives.
Data relating to the 5-BA may be placed in the confidential part of the DAR / RAR, but the specified results must appear in the respective non-confidential sections.

Evaluation principle
(i). Identification of the MPCA at strain level

Please refer to A.1.3.

(ii). Defining the specification for the preparation

The MPCP specification is the product-level counterpart of the MPCA-AM specification and should include all elements that have been established for the MPCA-AM. In general, the

MPCP-specification can be derived from the MPCA-AM specification by simple calculation (see 'Ideal derivative' below), but other approaches may be chosen when appropriate, i.e., when derivation by calculation is not practical (see 'Non-ideal derivative'), or when there is no MPCA-AM specification in the first place (see 'Non-derivative').

IDEAL DERIVATIVE

In general, an MPCA-AM specification is available for the microbial active substance, and the MPCP is an ideal derivative of the MPCA-AM. In other words, the specification elements that have been established for the MPCA-AM (see A.1.4.1 and A.1.4.2) are not intrinsically affected by the formulation process and their content can be translated to the MPCP-level by simple calculation:

$C_{EA} \times C_{AP} = C_{EP}$

Where 'C_{EA}' represents the content of a given element in the MPCA-AM, 'C_{AP}' is the content of MPCA-AM in the MPCP, and 'C_{EP}' is the content of the respective element in the product.

In this way, corresponding ranges (including min. and/or max. limits, wherever available) are derived for the MPCP for all established elements, except for the contaminating micro-organisms, which are separately covered on the product-level in the storage stability test (see P.2.6.2, 'Effects of temperature and packaging; Main long-term test – custom temperature'). Given the fact that the MPCA is a living entity, some unforeseen, baseline variation in the content of the micro-organism itself, and in that of any associated claimed active metabolites and MoCs may occur. For ideal derivatives, the specification ranges should however be sufficiently broad to allow for this.

NON-IDEAL DERIVATIVE

In some cases, the content of the MPCA in particular may not be so easily translated from the MPCA-AM specification, as the micro-organism has been substantially affected by the formulation process and any resulting changes to the matrix. As discussed in A.2.4, shifts in pH, temperature, osmotic pressure, or chemical composition of the environment, that commonly occur during formulation, may significantly affect the capacity of spores to form colonies or to germinate – and the subsequent enumeration results in terms of CFU or viable spores, respectively. In addition, but more subtle, the generally higher, co-formulant-enhanced dispersibility potential of the MPCP may prevent spore aggregation to a higher degree than is the case in the MPCA-AM. As a result, spores tend to be more clumped in the latter and may generate biased CFU-enumeration outcomes, as one clump of spores only counts as one colony.

Any mismatch between MPCA-AM and MPCP is likely to become apparent when comparing the CFU-count in the storage stability test with the MPCP-limits derived under the assumption of ideal derivation (see above). If not, the applicant will in any case be aware of any mismatches from archived QC-data. Depending on the severity (as evidenced by the percentage of product batches falling outside of the specified limits), it may be warranted to perform a separate 5-BA on the MPCP to determine a representative product-level range for the MPCA only (all other specification elements are simply calculated assuming ideal derivation).

Of course, the amended range must, on MPCP-level, comply with the criteria described in A.1.4.3 – the most important of which is in this context that the minimum will guarantee minimal effectiveness and the maximum safe use.

If needed, i.e., when the required quality cannot be guaranteed for product output, adaptations to the production process may be necessary.

NON-DERIVATIVE
Whenever no MPCA-AM specification is available (see A.1.4, 'Conditional / waiving') there is nothing from which an MPCP specification can be derived in the first place. In this case, an MPCP-dedicated specification needs to be established from scratch.
The approach and conditions are essentially the same as those described for MPCA-AMs in A.1.4. A notable difference is that MPCPs may be mixtures of MPCAs, whereas this is more of a theoretical option for MPCA-AMs. An MPCP specification that is newly established must cover all relevant specification elements for all MPCAs included in the mixture. If the elements get tangled up between the separate MPCAs and cannot be resolved by analytical means, it is desirable to establish an MPCA-AM specification anyway (provided that this is possible).

(iii). Composition of the preparation in terms of co-formulants, other active substances, and safeners and synergists

All ingredients in the preparation, i.e., active substances, co-formulants, and safeners / synergists, must be described in terms of identity (see (EU) No 284/2013, Part B, 1.4 for details) and gravimetric content. Content ranges are not allowed, as these would enable significantly different recipes (with potentially different properties) for the same MPCP. Formally, (EU) No 284/2013 approves of min. and max. contents for the MPCA-AM only, to enable additional stretching of the MPCA's specified range. As the CA-advised, one-log-unit broad MPCA-range (see A.1.4.3) already represents the practical maximum, more flexibility is deemed unnecessary. Besides, the MPCA-AM is likely to affect the rheological parameters of the preparation; modifying its content in the MPCP may therefore affect relevant physical properties.

(iv). Co-formulant function

No specific interpretation necessary for this point.

(v). Relevant contaminating micro-organisms

As mentioned under P.1.4 (ii) 'Ideal derivative', these will be addressed in the course of storage stability testing (see P.2.6.2).

P.1.5 Physical state and nature of the preparation

Corresponding data requirement:	(EU) No 284/2013, Annex, Part B, 1.5
Relevant evaluation criterion:	(EU) No 546/2011, Annex, Part B, 1.1.3
Relevant decision making criterion:	-
GLP-compliance:	Not relevant

Purpose of this point:
The definition of formulation type is a determinant of the technical characteristics that need to be investigated and of the exposure context. The assigned formulation type must align with the physical and compositional background of the product and with its intended use.

Conditional / waiving
Not relevant.

Confidentiality
Not relevant.

P.1.6 Method of production of the preparation and quality control

Corresponding data requirement:	(EU) No 284/2013, Annex, Part B, 1.6
Relevant evaluation criterion:	(EU) No 546/2011, Annex, Part B, 1.1.4
Relevant decision making criterion:	(EU) No 546/2011, Annex, Part B, 2.1.3 and 2.1.5
GLP-compliance:	Not relevant

Purpose of this point:
The formulation process must, *mutatis mutandis*, be a consistent continuation of the preceding manufacturing process in terms of control, efficiency, hygiene, and monitoring.

Conditional / waiving
Not relevant.

Confidentiality
Confidentiality can be claimed for details of the formulation process that comply with the criteria in (EC) No 1107/2009, Art. 63.

Evaluation principle
The formulation process must be described in detail so that it covers the consecutive order of component addition and corresponding conditions under which they are added.
Describe quality control steps implemented in the formulation process as outlined for the manufacturing process under A.1.5.1, 'The essential process checkup; Quality control', with regard to the placement of QC-steps in the process, methodology, and criteria.

P.1.7 Packaging and compatibility of the preparation with proposed packaging materials

Corresponding data requirement:	(EU) No 284/2013, Annex, Part B, 1.7
Relevant evaluation criterion:	(EU) No 546/2011, Annex, Part B, 1.2.2.1
Relevant decision making criterion:	-
GLP-compliance:	Not relevant

Purpose of this point:
The specifications of the MPCP's commercial packaging must be described in sufficient detail to allow (i) evaluation against European and possible national requirements regarding handling / storage / transport / disposal, (ii) verification of the equivalence with the packaging material tested in the storage stability test, and (iii) support of packaging extrapolation.

Conditional / waiving
Not relevant.

Confidentiality
Not relevant.

P.2 PHYSICAL, CHEMICAL AND TECHNICAL PROPERTIES OF THE PLANT PROTECTION PRODUCT

P.2.1 Appearance (colour and odour)

Corresponding data requirement:	(EU) No 284/2013, Annex, Part B, 2.1
Relevant evaluation criterion:	(EU) No 546/2011, Annex, Part B, 1.2.2.2
Relevant decision making criterion:	-
GLP-compliance:	Not relevant

Purpose of this point:
Clear characteristics are established for the MPCP that may be confirmed by simple visual and olfactory assessment. These may serve to identify the MPCP at a glance, and possibly any obvious product defects.

Conditional / waiving
Not relevant.

Confidentiality
Not relevant.

Evaluation principle
Color, physical state, and odor are commonly assessed according to US EPA Product Properties Test Guidelines OPPTS 830.6302, 830.6303, and 830.6304, respectively.

P.2.2 Explosivity and oxidising properties

Corresponding data requirement:	(EU) No 284/2013, Annex, Part B, 2.2
Relevant evaluation criterion:	(EU) No 546/2011, Annex, Part B, 1.2.2.2
Relevant decision making criterion:	-
GLP-compliance:	Only relevant for experimental data

Purpose of this point:
Any tendency of the MPCP to explode or to exhibit oxidizing behavior must be correctly assessed to avoid accidental combustion.

Conditional / waiving
In all conceivable cases, this Annex point is waivable, provided that the lack of explosive and oxidizing behavior of the preparation has been reasonably substantiated at component-level.

Confidentiality
Not relevant.

P.2.3 Flash point and other indications of flammability or spontaneous ignition

Corresponding data requirement:	(EU) No 284/2013, Annex, Part B, 2.3
Relevant evaluation criterion:	(EU) No 546/2011, Annex, Part B, 1.2.2.2
Relevant decision making criterion:	-
GLP-compliance:	Only relevant for experimental data

Purpose of this point:
Any capability of the MPCP to burn must be correctly assessed to avoid accidental ignition.

Conditional / waiving
In all conceivable cases, this Annex point is waivable, provided that the lack of flammable and self-heating behavior of the preparation has been reasonably substantiated at component-level. A notable exception is flammability of powdered formulations, which may not always be easily put aside by theoretical argumentation. In some cases, testing – according to recommended methodology and in compliance with GLP-criteria – may actually be preferable.

Confidentiality
Not relevant.

P.2.4 Acidity, alkalinity and if necessary pH value

Corresponding data requirement:	(EU) No 284/2013, Annex, Part B, 2.4
Relevant evaluation criterion:	(EU) No 546/2011, Annex, Part B, 1.2.2.2
Relevant decision making criterion:	-
GLP-compliance:	Not relevant

Purpose of this point:
The MPCP's pH must be established. The pH value is a robust and convenient indicator of any unintended changes to the preparation and of any tendency of the MPCP towards corrosiveness.

Conditional / waiving
No data are required for solid or non-aqueous products that will not be applied as aqueous dilutions.

Confidentiality
Not relevant.

Evaluation principle
No specific interpretation necessary. Contrary to what is suggested by the title of this Annex point, pH is always required and the necessity to determine respectively acidity and alkalinity is triggered by a pH below 4 or above 10.

P.2.5 Viscosity and surface tension

Corresponding data requirement:	(EU) No 284/2013, Annex, Part B, 2.5
Relevant evaluation criterion:	(EU) No 546/2011, Annex, Part B, 1.2.2.2
Relevant decision making criterion:	-
GLP-compliance:	Only relevant for viscosity testing, when the MPCP will be classified as aspiration hazard

Purpose of this point:
The viscosity is a determinant of H304-classification of the MPCP, in case it consists for ≥ 10 % of components that are classified as aspiration hazards themselves.

Based on the surface tension, it is established whether GAP-proposed dilutions of the MPCP can be considered surface active or not. Surface activity is required for spreading over and penetrating surfaces and is therefore a relevant parameter for product efficacy.

Conditional / waiving
Surface tension is only relevant for MPCPs that will be applied to the crop by spraying.

Confidentiality
Not relevant.

Evaluation principle
To allow efficient assessment of the surface activity of the product within the in-use range, the surface tension needs to be determined at the highest dilution. If the surface tension will be below 60 mN/m water at that level, the product can be considered surface active at all intended dilutions.

P.2.6 Storage stability and shelf life

Corresponding data requirement:	(EU) No 284/2013, Annex, Part B, 2.6
Relevant evaluation criterion:	(EU) No 546/2011, Annex, Part B, 1.2.2.1
Relevant decision making criterion:	-
GLP-compliance:	Only required for storage stability data relating to contaminating micro-organisms, relevant impurities, and MoCs

Purpose of this point:
The MPCP must be evidenced to retain its critical performance parameters, i.e., (i) viability of the MPCA(s), (ii) content of any claimed active metabolites, (iii) absence or acceptable quantities of microbial contamination, (iv) acceptable contents of any defined MoCs and relevant impurities, (v) packaging integrity, and (vi) acceptable technical properties, under relevant storage conditions. Furthermore, the MPCP's stability under the influence of environmental parameters must be demonstrated.

Conditional / waiving
The contaminating micro-organisms should be determined before and after storage, unless a reasoned case can be made that these are unlikely to be introduced or grow during storage.

Confidentiality
Not relevant.

Evaluation principle

P.2.6.1 Use concentration
The in-use concentration range must be indicated in appropriate terms (generally in % v/v or % w/v for liquid and solid formulations, respectively). The range should be covered in the tests conducted for the relevant technical properties.

P.2.6.2 Effects of temperature and packaging
In principle, a storage stability test is considered successful when, for the full duration of the test, (i) all relevant specification elements remain within their established ranges, (ii) the proposed packaging retains its integrity, and (iii) the technical properties associated with the

respective formulation type stay within acceptable limits.
For MPCPs, three types of storage stability tests are recognized, each intended to address a particular feature of the shelf-life. Other factors that may potentially affect stability are discussed under P.2.6.3.

SHORT-TERM TEST – HIGH TEMPERATURE

In accordance with OECD 85, 'accelerated storage stability tests' can in most cases not be considered to support a provisional long-term shelf-life for MPCPs. Despite this, the tests can however serve a useful purpose in MPCP-context as 'high temperature storage stability test'; a successful 18-week long test at 30 °C provides sufficient evidence that the respective MPCP may likely retain its efficacy when stored in a non-temperature controlled environment throughout a typical summer in the Northern -and Central Zone. Also, the test reasonably covers for any inevitable short-term high temperature exposure of the product during application in hot weather.
For MPCPs whose principal efficacy is caused by the activity of one or more claimed active metabolites, and for which the viable fraction is of minor direct or indirect importance, the additional 'accelerated storage'-functionality is regarded in the same way as for conventional chemical PPPs and may thus be used to support a provisional long-term shelf-life when the main long-term test is not yet available. In this case, the test must be carried out in appropriate commercial packaging. Also, the extant data package must at least contain adequate pre-storage data on contaminating micro-organism-screening; again, as it concerns viable components, post-high temperature storage screening is not supported. Except for the obvious differences, a high temperature test is performed in the same way as the main long-term test (see below).

SHORT-TERM TEST – LOW TEMPERATURE

The low temperature stability test is intended to assess the stability of liquid formulation types after exposure to frost. The test is mandatory from a practical perspective when the intended shelf-life for a liquid preparation demands storage at a temperature close to 0 °C, at which unintentional freezing of the MPCP due to temperature fluctuations cannot be ruled out.
In other situations, submission of the test is not tightly enforced; its absence may effectively be covered by a recommendation for the label: '*protect from frost*'.

MAIN LONG-TERM TEST – CUSTOM TEMPERATURE

The main long-term test may be carried out at any temperature that is favorable for the MPCP and practical for the seller/end-user, and may continue for as long as the applicant deems feasible. A shelf-life will be established based on any set of conditional parameters (temperature, duration, packaging) for which complete and acceptable data have been presented. There is no limit to the amount of shelf-lifes that may be assigned to a given MPCP.
The test report must include pre -and post-storage data on MPCA (and if relevant, claimed active metabolite) content, packaging integrity, physical/chemical/technical properties required for the respective formulation-type, contaminating micro-organism-screening, and, if relevant, on MoCs and relevant impurities. Specification elements, like the MPCA, claimed active metabolites, and components of concern, are expressed in line with the established specification.
Because stability and temperature resistance of a viable active are not always as reliable as would benefit long-term planning, inclusion of fully supportive interim timepoints may turn out to be hugely advantageous. The Competent Authority maintains a pragmatic opinion on the status of interim reports; as long as submission of a final version is guaranteed – i.e., by provision of a study plan that states a clear finalization date – interim data are used without any special reserve. Regarding GLP-status (whenever relevant), an interim report that (i) has been produced by a lab whose GLP-status could be verified, (ii) includes a GLP-statement

from the study director and a QA-statement from the QA-officer, and (iii) has an unmistakable appearance of an interim report, is considered to be GLP-compliant. Alternatively, the interim report may be drafted as a final version, whereas the actual final version may be submitted as an amendment to the final report.
Last, some leniency is allowed with regard to submission of long-term storage stability data for the context of an approval dossier; the data predominantly relate to the product-level and may therefore for the largest part be evaluated in the course of the product assessment. As long-term stability of the microbial substance itself is considered vital for approval, post-storage data relating to MPCA -and claimed active metabolite contents are required at the substance-level, whereas phys/chem/tech properties may be addressed at a later stage.

P.2.6.3 Other factors affecting stability
Under A.2.4, the relevant conditions are discussed that are required for growth and proliferation of the MPCA. In some cases, the MPCA's sensitivity to factors such as UV, humidity, pH, temperature, and osmotic potential may interfere with the context of (effective) use. In some cases, formulation design may serve to mitigate such interferences (e.g., by adding a solar protectant to a product containing a UV-sensitive species, that is nonetheless intended to be applied via foliar spray). The effectivity of such solutions must be evidenced, by rationale or simple test, e.g., in which two preparations (one containing a protectant and one that does not) may be exposed to a corresponding limiting factor, followed by a comparison of MPCA-viability in the two media.

Note that the scope of this point is limited to stability-decreasing factors – and corresponding mitigators – that come into play upon 'opening the MPCP-packaging'. Factors (but also any associated countermeasures) that are already expected to be in effect during storage of the product (e.g., humidity, but also potentially deleterious effects caused by co-formulants themselves) are already covered by typical storage stability testing, as it includes pre -and post-storage checking on all parameters that are possibly affected (viability, growth of contaminating micro-organisms, and technical properties).

P.2.7 Technical characteristics of the plant protection product

Corresponding data requirement:	(EU) No 284/2013, Annex, Part B, 2.7
Relevant evaluation criterion:	(EU) No 546/2011, Annex, Part B, 1.2.2.2
Relevant decision making criterion:	-
GLP-compliance:	Not relevant

Purpose of this point:
Technical characteristics need to remain within acceptance limits to ensure convenient and effective use of the MPCP. Suboptimal behavior under relevant conditions must be identified and resolved.

Conditional / waiving
Substantiated waiving may be accepted when the context of use of a product would render a particular technical property irrelevant.

Confidentiality
Not relevant.

Evaluation principle
(EU) No 284/2013, 2.7 states which technical characteristics shall be investigated for which

formulation type. Furthermore, the Commission Communication concerning Part B of the Annex to (EU) No 284/2013 (Official Journal of the European Union, 2023/C 202/02) provides information on recommended methodologies with which to assay these characteristics. Additionally, the FAO Manual includes formulation type-specific information on characteristics that need to be checked post-storage. Last, the respective CIPAC (-or equivalent) sources provide detailed guidance as to how tests are to be conducted.
The Competent Authority maintains a very limited degree of specific interpretation that provides any additional depth to the existing framework.

Currently, only suspensibility and spontaneity of dispersion require an alternative approach for micro-organisms. More than for chemicals, the distribution of the active substance is detached from the distribution of weight in the solution. Consequently, reporting suspensibility / spontaneity on a gravimetric basis for MPCPs does not allow a clear assessment of this property. The test results should therefore be presented as percentages derived from CFU-counts (or, of course, any other metric that is compatible with the MPCA's specification) in the respective solution samples.
In case of multiple MPCAs in the MPCP, the distribution of several of them should be assessed, as their dispersibility is not necessarily equivalent.

P.2.8 Physical and chemical compatibility with other plant protection products including plant protection products with which its use is to be authorised

Corresponding data requirement:	(EU) No 284/2013, Annex, Part B, 2.8
Relevant evaluation criterion:	(EU) No 546/2011, Annex, Part B, 1.2.2.3
Relevant decision making criterion:	-
GLP-compliance:	Not relevant

Purpose of this point:
Mixing of the MPCA with other products or adjuvants must not disturb the physical and chemical properties that are critical for the particular MPCP to a degree that the overall plant protection action may be affected. This point serves to investigate the compatibility between proposed mixing partners.

Conditional / waiving
This point cannot be waived, once tank mixing partners have been defined on the label. Otherwise this point can be considered not relevant.

Confidentiality
Not relevant.

Evaluation principle
No specific interpretation available.

P.2.9 Adherence and distribution to seeds

Corresponding data requirement:	(EU) No 284/2013, Annex, Part B, 2.9
Relevant evaluation criterion:	(EU) No 546/2011, Annex, Part B, 1.2.2.2
Relevant decision making criterion:	-
GLP-compliance:	Not relevant

Purpose of this point:
Tests submitted under this point must demonstrate that the MPCP-coating created around treated seeds contains sufficient, and sufficiently constant amounts of the MPCA(s) to ensure the level of plant protection action intended for the application. In addition, test results must show that the coating is tough enough to stick to the seeds during representative seed handling.

Conditional / waiving
This point cannot be waived, once the GAP includes applications as seed treatment. Otherwise this point can be considered not relevant.

Confidentiality
Not relevant.

Evaluation principle
Dedicated methods CIPAC MT 175 (seed loading and uniformity of distribution) and MT 194 (adherence to seed) provide sufficient practical information to carry out the respective tests. Furthermore, the GD on phys/chem/tech properties, SANCO/10473/2003 – rev.5, presents some additional notes under 2.10 of that document, especially regarding seed types that are not explicitly covered by the CIPAC-methodology, and representative seed treatment procedures.
As these sources are not specifically tailored for Part B active substances, some considerations must be added for the particular context of this EM.

REPRESENTATIVENESS OF THE SEED TREATMENT TECHNIQUE
The technique used to treat seeds (e.g., seed dressing, film coating, pelleting, slurry coating) is a major determinant of the overall beneficial effect for the plant that is achieved by this particular mode of application. As a rule, the technique used to generate test batches of treated seeds should be representative of the actual, commercial-scale seed treatment technique.
Formulations based on microbial active substances are generally less compatible with default seed coating processes, mainly due to a higher tendency towards inhomogeneity, and a narrower choice range of coating-enhancing formulants that are suited for MPCP. As a consequence, some modifications may be required to the process to secure the intended quality in terms of adherence, loading, and distribution. For the sake of representativeness, any process modifications need to be described and employed in the treatment of seed batches that are submitted to testing.

TROUBLESHOOTING DATA
Seed treatment with MPCPs is challenging and includes multiple steps that are critical to ensure effective application. Whenever submitted test data demonstrate unacceptable performance, it is often difficult to pinpoint a causative. To enable a more targeted evaluation, the test report must include the following data (that are mostly expected to be available anyway):

- the specification of the MPCP-batches used in the treatment process;
- pre-treatment of seed if relevant;
- the critical process conditions, i.e., the dilution factor of the product used to produce the slurry (in L product per L solvent), the composition of the solvent, the seed:slurry ratio (in g seed per L of slurry), the process temperature and duration;
- the post-process conditions, i.e., duration and conditions during drying and subsequent storage of the coated seeds – especially with regard to stressants (see A.2.4 and P.2.6.3).

DEFINITION OF TEST CRITERIA

Worst case testing – As the number of crops or crop groups for which seed treament is proposed, and the range of dilution factors for the slurry that is stated per crop easily lead to a large number of conditional combinations, testing only needs to cover one (if possible) or more (if needed) worst case scenarios.
What can be interpreted as worst case for seed type depends on the tested parameter; (i) smooth seeds are reasonably considered worst case regarding adhesion, (ii) smaller seeds may be worst case with regard to loading capacity per seed, and (iii) irregularly shaped seeds with a variable size distribution are worst case regarding distribution.
For dilution factors, the most diluted slurry according to GAP-specifications is pragmatically considered worst case, due to expected less favorable rheological conditions, and a lower overall loading.
The selected scenario(s) should be justified in perspective of the preceding information.

Compliance with GAP-specified loading – Pre -and post-agitation seed loading must be expressed in a way that is compatible with the GAP (usually as CFUs per g of seed), and need to fall within the GAP-specified range. Seed treatment parameters must be determined pre - and post-storage.

ANALYTICAL METHODOLOGY

In principle, the analytical method employed under this point is the same as the one used to determine the MPCA-content (or that of claimed active metabolite(s), if relevant) in the preparation (see P.5.1). The procedure is only different with regard to sample preparation, which involves (i) collection of most of the coating material from the treated seeds, and (ii) resuspension of the material in buffer, to a degree that limits the occurrence of colony aggregation and subsequent underestimation of CFUs (and to a smaller degree that of the claimed active metabolite content).
For (i), no specified criterion for recovery is defined, as recovery is commonly expected to easily exceed 50%, which already represents a pragmatically acceptable bias. Step (ii) is considered more critical, as it could potentially introduce a far greater artifact in the data. Along with the troubleshooting data, the performance of this step should be most closely evaluated in case of underperformance of the seed treatment process.
If the MPCP contains multiple MPCA(s), data must be submitted for at least two of them as this is deemed sufficiently representative. As chemicals behave differently, data on claimed active metabolite(s) must be reported as well.

P.3 DATA ON APPLICATION

The information provided in this section is essential for the risk assessment as they indicate both qualitative and quantitative information on the proposed uses (in accordance with Good Agricultural Practice).

P.3.1 Field of use envisaged

Corresponding data requirement:	(EU) No 284/2013, Annex, Part B, 3.1
Relevant evaluation criterion:	The information provided in this section forms the basis of the risk assessment. For relevant evaluation and decision making criteria is therefore referred to other sections of the risk assessment.
Relevant decision making criterion:	

Purpose of this point:
The indication of the field of use of the plant protection product will be used to assess the relevance of the information on the efficacy for the proposed use and to determine the appropriate exposure scenario for the risk assessments for humans, animals and the environment (if required)

Assessment principle:
The field(s) of use for the PPP, existing (in case of renewal) and proposed, can be specified from among the following:

- agriculture, horticulture, forestry, or viticulture,
- protected crops (e.g. in greenhouses)
- non-cultivated areas,
- home gardening,
- houseplants,
- stored food/feed items,
- seed treatment,
- other (needs to be specified).

If amateur/non-professional use is intended (whether or not in addition to professional use), this should be clearly indicated.

The current data requirement closely resembles the field of use described under A.3.2, with the distinction that under A.3.2. the field of use is specified for the **intended use** of the micro-organism, while here, the field use for the **representative PPP (active substance)** or **PPP to be registered** (**product**) should be listed. Note that the field(s) of use may deviate between products in case of more than one representative PPP (e.g. when the dossier for the active substance approval of the micro-organism is initiated by a taks force, each submitting the data for their own representative PPP formulation). In the case of a PPP registration, the field(s) of use may be more extensive than indicated previously for the representative product for active substance approval. However, all fields of use should be covered by the risk assessments performed in other sections.

In addition to the relevance of this information for the efficacy assessment, information on the field of use is needed to determine the appropriate exposure scenario for the risk assessments for humans, animals and the environment. The actual plants or plant products to be protected,

described under P.3.3, should as well be taken into account. For instance, (1) use in greenhouse may results in less exposure of non-target organisms than use in open fields, (2) use in forestry sector potentially may imply lower exposure for bystanders compared to use in home gardening, (3) use in stored food/feed items may indicate potentional exposure to consumers due to residues.

Interpretation of the framework in specific cases

Protected crops
Note that for the protected crops, a distinction should be made in the PPP dosier between crops cultivated in permanent greenhouses (high- and low-tech) and crops cultivated in non-permanent structures (eg. plastic walk-in tunnels). The first will be evaluated interzonally, while for the latter a zonal registration dossier should be prepared (in line with the Agreement of the Interzonal Steering Committee and applicable from June 1st, 2022 and onwards).

For more information regarding different types of protection see A.3.2, Field of use envisioned includes also a reference to the "EFSA Guidance Document on clustering and ranking of emissions of active substances of plant protection products and transformation products of these active substances from protected crops (greenhouses and crops grown under cover) to relevant environmental compartents" EFSA Journal 2014; 12(3):3651.

P.3.2 Mode of action on the target organism

Corresponding data requirement:	(EU) No 284/2013, Annex, Part B, 3.2
Relevant evaluation criterion:	The information provided in this section forms the basis of the risk assessment. For relevant evaluation and decision making criteria is therefore referred to other sections of the risk assessment.
Relevant decision making criterion:	

Purpose of this point:
In addition to the mode of action of the micro-organism on the target organism that has already been extensively described in accordance with point 2.3 of Part B of the Annex to Regulation No 2022/1439, at this point any information on the MoA regarding additional components in the PPP (e.g. co-formulants) that may have an effect (e.g on efficacy, and/or on human and animal health or the environment), and therefore requires further information, should also be considered.

Assessment principle:
A concise summary/conclusion of the information provided in accordance with point 2.3 of part B of the Annex to Regulation (EU) No 283/2013 (as described under point A.2.3) needs to be provided for PPP registration. It is essential to include this information in the dRR, as the MoA plays an important role in the efficacy assessment and the dRR should preferably be read as a stand-alone document. However, reference can be made to the active active substance dossier if needed. Possibility of extrapolation may, for instance, depend on the MoA. For more detailed explanation regarding extrapolation see P.6.3 on testing effectiveness.

In addition to the MoA of the micro-organism on the target organism, other components of the PPP (e.g. co-formulants, including also other micro-organisms or chemical active substances) may trigger significant difference in the mode of action described for the single active substance. Hence, also for these components information on the mode of action on the target

organism(s) should be provided. More details on the efficacy principles concerning co-formulated products are provided under point P.6.1 on “Preliminary data”.

P.3.3 Function, target organisms and plants or plants products to be protected and possible risk mitigation measures

Corresponding data requirement:	(EU) No 284/2013, Annex, Part B, 3.3
Relevant evaluation criterion:	(EU) No 546/2011, Annex, Part B, 1.3.1
	(EU) No 546/2011, Annex, Part B, 1.3.2
Relevant decision making criterion:	(EU) No 546/2011, Annex, Part B, 2.3.1.1

Purpose of this point:
The function, target organisms and plant or plant products to be protected needs to be specified. This is not only essential information for the assessment of efficacy, but also the risk assessment on human health, and the environment.

Assessment principle:
It should be indicated why the micro-organism will be applied as active substance for plant protection. The biological function can be specified as one of the following:
- control of bacteria,
- control of fungi,
- control of viruses,
- control of insects,
- control of mites,
- control of molluscs,
- control of nematodes,
- control of plants,
- other (shall be specified)

In addition, details on the target organism(s) are needed to provide an overview of specific crop/pest combinations. This also includes information regarding occurrence and agro-economical relevance of the pest. One requirement is documentation needed to asses whether significant damage to plants or plant products or loss of yield occur if the PPP is not used, in line with point 1.3.2 of Part B of Annex to regulation (EU) No 546/2011. Agro-economical relevance of target organism(s) may differ among cMS. Therefore, the information provided here can also be used to support the conclusion on which conditions will be considered worst case for the proposed claim (and hence should preferably be included within the efficacy tests). Note that no authorisation can be granted against target organism(s) that are not considered harmful for the crop or plant products to be protected. Neither can authorization be granted for those uses that are not considered a problem under the conditions applied for (e.g. against a target-organism that does not occur in the zone where authorization is requested)

To avoid misinterpretation of the intended target organims, EPPO codes and scientific names for the intended target organisms should be used.

Furthermore, information should be provided on the crops, crop groups, or plant products that are intended for the plant protection use. To avoid misinterpretation of ambiguous terms (e.g. ornamentals can encompass different plant groups in different memberstates) EPPO codes and scientific names for the intended crops, crop groups or plant products should be used. If

relevant, the crop destination or purpose of the crop can be added (e.g. oilseed rape can be cultivated as oilseed crop but also as green manure crop, poppy seeds can be cultivated as oilseed crop, but also as herb seed crop, for potatoes there is a difference between seed, ware and starch potatoes). When the proposed uses are limited to a specific subset of crop uses (e.g. only for seed production, or fodder), this should be clearly indicated.

If relevant also the part of the plant that will be used may be indicated (e.g. for medical crops roots, leaves or seeds). Ctgb uses the DTG 2.2 crop definition list, although different crop definitions are applicable for different Member States. Therefore, it is essential to indicate the proposed uses as clearly as possible, to avoid misunderstanding.

The information provided here should be in line with the information provided in the GAP table as presented in appendix 1 of the template for dRR B0 for product approvals In case of active substance approval: Document D generated by the report generator tool in IUCLID.

P.3.4 Application rate

Corresponding data requirement:	(EU) No 284/2013, Annex, Part B, 3.4
Relevant evaluation criterion:	(EU) No 546/2011, General Introduction, point 2.4
Relevant decision making criterion:	The information provided in this section forms the basis of the risk assessment. For relevant decision making criteria is therefore referred to other sections of the risk assessment.

Purpose of this point:
The application rate of the PPP (for each use, using the most relevant units) is essential information for all other aspects of the risk assessment (efficacy, physical, chemical and technical properties of the PPP, and the risk assessment on human and animal health or the environment).

Assessment principle:
For each method of application and each use, the rate of application per unit treated, in terms of g, kg, ml, or l for the plant protection product and in terms of appropriate units for the micro-organism (e.g. number of active units, colony forming units (CFU) or international units per volume or weight), shall be provided. For protected crops and home gardening use rates shall be expressed in g or kg/100 m^2, or g or kg/m^3, ml or l/100 m^2, or ml or l/m^3.

A correctly indicated application rate is essential information for all other aspects of the risk assessment (efficacy, physical, chemical and technical propterties of the PPP, and the risk assessment on human and animal health or the environment).

EPPO standard PP1/239(3) on “Dose expression for plant protection products” explains in detail the dose expression for plant protection products. Detailed information on how to draft a GAP table is provided by Ctgb, and guidance can also be found in Appendix 1 of the dRR B0 template.

The GAP table is based on the min. max. or mean CFU per unit formulated product.
For micro-organisms, in addition to the rate of application in kg or l product/ha, the number of CFU, IU, or OB (or other relevant unit) per ha should be indicated. As PPP based on micro-organisms can be more variable in composition than conventional chemical products, it should

be indicated what the range of CFU, IU, or OB (or other relevant unit) in the formulated product is. Furthermore, it is highly recommended to explain in detail which numbers of this range were used to generate the GAP table.
Besides the range in content of the micro-organism, PPPs based on micro-organisms can also have a range in their application rate (for instance 0.5 to 1 l product/ha, depending on e.g disease pressure) and a range in water spray volume to be used (if applicable). As a result, when calculating the numbers of e.g. CFU/ha, these numbers can deviate substantionally when based on the minimum amount of CFU in the formulated product compared to the maximum amount of CFU.
It is considered extremely helpful if information on the minimal and maximal amount of CFU/ha is provided. This information can be included as "Remarks on application rate" in IUCLID (See IUCLID active substance application manual, paragraph 3.1 "Use of the plant protection product (GAP)"). Including these details prevents misunderstanding and unnecessary re-calculations of alternative approaches.
It should be noted that, while from an efficacy point of view, the minimum amount is the most relevant to assess negative side-effects on human and animal health or the environment the maximum amount is the most informative value. The mean (nominal or average) of the 5-batch analysis provided for the formulated product is an arbitrary value, and as such not meaningful.

Interpretation of the framework in specific cases

Dose rate expressions (list is not exhaustive)

Dose rates in high crops – Because of historical reasons, many different dose rate systems exist on national labels for high growing crops, this greatly complicates the writing and evaluation of dossiers

For the central registration zone dates have been set for introduction of LWA as the mandatory dose expression system in pomefruits, grapevine and high growing (fruiting) vegetables. All trials carried out in these crops after 1-1-2018 must be planned and carried out on the basis of LWA. Furthermore, per 1-1-2020 all dossiers submitted under article 33 must be supported by trials planned and carried out based on LWA as the efficacy unit of dose expression. The dose rate in LWA should be included in the GAP table. It is important to note that the rate per unit of surface area (e.g. kg/ha) should always be included as well, as it is required for risk assesments. The dose rate in LWA is needed for the efficacy section only. EPPO standard PP1/239(3) on "Dose expression for plant protection products" explains the principle and necessity of LWA in more detail.

Seed treatment – Typical dose rate for seed treatment is given in a relevant unit per number of seeds or 100 kg seeds. The amount per ha can be calculated from this dose rate via the maximum number of seeds that will be sown per ha. The competent authority in NL (Ctgb) uses the following the following list of seed amounts and planting density for application in the Netherlands:
Seed sowing rate and plant density in the Netherlands | Assessment framework PPP | Board for the Authorisation of Plant Protection Products and Biocides (ctgb.nl). Similar list may be available at other competent authorities.

Incorporation – For incorporation (e.g. in potting soil), the dose expression can be provided in kg or l product/m^3. In that case an estimation of the amount of m^3 potting soil per ha should be provided, unless it can reasoned that there is no emission to soil, surface water of groundwater (e.g. for granular soil incorporation applications in greenhouses)

Row, strip or spot treatment – For row or strip treatment, the percentage of treated area

should be indicated. For spot treatments (e.g. to control individual weeds) it is assumed that this will consist of only a maximum of 10% of the entire area to be treated. For strip treatment, typically 50% of the area will be treated. Unless stated otherwise, in these cases both the local dose rate and the dose rate for the entire area (e.g. 10 or 50% of the the local dose rate, depending on the treated area) should be indicated.

P.3.5 Content of micro-organism in material used (e.g. in the diluted spray, baits or treated seed)

Corresponding data requirement:	(EU) No 284/2013, Annex, Part B, 3.5
Relevant evaluation criterion:	(EU) No 546/2011, General Introduction, point 2.4
Relevant decision making criterion:	The information provided in this section forms the basis of the risk assessment. For relevant decision making criteria is therefore referred to other sections of the risk assessment.

Purpose of this point:
The content of the micro-organisms in the material used needs to be reported, using appropriate units, such as number of active units (e.g. CFU, IU, OB, or other) per volume or weight formulated product, including information regarding water spray volumes used (if relevant) or amount of micro-organisms per number of seeds (in case of seed treatment). This information is essential for all aspects of the risk assessment (efficacy, physical, chemical and technical properties of the PPP, and the risk assessment on human and animal health or the environment), as it forms the basis for the calculation of the amount of CFU (or other relevant unit) applied per ha.

Assessment principle:

Content of the micro-organism in formulated product
The content (min.-max.) of the micro-organism in the formulated product will be the basis of the calculation of the amount of micro-organism applied per ha (or other relevant unit) and is thus important for the evaluation on efficacy and the risk assessment on human and animal health or the environment. As described earlier under P.3.4, it will be highly appreciated to (briefly) explain whether the calculated GAP values are based on the minimal or maximum amount of CFU (or other relevant unit) in the formulated product.

Water spray volume
Water spray volumes (if relevant) should be indicated here. Water spray volume is not only relevant for efficacy, but also for human toxicology and/or ecotoxicology (the most diluted version and the most concentrated uses of the product should be indicated), fate and behaviour in the environment (to asses spray drift if required), but also to correctly asses physical, chemical and technical properties of the product.

Seed treatment
As indicated above under P.3.4., the amount of micro-organisms (using the appropriate unit) should be indicated per number of seeds or 100 kg seeds. For instance, this is important for the risk assessment of ecotoxicology (e.g. for birds and/or mammals who may potentially eat these treated seeds). Note that for seed treatment, the volume of diluent (slurry volume used for the coating itself) should be specified.

Dipping of flower bulb and flower tuber crops
Fluid uptake during dipping application and planting density per ha, resulting in the actual amount (in the appropriate unit) applied per ha, should be provided.

P.3.6 Method of application

Corresponding data requirement:	(EU) No 284/2013, Annex, Part B, 3.6
Relevant evaluation criterion:	(EU) No 546/2011, General Introduction, point 2.4
Relevant decision making criterion:	The information provided in this section forms the basis of the risk assessment. For relevant decision making criteria is therefore referred to other sections of the risk assessment.

Purpose of this point:
The method of application of the PPP is used for instance to determine the exposure to humans or the environment (if required).

Assessment principle:
The proposed method of application needs to be described, indicating the type or equipment to be used, if any, as well as the type and volume of diluent to be used per unit of area of application, or volume of plant protection product. Examples of methods are (but not limited to): high volume spraying, low volume spraying, spreading, dusting, drench, drilling, etc. It should also be specified where the application will be performed, e.g. overall, broadcast, row, individual plant, between the plants etc. (see also the example provided for application rate of row treatment under P.3.4). When a mandatory tank mix is proposed for the PPP, this should be clearly specified (as this information must be considered by all other aspects of the risk assessment).

Information on the method of application is essential information for the risk assesment as for instance the use of machinery that has the potential to generate drift during spray application, might pose a higher risk for bystanders. This is only relevant in case potential hazards for humans are indicated for the PPP. In contrast, the risk for bystanders may be neglible for e.g. paint application on tree trunks for the use in forestry.

P.3.7 Number and timing of applications on the same crop, duration of protection and waiting period(s)

Corresponding data requirement:	(EU) No 284/2013, Annex, Part B, 3.7
Relevant evaluation criterion:	(EU) No 546/2011, General Introduction, point 2.4
Relevant decision making criterion:	The information provided in this section forms the basis of the risk assessment. For relevant decision making criteria is therefore referred to other sections of the risk assessment.

Purpose of this point:
The maximum number of applications to be used on the same crop provides information on the maximum amount of product that can be used on a crop and is needed for the risk

assessment of several aspects (e.g. residue and the effects on non-target organisms). If applicable, the interval between applications (in days) needs to be provided.

Also the timing/growth stages of the crops to be protected is essential information for various aspects of the risk assessment (e.g. , residue, efficacy, effects on non-target organisms)

The developmental stages of the target organisms may be needed in the efficacy assessment.

Assessment principle:
Information on maximum number of applications on the same crop indicates if the intended pest control strategy would be because the application of the micro-organism acts *via* an inocculative approach (where the micro-organism is expected to multiply), or an inundative approach (where directly a high number of micro-organism is applied to promote a rapid control of pests over the short term). If several crop cycles are envisioned during the growing season, this should be clearly indicated (as this determines the max. amount of product may be used on a yearly basis at the same location).

Information regarding the number of applications, in combination with interval and the growth stage of the crop provides essential information for the assessment of residues. Analogously, information on growth stage of the crop provides information to correctly assess exposure of non-target organisms (e.g. pollinators and application during flowering). Growth stages are indicated as BBCH stages (if applicable), e.g. as described by Meier (2018). Note that it is highly recommended to also provide months of application, as BBCH-stages will be achieved in individual member states in different time frames.

Information on the development stage of target organisms may support the assessment of efficacy.

P.3.8 Proposed instructions for use

Corresponding data requirement:	(EU) No 284/2013, Annex, Part B, 3.8
Relevant evaluation criterion:	-
Relevant decision making criterion:	(EU) No 546/2011, General Introduction, point 3.6

Purpose of this point:
The proposed instructions for use of the plant protection product to be printed on labels and leaflets need to be provided. Details on the risk mitigation measures (if relevant) should be included.

Assessment principle:
A draft label needs to be submitted, in accordance with the information provided in the Good Agricultural Practice table and including possible risk mitigation measures (if relevant).

Note that risk mitigation measures should follow from and be supported by the data provided under the other sections (e.g. P.7 on effects on humant health, P.8 on residues, P.9 on fate and behaviour in the environment and P.10 on the effect on non-target organisms), as also discussed below under point P.3.9.

For the representative product used during active substance approval, a general draft label can be drawn up. In contrast, for product registration, when drafting the label, national requirements of individual member states should be taken into account. For specific details contact can be sought with relevant competent authorities prior to submission.

P.3.9 Safety intervals and other precautions to protect human health, animal health and the environment

Corresponding data requirement:	(EU) No 284/2013, Annex, Part B, 3.9
Relevant evaluation criterion:	(EU) No 546/2011, General Introduction, point 2.4
Relevant decision making criterion:	The information provided in this section forms the basis of the risk assessment. For relevant decision making criteria is therefore referred to other sections of the risk assessment.

Purpose of this point:
Information provided here would support the risk assessors in evaluating possible hazards liked to human and animal health, residue, and non-target organisms.

Assessment principle:
The provided information needs to follow from and be supported by the data provided for the micro-organism(s) and that provided under Sections 7 to 10.

(i) Where relevant pre-harvest intervals, re-entry periods or withholding periods necessary to minimise the presence of residues in or on crops, plants and plant products, or in treated areas or spaces, with a view to protecting humans or livestock, needs to be indicated e.g.:

- pre-harvest interval (in days) for each relevant crop,

- re-entry period (in days) for livestock, to areas to be grazed,

- re-entry period (in hours or days) for humans to crops, buildings or spaces treated,

- withholding period (in days) for animal feedingstuffs and for post-harvest uses,

- waiting period (in days), between application and handling treated products.

- waiting period (in days), between last application and sowing or planting succeeding crops.

(ii) Where necessary, in the light of the test results, information on any specific agricultural, plant health or environmental conditions under which the plant protection product may or may not be used should to be indicated.

P.4 FURTHER INFORMATION ON THE PLANT PROTECTION PRODUCT

P.4.1 Procedures for cleaning and decontaminating of application equipment

Corresponding data requirement:	(EU) No 284/2013, Annex, Part B, 4.1
Relevant evaluation criterion:	(EU) No 546/2011, Annex, Part B, 1.3.3 (i)
Relevant decision making criterion:	(EU) No 546/2011, Annex, Part B, 2.3.2.8
GLP-compliance:	Not required for method validation

Purpose of this point:
Cleaning / decontaminating procedures must be sufficiently effective to avoid an impact on efficacy and to prevent crop damage caused by carry-over of residual MPCP that may be present in a spray tank.

Conditional / waiving
When the MPCP is unlikely to negatively affect plant health, the effectivity of cleaning procedures does not need to be evidenced.

Confidentiality
Not relevant.

Evaluation principle
Adequate cleaning and decontaminating procedures (for both application equipment and protective clothing) needs to be described.

EPPO standard PP1/292(1) on “Cleaning pesticide application equipment (PAE) – efficacy aspects” describes methods that can be used to examine wether cleaning procedures are sufficient to ensure that residues of PPPs do not remain in the PAE after cleaning.

If significant (>50%) phytotoxicity is observed, further testing is required. According to EPPO standard PP1/292(1) dose response relationships should be established. However, when the observed phytotoxicity is not due to a chemical component such as a co-formulant, a different approach may be required. Hence, for micro-organisms, in case of phytotoxicity, it will be necessary to deviate from EPPO standard PP1/292(1) and, for instance, to demonstrate with small scale testing that appropriate cleaning procedures are sufficient.

It should be noted though, that for the majority of micro-organisms severe phytotoxicity symptoms are not reasonably expected.

The word “decontamination” suggests complete disinfection. However, adequate cleaning and decontaminating procedures should always be viewed in light of the risk assessment. In the absence of demonstrated negative effects of the micro-organism, the survival of a single cell or spore may not be considered a potentional risk. Nonetheless, if required, adequate cleaning and decontaminating procedures needs to be provided. But for example washing may already be sufficient in these cases.

P.4.2 Recommended methods and precautions concerning: handling, storage, transport, fire or use

Corresponding data requirement:	(EU) No 284/2013, Annex, Part B, 4.2
Relevant evaluation criterion:	(EU) No 546/2011, Annex, Part B, 1.5.1.3 (d)
Relevant decision making criterion:	-
GLP-compliance:	Not required for method validation

Purpose of this point:
Precautionary methods must be defined for safe operation in the context of handling, storage, transport, fire, or use.

Conditional / waiving
Not relevant.

Confidentiality
Not relevant.

P.4.3 Measures in case of accident

Corresponding data requirement:	(EU) No 284/2013, Annex, Part B, 4.3
Relevant evaluation criterion:	-
Relevant decision making criterion:	-
GLP-compliance:	Not required for method validation

Purpose of this point:
Practical response actions must be defined to mitigate the effects of MPCP-related accidents (i.e., spillage, contamination, damage to packaging, calamities, injury).

Conditional / waiving
Not relevant.

Confidentiality
Not relevant.

P.4.4 Procedures for destruction or decontamination of the plant protection product and its packaging

Corresponding data requirement:	(EU) No 284/2013, Annex, Part B, 4.4
Relevant evaluation criterion:	-
Relevant decision making criterion:	-
GLP-compliance:	Not required for method validation

Purpose of this point:
Controlled measures to dispose of the product and its packaging must be evidenced to adhere to principles of environmental friendliness, economy, and practicality.

Conditional / waiving
Not relevant.

Confidentiality
Not relevant.

P.5 ANALYTICAL METHODS

P.5.1 Methods for the analysis of the preparation

Corresponding data requirement:	(EU) No 284/2013, Annex, Part B, 5.1
Relevant evaluation criterion:	(EU) No 546/2011, Annex, Part B, 1.4.1
Relevant decision making criterion:	(EU) No 546/2011, Annex, Part B, 2.4.1
GLP-compliance:	Not required for method validation

Purpose of this point:
The differences between MPCP and MPCA-AM may necessitate adaptation of the analytical methodology evaluated under A.4.1, to maintain functionality. Under this point, the need for such adaptations is discussed, and effectuated adaptations are described and evaluated.

Conditional / waiving
Whenever MPCA-AM and MPCP are the same (or at least bridgeable for analytical purposes) and the required method validations have already been provided under A.4.1, no data are required in addressal of this point.

Confidentiality
Not relevant.

Evaluation principle

IDENTIFICATION METHODS FOR THE PRODUCT LEVEL
The product level methods are essentially the same as those described for the substance level. Please refer to A.4.1.

METHODS TO DETERMINE THE CONTENT OF SPECIFICATION ELEMENTS IN THE MPCP
The largest part of the information provided under A.4.1 applies *as is* for the MPCP. Excepting the cases in which there is no distinction between the two, MPCA-AM and MPCP are different matrices for the purpose of analytical method performance, as (i) concentrations of specification elements are generally lower in the MPCP due to dilution during formulation, (ii) the components added during formulation may interfere with the analysis of the specification elements (chemical constituents may affect the analysis of claimed active metabolites, MoCs and relevant impurities, whereas additional MPCAs may complicate easy distinction during enumeration), and (iii) the physically different MPCP may necessitate alternative sample preparation.

MPCA
Depending on the nature of the difference between MPCA-AM and MPCP, translation of the enumeration method validated for the MPCA-AM may not require a full re-evaluation for the MPCP;
'Specificity' only needs amendment when the MPCP contains more MPCAs than the MPCA-AM, as it needs elaboration how the additional micro-organisms may be distinguished from

those that were already present.
'Accuracy' needs no further addressal, once stability of the MPCP, as supported by e.g., suspensibility or dispersion stability, has been adequately evidenced.
Last, 'linearity' and 'precision' are not reasonably expected to be affected by changes to the matrix brought about by the formulation process.

Chemical components
For the specification elements with a chemical character (claimed active metabolites and MoCs[37]), methods must be separately validated for the product.
Obviously, the MPCP-level method for claimed active metabolite determination must be sufficiently sensitive to allow for any formulation process-related dilution of the matrix.
According to SANCO/3030/99 – rev.5, the LOQ for MoCs must also be derived for the MPCP, based on the maximum limit of the substances in the MPCA-AM and the content of MPCA-AM in the MPCP. Whenever this would result in a level that would be too low to measure, validation must be performed at the lowest possible level. In that case, the nature of the technical limitations that necessitate a higher LOQ must be described, and the LOQ's fitness for purpose with regard to relevant thresholds must be evidenced.

P.5.2 Methods to determine and quantify residues

Corresponding data requirement:	(EU) No 284/2013, Annex, Part B, 5.2
Relevant evaluation criterion:	(EU) No 546/2011, Annex, Part B, 1.4.2
Relevant decision making criterion:	(EU) No 546/2011, Annex, Part B, 2.4.2
GLP-compliance:	Not required for method validation

Purpose of this point:
Maintaining symmetry in the framework.

Conditional / waiving
Not relevant.

Confidentiality
Not relevant.

Evaluation principle
Please refer to A.4.2.

P.6 EFFICACY DATA

Representative product during active substance approval versus PPP registration
For the approval of new active substances, evidence must be submitted to demonstrate that the dose(s) proposed is/are sufficiently effective and selective. In other words, the proposed dose rate for at least one of the intended uses of the representative product should be realistic. These intended use(s) should encompass the "worst case" GAP. Confirming the dose rate(s) indicated in the GAP, is of vital importance, since the risk assements on human health, fate and behaviour in the environment, and the effect on non-target organisms in the active

[37] Note that, in (EU) No 284/2013, Part B, 5.1, methods for MoC-quantification in the MPCP are not mentioned. These are however covered by the requirement for methods 'used to determine the storage stability and shelf life of the plant protection product'; 2.6.2 explicitly states that, within the context of storage stability and shelf life testing, the presence of MoCs must be identified pre -and post-storage. Obviously, this necessitates validated methodology.

substance dossier are based on this dose rate. Typically, for **active substance approval** only a limited number of representative trials are needed to support the dose rate of the representative product. In contrast, during Plant Protection Product (**PPP**) **registration**, efficacy needs to be demonstrated for all intended uses by a full data-package for each climatic zone. This can result in >100 efficacy trials when many crop-pest combinations are applied for. Therefore in this section, where relevant, a distinction will be made between the representative product for **active substance approval** and **PPP registration**.

Guidances/standards
Standards for the efficacy evaluation of plant protection products are provided by the European and Mediterranean plant protection organization (EPPO). These standards encompass general standards, which cover general aspects of the efficacy evaluation, and specific standards (covering one type of PPP, e.g. fungicide or herbicide, and often for a specific crop-pest combination). The general standards are freely available in the EPPO database on PP1 Standards. In this evaluation manual, several of these standards (but not all) will be discussed briefly in the appropriate context.

Regarding PPPs based on micro-organisms, special attention should be paid to the following three standards, as these include considerations that are specific for PPPs based on micro-organisms.

EPPO standard PP1/276(1) on the “Principles of efficacy evaluation for microbial plant protection products” refers to PPPs based on micro-organisms, including microbial products that are not neccesarily low-risk. Relevant for all PPPs based on micro-organisms.

EPPO standard 296(1) on “The evaluation for low-risk plant protection products” contains essential information on reduced data and efficacy requirements for low-risk products and should be taken into account when writing a dossier for a low-risk PPP. This standard discusses both microbial and non-microbial low-risk (chemical) products. Relevant for low-risk PPPs based on micro-organisms.

EPPO standard PP1/319(1) on the “General principles for efficacy evaluation of plant protection products with a mode of action as plant defence inducers” refers to PPPs based on plant defence inducers (PDIs) or elicitors that induce plant defenses as MoA. This standard includes both micro-organisms and other type of elcitors (e.g. chemical, or in-activated micro-organisms). Relevant for PPPs based on micro-organisms that have as MoA the induction of plant defence.

P.6.1 Preliminary tests

Corresponding data requirement:	(EU) No 284/2013, Annex, Part B, 6.1
Relevant evaluation criterion:	-
Relevant decision making criterion:	-

Purpose of this point:
Preliminary tests (for the representative PPP for active substance aproval or PPP to be registered) may consists of laboratory, greenhouse and field studies.

In case the (representative) PPP is based on a micro-organism the information provided under this point may support the biological activity, MoA and dose-range finding of the PPP.

In case of a combination of several active substances, safeners and/or synergist is intended, information should be provided on the ratio that is envisioned.

In case of bridging a PPP to another formulation (e.g. a previous formulation or other registered PPPs) based on the same active substance, this section should contain test demonstrating comparibility between the different formulations.

If preliminary data is not deemed necessary (e.g. when the micro-organism has already been used as plant protection for a long time and is the sole active component in the (representative) PPP, a justification should be provided instead.

Assessment principle:
According to EPPO standard PP1/276(1) on the "Principles of efficacy evaluation for microbial plant protection products" and the EPPO standard PP1/296(1) on the "Principles of efficacy evaluation for low-risk plant protection products", data from other sources (e.g. published papers, laboratory studies) may be used to supplement the efficacy data. This data can consist of information regarding the MoA, susceptibility of the target pests or hosts, dose response behaviour, and/or the effect on environmental, agronomic and other factors of the product. Data from well-designed small-scale laboratory and/or growth chamber studies can provide data to reduce the number of field/glasshouse trials to test effectiveness (further discussed under point P.6.3). These studies are generally not GEP certified. This supportive data can be submitted under preliminary tests.

Furthermore, preliminary tests (consisting e.g. of laboratory, greenhouse or field studies) should be provided in the following situations:

Co-formulation, active substance approval
For the active substance approval it should be demonstrated that the micro-organism is efficacious and selective on itself (unless the micro-organism is applied for as part of a qualitatively defined combinations of strains, e.g. a consortia). The possibility that the efficacy is derived from other components in the formulation and not from the active substance itself should be ruled out. It can occur that components are added to the formulation (e.g. as preservatives) that may directly contribute to the efficacy of the formulated product. In these cases it may be possible to theoretically exclude (justification) that these components will contribute to the efficacy of the representative product (e.g. in case when the proposed dose rate is much lower than expected to be efficacious for the co-formulant, or when the proposed function is not similar etc). If it cannot be adequately justified that the additive/co-formulant does not contribute significantly to the efficacy of the representative product, than this should be demonstrated in efficacy trials (e.g. by testing the efficacy of the formulation in the presence and absence of the micro-organism for which approval is sought as new active substance). This has been described in SANCO/10054/2013-rev. 3, the Guidance document on data requirements on efficacy for the dossier to be submitted for the approval of new active substances contained in plant protection products. The principle described here is similar to the principle for the evaluation of chemical active substances.

Co-formulation with more than one active substance, PPP registration
For PPP registration of PPPs based on co-formulated mixtures with more than one active substance, a justification for the ratio of active substances within the micture should be provided (in line with EPPO standard PP1/225(2)) In addition, a rationale behind the inclusion of each active substance should be provided. Examples of potentional advantages and disadvantages of mixtures with respect to effectiveness and other considerations regarding these mixtures are provided in EPPO standard PP1/306(1) on the "General principles for the

development of co-formulated mixtures of plant protection products". The principles described here are similar to the principles for the evaluation of PPPs based on chemical active substances.

Using different formulations, active substance approval
For active substance approval it can occur that efficacy data is (partly) based on formulations under development. This should be clearly indicated. An explanation of the differences of the used formulation(s) relative to the final representative product should be provided. It should be noted that when only formulations under development are used, evaluation of efficacy may not be possible.

Bridging, PPP registration
In case a biological significant change in the composition of PPPs is made it should be demonstrated (by reasoned case and/or data, depending on the nature of the change) that efficacy of the new formulation is comparable to the previous formulation. Similar is the development of a new product, which is to be based on the principle of comparing with, and "bridging" to an existing formulation based on the same active substance. Details on the data required are described in EPPO standard PP1/307(2) on "Efficacy considerations and data generation when making changes to the chemical composition or formulation type or plant protections products". The principles described here are similar to the principles applied for the evaluation of PPPs based on chemical active substances.

Absence of data
If preliminary data is not deemed necessary (e.g. when the micro-organism has already been used as plant protection for a long time and is the sole active component in the (representative) PPP, a justification should be provided to explain the absence of preliminary data.

P.6.2 Minimum effective dose

Corresponding data requirement:	(EU) No 284/2013, Annex, Part B, 6.2
Relevant evaluation criterion:	
Relevant decision making criterion:	(EU) No 546/2011, Annex, Part B, 2.3.1.2

Purpose of this point:
It should be justified what is the minimum effective dose that is still sufficiently effective for the intended use(s). This is required to prevent unnecessary overdosing of PPPs, to reduce the exposure to PPPs in the environment.

Assessment principle:
The minimum effective dose (MED), needs to be reported. The MED is the minimal dose rate that that is necessary to achieve sufficient control for the intended use(s). EPPO standard PP1/225(2) on the "Minimum effective dose", described the requirements for efficacy testing to establish the MED. However, especially for PPPs based on micro-organisms, there are several aspects that should be taken into consideration when addressing the MED (some are described in EPPO standard PP1/276(1) on the "Principles of efficacy evaluation for microbial plant protection products"):

(a) If the micro-organism species already occurs naturally in the EU environment, the concern of reducing exposure to this micro-organism in the environment may be less critical (even more so when the PPP is considered as low risk).

(b) Micro-organisms are capable of reproduction and may therefore multiply, rendering the concept of a MED both less relevant and more difficult to establish.
(c) Product performance of PPPs based on micro-organisms may be more prone to environmental conditions compared to chemical products, and hence the data more variable. Hence a dose response may be more difficult to obtain.
(d) Whereas for PPPs based on chemical PPPs, a more linear dose response is expected, the dose response of PPPs based on micro-organisms may have a more logarithmic nature (hence, applying twice as much product, may not be sufficient to trigger a dose response).

Therefore, due to the nature of PPPs based on micro-organisms, field testing to address the MED may not be necessary. Nonetheless, an appropriate explanation for the proposed dose remains required, including a justification in the eventuality of the absence of field data. Explanations can include information regarding the MoA and any other information provided like preliminary tests or literature (as discussed previously under point P.6.1.).

The principles regarding the MED of PPPs based on micro-organisms, are applicable for both active substance approval and PPP registration, with the distinction that for active substance approval, this is not mandatory (nor for chemical active substances). Nevertheless, it is considered useful to include lower dose rates in the tests submitted to support active substance approval.

P.6.3 Testing effectiveness

Corresponding data requirement:	(EU) No 284/2013, Annex, Part B, 6.3
Relevant evaluation criterion:	(EU) No 546/2011, Annex, Part B, 1.3.3
	(EU) No 546/2011, Annex, Part B, 1.3.4
Relevant decision making criterion:	(EU) No 546/2011, Annex, Part B, 2.3.1.3
	(EU) No 546/2011, Annex, Part B, 2.3.1.4
	(EU) No 546/2011, Annex, Part B, 2.3.1.5

Purpose of this point:
Efficacy should be demonstrated to be beneficial under the agricultural, plant health and environmental (including climatic) conditions in the area of proposed use. In addition to confirmation of the claimed protection of the PPP, testing efficacy is also essential to avoid unnecessary exposure to PPPs in the environment.

Assessment principle:
As indicated prior, under the Introduction of point P.6, the purpose of the efficacy consideration for active substance approval compared to PPP registration is not the same. While for the first the principal objective is to confirm that the dose rate is realistic, for the second, for all proposed uses it should be demonstrated (or made plausible via extrapolation) that efficacy is sufficient, when applied under the relevant climatic and agronomical conditions.

Active substance approval
According to Regulation (EC) No 1107/2009, ANNEX II, 3.2, an active substance, alone or associated with a saferner or syngergist, shall only be approved where it has been established for one or more representative uses that the PPP, when applied under the proposed conditions, is sufficiently effective. SANCO/10054/2013-rev. 3, the Guidance document on data requirements on efficacy for the dossier to be submitted for the approval of new active substances contained in plant protection products, describes how and why efficacy needs to be addressed for the approval of new active substances. This guidance document includes considations for microbials. Typically, only a few representative trials may suffice. While it is

not mandatory to submit individual trial reports, it will be highly appreciated by the competent authorities to do so. Furthermore, in addition to the obtained efficacy across all tests, it is advisable to add also the minimum and maximum efficacy that is obtained in individual trials, as this may gives information on the variability of the efficacy of the representative product and/or micro-organism. Although it is noted (and fully acceptable when properly explained) that due to their nature and/or MoA, PPPs based on micro-organisms may have a more variable effect than PPPs based on chemicals. For the principles of determining acceptable efficacy is referred to the relevant section below, which is applicable for both active substance approval and PPP registration.

For renewals of active substances the draft Guidance document on the renewal of approval of active substances to be assessed in compliance with Regulation (EU) No 844/2012 (the Renewal Regulation) can be referred to (SANCO/2012/11251-rev.5). Considering that PPPs containing the active substance have already been evaluated previously, efficacy does not need to be re-evaluated for active substance renewal. An overview of representative uses and all supported uses already authorized in Member States should be provided.

Number of trials, PPP registration
Sufficient data needs to be provided to permit the evaluation on the level, duration, and consistency of intended effects of the PPP. The EPPO standard PP1/226(3) on the “Number of efficacy trials”, describes the number of trials that is required to asses efficacy, taking into consideration e.g. crop and pest status (major or minor), supporting evidence, and extrapolation possibilities (see below for a more detailed explanation regarding extrapolation). It should be noted that for low risk PPPs the number of trials considered as full data package is somewhat lower than for regular PPPs (both for PPPs based on micro-organisms and chemical active substances). This is described in the EPPO standard PP1/296(1) on the “Principles of efficacy evaluation for low-risk plant protection products”.

Especially for micro-organisms non-GEP trails can be used as supportive information (e.g. on the MoA, susceptibility of the target pests or hosts, dose response, and/or the effect on environmental, agronomic and other factors of the product). This information provides support to reduce the number of large scale GEP certified field trials (in line with EPPO standard PP1/276(1) on the “Principles of efficacy evaluation for microbial plant protection products” and EPPO standard PP1/296(1) on the “Principles of efficacy evaluation for low-risk plant protection products”). Especially for low-risk products, non-GEP trial data may also be acceptable to test effectiveness, if scientifically sound and in line with other applicable EPPO standards. It should be noted though, that data protection can only be granted for GEP/GLP certified trials and not for non-GEP trial data. Non-GEP trial data can be used to reduce the number of required GEP certified trials, but cannot completely replace GEP-certified trials.

Acceptable efficacy, active substance approval and PPP registration
The EPPO standard PP1/214(4) on the “Principles of acceptable efficacy”, describes how to determine wether the efficacy of a PPP is acceptable for the purposes of registration, taking into consideration both the positive effects of the treatment and possible negative effects (e.g. development of resistance, phytotoxicity, reduction on yield, etc). The net result of the positive and negative effects should be of sufficient overall agricultural benefit to justify the use of the PPP.

In line with EPPO standard PP1/276(1) on the “Principles of efficacy evaluation for microbial plant protection products” and EPPO standard PP1/296(1) on the “Principles of efficacy evaluation for low-risk plant protection products”, it is generally accepted that PPPs based on micro-organisms can have a lower efficacy than PPPs based on chemical active substances. For PPPs based on micro-organisms, the observed effects in the trials should (on average) at

least be significantly higher than those observed in the untreated control, and when possible similar to suitable reference products. This is in contrast to PPPs based on chemical active substances, for which the level of control must be similar to suitable reference products (in line with (EU) No 546/2011, Annex, Part A, 2.1.2). For PPPs based on micro-organisms, similar microbial products are most appropriate as reference products. However, when not possible, a conventional chemical product should be included (and it will be fully acceptable when the level of control of the PPP based on micro-organisms will fall below that of the chemical product). This reference then act as control for the success or failure of the trial.

A lower level of benefit obtained by the use of PPPs based on micro-organisms can still be acceptable, when taking into consideration their advantages. PPPs based on micro-organisms, especially those that are considered low-risk, may have the following advantages (list not exhaustive): (a) they can often be used over a wider range of growth stages of the crop (due to a shorter or complete absence of a pre-harvest interval (PHI), (b) they often are (better) compatible with Integrated Pest Management (IPM) or organic farming, (c) they may have a lower probability of developing resistance in the target organisms and can therefore be important as part of a resistance management strategy, (d) they may have fewer undesirable effects of the PPP (e.g. on beneficial organisms), and (e) there may be less need for specific mitigation measures. To take into consideration possible benefits (other than the claimed protection) these should be well explained in the dossier. Often, PPPs based on micro-organisms, are used as a component of an IPM programme. As this program is designed to lower the pest populations by all available means that are ecologically justified, a moderate effectiveness of the PPP based on micro-organisms may still be of use within such a program (as pest pressure is kept low). See also point P.6.7 on “Compatibility in plant protection programmes”.

Protection by PPPs based on micro-organisms can often be more variable, as micro-organisms may be more susceptible to unfavourable environmental conditions (e.g. too hot, cold or dry for the micro-organism, resulting in a reduced performance of the PPP). For PPPs based on micro-organism, this variability is more acceptable than for PPPs based on chemical active substances, as long as the reasons for inconsistencies in pest control by the PPP are explained. If adequately justified, recommendations can be proposed for the user to ensure the PPP will be applied under conditions that may provide optimal performance (in line with (EU) No 546/2011, Annex, Part B, 2.3.1.5). If a PPP performs variable and there is no sound explanation that can enable the situations to be identified were effective control might be expected, authorization might be refused until a robust demonstration or explanation of the factors affecting performance are provided.

Extrapolations, PPP registration
Extrapolation is based on the principle that certain groups of pests or groups of crops are considered to be more or less equivalent in relation to efficacy. Extrapolation may be used to extent an accepted plant protection claim to additional crops or pests in the absence of specific data, or used to allow a more reduced data package. Regular extrapolation principles (also applicable for conventional chemical products) are described in EPPO standard PP1/257(2) on the “Efficacy and crop safety extrapolations for minor uses”. Typically, these extrapolations are currently only applicable to crops or pests with a minor use status (although the competent authority of the Netherlands takes a more flexible approach and also allows extrapolation to major uses). Extrapolations are either based on Extrapolation tables provided by EPPO, or on expert judgement (the national extrapolation tables used by the Dutch competent authority, can be referred to using expert judgement, but unfortunately, this national document is currently only available in Dutch).

The above-mentioned extrapolation tables have mostly been written for conventional crop protection products. For PPPs based on micro-organisms, extrapolation by expert judgement may be possible based on the mode of action of the micro-organism, the biology of the target pest or disease, and the micro-organism itself. The EPPO standard PP1/296(1) on the "Principles of efficacy evaluation for low-risk plant protection products" provides detailed information regarding extrapolation possibilities for low-risk products. Within this standard a distinction is made between a direct MoA (in case of micro-organisms e.g. pathogenicity, infectivity or parasitism or the production of toxins or antimicrobial compounds) and an indicrect MoA (e.g. competition, induction of plant defence). With a direct MoA, the claimed crops are considered of less relevance and extrapolation of data between crops may be possible (taking into account crop morphology, cropping system, application technique, feeding area on the plant etc.). With an indirect MoA, the claimed pest is considered as less relevant and extrapolation to other pests may be possible (taking into account life cycle of the pest, feeding behaviour etc.). While described in the EPPO standard PP1/296(1) on the "Principles of efficacy evaluation for low-risk plant protection products", these extrapolations are applicable for all PPPs based on micro-organisms, with the distinction that for low-risk products also extrapolation towards major uses is allowed.

For all proposed extrapolations, it is important that *e.g.,* the mode of action of the active substance and the reasoning behind the extrapolations are well explained within the dossier, possibly supported by literature studies. Furthermore, it will be considered better to submit a full data package on one crop and extrapolate the results (including full justification) to other crops than to submit 1-2 trials on individual crop-pest combinations (especially taking into consideration that efficacy of PPPs based on micro-organisms may be more variable). Hence, the choice of crop-pest combinations that will be tested in the efficacy trials, should be considered carefully. What is the most difficult target-organism to control? Which crop should be tested? And what are the worst case conditions for the chosen crop-pest combination?

P.6.4 Information on possible development of resistance in target organisms

Corresponding data requirement:	(EU) No 284/2013, Annex, Part B, 6.4
Relevant evaluation criterion:	(EU) No 546/2011, Annex, General introduction, 2.1 (EU) No 546/2011, Annex, Part B, 1.3.4 (d) (EU) No 546/2011, Annex, Part B, 1.3.11
Relevant decision-making criterion:	(EU) No 546/2011, Annex, General introduction, 3.3

Purpose of this point:
Information on possible development of resistance in target organisms is essential to ensure a lasting efficacy of the micro-organism used in the plant protection product(s).
If there are reasons to believe that the use of the plant protection product may lead to resistance in certain target organisms, this should be addressed. If data is available from literature or experimental studies, but does not refer to the organisms claimed as the target one, this data canl still be provided as it may support the evaluation of the possibility of resistance in the target organism.

Assessment principle:
The assessment principles described earlier under A.3.4 are also applicable here. Where A.3.4. focusses only on the inherent risk of the micro-organism to trigger the development of resistance in the target organism, here under P.6.4 also the inherent risk of the claimed target

organisms, and the agronomic risk deriving form the conditions of use of the product can be taken into account. Steps of the resistance risk assessment and resistance risk management are described in EPPO standard PP1/213(4) on “Resistance risk analysis”.

As indicated earlier, EPPO standard PP1/276(1) on the “Principles of efficacy evaluation for microbial plant protection products”, makes a clear distinction between micro-organisms with a direct MoA and micro-organisms with an indirect MoA in respect to the risk of inducing the development of resistance in the target organism. Micro-organisms with an indirect MoA (e.g. host plant defence induction or competition for nutrients) are often not at risk of inducing resistance development in target organisms. This is because there is no direct selection pressure on the target organism. In such cases this data point can be addressed with a justification.

Only when there is reason to believe that the use of the PPP may lead to resistance in certain target organisms, which is more likely for micro-organisms with a direct MoA on the target organisms, a more thorough resistance risk assessment, following EPPO standard PP1/213(4) on “Resistance risk analysis” is required.

Nonetheless, in general, micro-organisms used as active substances often use completely new MoAs compared to chemical active sustances and can therefore be beneficial for resistance management purposes.

Resistance may be also of less relevance when the activity of the micro-organism is based on multiple MoA.

It should be noted that for product renewals, the section on the “Information on possible development of resistance in target organisms” should always be updated and re-evaluated, whereas for the rest of the efficacy section can be referred to the previous evaluation (if the GAP remains the same).

P.6.5 Adverse effects on treated crops

Corresponding data requirement:	(EU) No 284/2013, Annex, Part B, 6.5
Relevant evaluation criterion:	EU) No 546/2011, Annex, Part B, 1.3.5
Relevant decision making criterion:	(EU) No 546/2011, Annex, Part B, 2.3.2.1 (EU) No 546/2011, Annex, Part B, 2.3.2.2 (EU) No 546/2011, Annex, Part B, 2.3.2.3 (EU) No 546/2011, Annex, Part B, 2.3.2.4

Purpose of this point:
Absence of unnacceptable effects on treated plant or plant products should be demonstrated or adequately justified. This is essential as the use of the PPP should have a sufficient overall agricultural benefit (which is the net results of the positive and negative effects). If adverse effects are expected, appropriate limitations of use will be put on the label.

EPPO standard PP1/135(4) on “Phytotoxicity assessment” provides detailed information on how phytotoxicity of PPPs to treated plants or plant products (including propagating material) can be accurately assessed and recorded. This standard also describes the effects on quantity and quality of the yield. This standard is relevant for points P.6.5.1 to P.6.5.5. described below.

Note that crop safety is also addressed in Extrapolation tables provided by EPPO (to be read

in conjuncture with in EPPO standard PP1/257(2) on the "Efficacy and crop safety extrapolations for minor uses") and in the national extrapolation tables used by the Dutch competent authority.

P.6.5.1 Phytotoxicity to target plants (including different cultivars) or to target plant products

Purpose of this point:
It should be demonstrated that there will be no relevant phytotoxic effects on the treated plants or plant product. If phytotoxic effects are expected, limitations of uses will be proposed on the label to mitigate these adverse effects.

Assessment principle:
For PPPs based on micro-organsims, in most cases it may be sufficient to asses phytotoxicity in the efficacy trials. This is because the majority of PPPs based on micro-organisms (currently) have a function as insecticide or fungicide, and for these types of products phytotoxicity can be firstly assessed in the efficacy trials and only when phytotoxicity symptoms are observed further testing is needed (similar to conventional chemical products). Further testing would for instance include using twice the recommended dose rate in efficacy or sensitivity trials. When negative effects are considered unimportant in comparison with the benefits or of a transient nature, there should be supportive evidence (e.g. by submitting yield measurements demonstrating that the observed negative effects does not affect yield or by submitting data demonstrating improved quality of the treated plant or plant product). Based on the results, an appropriate warning can be placed on the label (e.g. to alert the user that phytotoxicity symptoms are of a transient nature).

Interpretation of the framework in specific cases

Cases where phytotoxicity testing in efficacy trials is not sufficient
In line with EPPO standard PP1/135(4) on "Phytotoxicity assessment", there are several exceptions, were addressing phytotoxicity in the regular efficacy trials may not be sufficient and specific selectivity trials are required (trials in the absence of pests, and typically including different varieties of the treated crops). Nonetheless, when phytotoxic effects are observed in the efficacy trials, they should still be accurately assessed and recorded, as this information will supplement the phytotoxicity assessment done in the selectivity trials.

Herbicides – For herbicides specific selectivity trials are required in which also a double (2N) dose rate needs to be tested. Furthermore, selectivity trials should be set up with a number of different cultivars. This would include common varieties, but also those known to be sensitive.

Growth regulators – For growh regulators, doses higher than the intended dose (e.g. 2N dose rate) should be tested to determine the margin of crop safety.

Seed treatment – For seed treatment specific selectivity trials are required in which germination is tested, which includes usually at least 3 common cultivars. See EPPO standard PP1/135(4) on "Phytotoxicity assessment" for further information regarding the timing between seed treatment and these phytotoxicity trials.

P.6.5.2 Effects on the yield of treated plant or plant products

Purpose of this point:
It should be demonstrated, or adequately justfified, that there will be no negative effect on yield at harvest due to the use of the PPP, unless a possible reduction in yield is compensated for by other advantages beside the plant protection action, such as an enhancement of the quality of the treated plants or plant products.

Assessment principle:
For PPPs based on micro-organisms used as fungicides or insecticides, as for conventional chemical products, in the absence of phytotoxicity in the efficacy trials, assessing yield in selectivity tests is not required (note that yield specific parameters may also already be included for testing effectiveness, when required by any of the EPPO standards for specific corp-pest combinations, which may provide additional information). Only for herbicides and growth regulators, yield should be assessed in selectivity trials.

P.6.5.3 Effects on the quality of plants or plant products

Purpose of this point:
It should be demonstrated, or adequately justified, that there will be no unacceptable adverse effects on the quality of treated plants or plant products, except in the case of adverse effects on food and feed transformation processes (e.g. wine making, brewing, bread making, or silage productions as feed) where proposed label specifies that the plant protection product will not be applied to crops to be used in transformation processes.

Assessment principle:
The criteria for assessing quality of yield are generally crop-specific and can be found in specific EPPO standards. If occurrence of effects on quality aspects are observed, this may also provide information for the risk assessment related to residues or effects on human health.

For certain crops there may be need to address taint. EPPO standard PP1/242(2) on “Taint test” gives further guidance on making relevant cases and where data may be required. If taint is observed, this may be indicate, for instance, of spoilage of edible parts. This would then eventually also provide information for the risk assessment related to residues or effects on human health.

P.6.5.4 Effects on the transformation process

Purpose of this point:
The exclude that the use of the PPP will not have a negative effect on transformation processes, tests to demonstrate the absence of negative effects on intended transformation processes are required under the following conditions:

When the treated plants or plant products are normally intended for use in transformation process (e.g. wine making, brewing, or bread making, but also cider production, fermentation or crops for silage) and significant residues are present at harvest. In addition, there are indications that the PPP could have an influence on transformation processes, or PPPs based on the same or closerly similar active substances have been shown to have an adverse effect on these transformation processes.

Assessment principle:
EPPO standard PP1/243(2) on “Effects of plant protection products on transformation processes” describes when transformation should be addressed. Data from preliminary screening tests for biological activity, may already provide information on the absence of effects on e.g. yeast or lactic bacteria used in transformation processes. If biological activity on yeast or lactic bacteria cannot be ruled out, further testing may be needed.

Testing the effects on actual transformation processes is only necessary as a last resort.

If not sufficiently addressed, transformation processing of the product may be excluded from the label.

P.6.5.5 Impact on treated plants or plant propagating material

Purpose of this point:
It should be demonstrated, or adequately justified, that there will be no unacceptable adverse effects on treated plants or plant products used for propagation or reproduction, such as effects on viability, germination, sprouting, rooting and establishment, except where proposed label specifies that the plant protection product will not be applied to plants or plant products to be used for propagation or reproduction.

Assessment principle:
Propagating material may include (depending on the crop): seeds, cuttings, runners, tubers, or bulbs and corns. EPPO standard PP1/135(4) on “Phytotoxicity assessment” describes the circumstances under wich data on plant parts for propagation are required. For fungicidal and insecticidal products, data are generally not required unless the product has systemic activity, is applied close to harvest, or phytotoxicity effects have been observed. Hence, for most microbial products (with a function as insecticide or fungicide), generally, a reasoned case may suffice *in lieu* of data (including reference to the absence of phytotoxicity).

P.6.6 Observations on undesirable or unintended side-effects on succeeding crops and other plants

Corresponding data requirement:	(EU) No 284/2013, Annex, Part B, 6.6
Relevant evaluation criterion:	(EU) No 546/2011, Annex, Part B, 1.3.5
	(EU) No 546/2011, Annex, Part B, 1.3.8
Relevant decision making criterion:	(EU) No 546/2011, Annex, Part B, 2.3.2.5
	(EU) No 546/2011, Annex, Part B, 2.3.2.5

Purpose of this point:
Absence of unnacceptable effects on succeeding crops and/or adjacent crops should be demonstrated or adequately justified. Possible negative effect on succeeding crops are also taken into account when defining the net result of positive and negative effects of the use of PPP. If adverse effects are expected, appropriate limitations of use will be put on the label.

P.6.6.1 Impact on succeeding crops

Purpose of this point:
Absence of unnacceptable effects on succeeding crops should be demonstrated or adequately justified. If adverse effects on succeeding crops are expected, appropriate limitations of use will be put on the label (e.g. by warning the user for growing certain susceptible succeeding crops after use of the PPP).

Assessment principle:
In most cases, for micro-organisms it may be sufficient to make a reasoned case based on the results from the crop safety assessment and possible occurrence of the microbial species in EU environments relevant to agriculture.

For PPP based on micro-organisms, data to assess the impact on succeeding crops should be submitted in case the micro-orgasnims is a plant pathogen or in case metabolites of concern for which a hazard to plants was identified, which is demonstrated to remain present in significant amounts in soil or in plant materials up to sowing or planting time of succeeding crops.

EPPO standard PP1/207(2) on “Effects on succeeding crops” explains how and why the effects on succeeding crops (including replacement crops) should be assessed. It should be noted though that this standard is more appropriate for chemical active substances than for micro-organisms though, as within this standard the decision-support scheme on the extent of testing needed starts with $PEC_{soil\ actual}$ and TER values. While for micro-organisms for instance no PEC values are required for metabolites of concern that are produced *in situ* and are not present in the MPCP. Furthermore, for micro-organisms that are plant pathogenic, the host range and the population density of the micro-organism in specific environmental compartments (PED values, see also A.7.1) will be the most relevant characteristics of the micro-organism to assess the impact on succeeding crops. Nonetheless, the general principles that are discussed within EPPO standard PP1/207(2) on “Effects on succeeding crops” are still applicable for micro-organisms.

P.6.6.2 Impact on other plants, including adjacent crops

Purpose of this point:
Absence of unnacceptable effects on adjacent crops should be demonstrated or adequately justified. If adverse effects on adjacent crops are expected, appropriate limitations of use will be put on the label (e.g. by warning the user for the use of the PPP when certain susceptible crops are grown in the vicinity).

Assessment principle:
In most cases, for micro-organisms it may be sufficient to make a reasoned case based on the results from the crop safety assessment and possible occurrence of the microbial species in EU environments relevant to agriculture. Only when there are indications that other plants than the intended target plants (including adjacent plants) could be negatively affected (e.g. as discussed under P.10.6 on “Effects on non-target trerrestrial plants”) and that the PPP could affect these plants via drift, further testing may be required. Small scale screening test against a range or appropriate plant species may be sufficient to demonstrate safety of the PPP to adjacent crops. The general principles are described in the EPPO standard PP1/256(1) on “Effects on adjacent crops”, although some points of this standard are more applicable for chemical active substances.

If safety cannot be made plausible for certain adjacent crops, than it should be specified on the label that the plant protection product should not be applied when these particular adjacent crops are present.

P.6.7 Compatibility in plant protection programmes

Corresponding data requirement:	(EU) No 284/2013, Annex, Part B, 6.7
Relevant evaluation criterion:	(EU) No 546/2011, Annex, Part B, 1.3.9
	(EU) No 546/2011, Annex, Part B, 1.3.7
Relevant decision making criterion:	(EU) No 546/2011, Annex, Part B, 2.1.3.6
	(EU) No 546/2011, Annex, Part B, 2.3.2.7

Purpose of this point:
As PPPs based on micro-organisms will be used predominantly within an Integrated Pest Management (IPM) Programme, it should be assessed whether the PPP is compatibile with other available plant protection methods that are likely included within such a program (taking into consideration the field of use and intended target organism(s), especially when these are required for the conditions of use. This includes that the potentional effects (e.g. antagonism, fungicidal effects) of other PPPs (used within a tank mix or in sequence) on the activity of the micro-organism should be evaluated. In addition, potential negative effects of the micro-organism on beneficial organisms (e.g. natural enemies) should be evaluated.

Assessment principle:
PPPs based on micro-organism are predominantly used within an Integrated Pest Management (IPM) programme, in line with Directive 2009/128/EC establishing a framework for Community action to achieve the sustainable use of pesticides. As defined by the European Commission (see Integrated Pest Management (IPM) (europa.eu)), the IPM strategy means careful consideration of all available plant protection methods an subsequent integration of appropriate measures that discourage the development of populations of harmful organisms. This, to keep the use of PPPs and other forms of intervention to levels that are economically and ecologically justified and reduce or minimise risks to human health and the environment. 'Integrated pest management' emphasises the growth of a healthy crop with the least possible disruption to agro-ecosystems and encourages natural pest control mechanisms.

IPM may encompase the following methods (list not exhausitive): use of crop rotation, use of resistant/tolerant cultivars, use of certified disease free seed or planting material, monitoring of harmful organisms, use of biological control (which includes PPPs based on micro-organisms and other types of biopesticides, but also for instance the release of natural enemies) and lastly (if still required), the use of chemical control.

PPPs based on micro-organisms used in tank mix or spray sequence.
For PPPs based on micro-organisms it may be needed to include on the product label requirements for the use conditions with other PPPs in tank mix, spray sequences or other relevant types of applications to ensure control of the target organisms throughout the growing season. A typical example is provided in EPPO standard PP1/319(1) on the “General principles for efficacy evaluation of plant protection products with a mode of action as plant defence inducers.” This standard includes several paragraphs with guidance on how to test efficacy of these types of products in mixtures, or in spray programmes with other products. If properly motivated some of these principles may also be applied to PPPs based on micro-organisms with other MoAs.

In case the PPP based on micro-organisms is envisioned to be used with other PPPs in tank mix, spray sequence of other relevant types of application, information should be provided to address the potentional effects (e.g. anatagonism, fungicidal effects) on the activity of the micro-organism after mixing, spraying in sequence, or employing other relevant types of applications with other PPPs. For instance, applying a fungicide shortly after a PPP based on a micro-organism, which happens to be a fungus, may have potential adverse effects on the activity of the micro-organism. In that case, appropriate label recommendations (e.g. intervals between application of the PPP and other products) may need to be specified to avoid these potentional negative effects. As is the case for all label recommendations, these should be supported by appropriate information (e.g. justification).

For PPP based on micro-organisms, known incompabilities with other PPPs shall be reported on the label. A general precautionary statement can be proposed on the label, alerting the user about possible loss of efficacy of the micro-organism due to interaction in tank mix, spray sequence or other relevant types of applications with PPPs other than those indicated on the label.

Proposed labels of PPPs may include recommendations or requirements for the use with other PPPs and/or adjuvants as a tank mix. In these cases, the points discussed under P.6.5.1 till P.6.6.2 regarding adverse effects on treated crops or other undesirable effects on succeeding and/or adjacent crops apply in relation to the information provided for the tank mix (as specified in (EU) No 546/2011, Annex, Part B, 2.3.2.7). Therefore, mandatory tank mixes should be clearly indicated under method of application (as discussed under point P.3.6).
Potentional adverse effects on beneficial organisms
The use of natural enemies to reduce the population of harmful organisms is an important strategy of IPM. These natural enemies can be released on purpose, but also specific measures can be taken to promote the conservation of specific natural enemies already present within the agricultural set-up (for instance by planting specific plants on the border of the field that can be used as as refugees of natural enemies e.g. by providing shelter or food). In this light, potentional adverse effects on natural enemies should be discussed. This can be done by taking into account the host range of the micro-organism (as discussed under point A.2.3), by referring to the assessment on the effects on bees or non-target arthorpods other than bees (as discussed respectively under A.8.3, and P10.3 and A.8.4 and P10.4), and/or by providing any other relevant information.

Note that among the specific EPPO standards there are 4 specific standards that deal with side effects of PPP to beneficial organisms (including natural enemies like parasitic wasps and predatory mites). These are EPPO standard PP1/142(2) on the “Side effects on *Encarsia formosa*”, EPPO standard PP1/151(2) on the “Side effects on *Phytoseiulus pesimilis*”, EPPO standard PP1/180(2) on the “Side effects on Trichogramma cacoeciae”, and EPPO standard PP1/170(4) on the “Side effects on honeybees.However, it should be noted that these standards predominantly describe how to set-up (small scale) trials to asses the effects. Therefore these standards might be more relevant for PPPs based on chemical active substances. For PPPs based on micro-organisms a similar approach as taken for micro-organisms in the risk assessment for non-target organisms (see A.8 and P.10) may be more relevant, which follows the risk principle (i.e., risk = hazard x exposure) and allow for waiving either exposure-related data requirements or hazard-related data requirements, if the absence of the other can be concluded. Based on the body of knowledge on the micro-organism (e.g MoA, host range) absence of a hazard on beneficial organisms may be concluded.

P.7 EFFECT ON HUMAN HEALTH

Scope
According to the Introduction to Chapter 7 of Regulation (EU) No 284/2013:

'The information provided shall be sufficient to allow an evaluation of the risks to human health associated with the use of the plant protection products (e.g. operators, workers, bystanders, residents and consumers), the risks for human health handling treated crops, as well as the risk for human health and animals arising from residual traces remaining in food, feed and water. In addition, the information provided shall be sufficient to:

— Permit a decision to be made as to whether, or not, the plant protection product may be authorised,

— specify appropriate conditions or restrictions to be associated with any authorisation,

— specify hazard and precautionary statements for the protection of human health, animal health and the environment to be included on packaging (containers),

— identify relevant first aid measures as well as appropriate diagnostic and therapeutic measures to be followed in the event of infection or another adverse effect in humans.'

Hazard testing
According to the introduction of section 7 in the revised Regulation (EU) No 284/2013 the infectivity and pathogenicity of the micro-organism have already been assessed in Section 5 of Part B of the Annex to Regulation (EU) No 283/2013. Therefore, the purpose of this section is the following:

'This Section identifies the relevant additional tests to be carried out to determine the classification and labelling of the plant protection product and the acceptability of the risks related to its use. In some cases, already existing information on toxicity of co-formulants and other non-active ingredients of the plant protection product may be sufficient to conclude on the toxicity of the plant protection product.'

Therefore, medical data and an assessment of potential toxicity of the MPCP by using the weight of evidence approach shall be provided first. The assessment of these data demonstrate whether or not sufficient information is available to classify the plant protection product in accordance with Regulation (EC) No 1272/2008 with regard to toxicity to humans and whether or not acute toxicity studies on animals as described in points 7.3.1 to 7.3.6 of Regulation (EU) No 284/2013 are needed.

Information on toxicity of metabolites of concern, safeners, synergists, and relevant impurities shall be assessed also using a weight of evidence approach as explained further in the text under point 1.5.1.3 of Regulation (EU) No 546/2011 and data requirement 7.3 of Regulation (EU) No 284/2013. The explicit mentioning of the weight of evidence approach is an important update in the revised data requirements and supports the 3-R principle for replacement, reduction and refinement of animal use.

When testing is required, take into account the scope for replacement, reduction and refinement of animal tests which is strongly promoted in Regulation (EU) No 284/2013 and Regulation (EU) No 1107/2009 and please refer to the Commission Communication concerning Part B of the Annex to (EU) No 284/2013 (Official Journal of the European Union,

2023/C 202/03)[38]. This document provides a list of test methods as OECD guidelines and guidance documents relevant to the implementation of (EU) 284/2013.

Furthermore, it is important to take into account point 4.1 of ANNEX I to Regulation (EU) No 284/2013 on test material used in studies:

'Due to the influence that impurities and other components can have on toxicological and ecotoxicological behaviour, a detailed description (specification) of the test material used shall be provided for each study submitted. Studies shall be conducted using the plant protection product to be authorised or bridging principles may be applied, for example, by using a study on a plant protection product with a comparable/equivalent composition. A detailed description of the composition used shall be provided.'

Good laboratory practice (GLP)
All experimental data for the assessment for human and animal health should be GLP-compliant, as as laid down in Annex I of Regulation (EU) No 284/2013.

Data waiving
Please note that not submitting data for a particular data requirement is not acceptable without further justification.

P.7.1 Medical data

Corresponding data requirement:	(EU) No 284/2013, Annex, Part B, 7.1
Relevant evaluation criterion:	(EU) No 546/2011, Annex, Part B, 1.5.1
Relevant decision making criterion:	(EU) No 546/2011, Annex, Part B, 2.5.1
Eligible for substantiated waiving:	No

Purpose of this point:
Provide information on possible adverse effect on human health, including sensitisation and allergenic response of humans exposed to the plant protection product.

Please refer to A.5.1 for more information.

P.7.2 Assessment of potential toxicity of the plant protection product

Corresponding data requirement:	(EU) No 284/2013, Annex, Part B, 7.2
Relevant evaluation criterion:	(EU) No 546/2011, Annex, Part B, 1.5.1
Relevant decision making criterion:	(EU) No 546/2011, Annex, Part B, 2.5.1
Eligible for substantiated waiving:	No

Purpose of this point:
Combine available information on toxicity, such as from published literature, medical information, Integrated Approach to Testing and Assessment (IATA), results of CLP calculation rules in accordance with Regulation (EC) No 1272/2008, or bridging data from

[38] Communication from the Commission concerning Part B of the Annex to (EU) No 284/2013 setting out the data requirements for active substances in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market (Official Journal of the European Union, 2023/C 202/02).

similar plant protection products in a weight of evidence approach which may provide robust and reliable scientific indication on the toxicity of relevant chemical substances contained in the plant protection product, and be used for classification and labelling.

Information provided under Sections 2, 3, 4 and point 7.1 may be used in a weight of evidence approach to determine whether potential toxicity of the MPCP is to be expected, and be used for classification and labelling.

Assessment principle:
A weight of evidence approach shall be applied in order to evaluate whether the possible non-submission of certain studies required in points 7.3.1 to 7.3.6 of Part B of the Annex to Regulation (EU) No 284/2013 is justified. Although, the provisions of the CLP Regulation (Regulation (EC) No 1272/2008) cannot be used for the micro-organisms, the chemical constituents in a plant protection product, containing the micro-organisms, may trigger classification and labelling according to the CLP Regulation and other specific labelling requirements can apply.

P.7.3 Acute toxicity

Corresponding data requirement:	(EU) No 284/2013, Annex, Part B, 7.3
Relevant evaluation criterion:	(EU) No 546/2011, Annex, Part B, 1.5.1
Relevant decision making criterion:	(EU) No 546/2011, Annex, Part B, 2.5.1
Eligible for substantiated waiving:	Yes (see text)

Purpose of this point:
Provide information on the acute toxicity of the MPCP containing MPCA-AM to humans.

Conditional/Waiving: Please also refer to the data requirement explained under P.7.2.

Testing: if testing is required, then consider Commission Communication, section 7 (see footnote 21 on p. 58).

Considerations related to testing: In addition to the recommendations specified under the section “hazard testing”, it is highly recommended to:

Unless information can be provided to allow an assessment to be conducted on the skin sensitisation properties of the plant protection product from the available information regarding its chemical components (i.e. co-formulants, metabolites of concern and relevant impurities) as set out in point 7.2, a test for skin sensitisation when available, shall be carried out in accordance with the most appropriate guidelines. The test shall provide the potential for skin sensitisation of the chemical components.

Specific information regarding sensitisation

- If based on the co-formulants no classification for sensitisation (H317) is needed, the following precautionary warning phrase should be included on the label:

  ‘Contains [*name micro-organism*]: Micro-organisms may have the potential to provoke sensitising reactions’.

- In case (i) there is clear evidence in literature that a component from the microbial active substance is a respiratory sensitiser (H334), (ii) the product is liable to labelling according

to CLP calculation rules, and (iii) inhalatory exposure is expected, the product shall be classified H334.

- In case (i) the allergic potency of the responsible proteins will be strongly reduced, (ii) the exposure related to recommended use of the MPCP is negligible when compared to that pertaining the use of yeast by e.g. bakers, or (iii) no allergic reactions are expected for operators, H334-classification is not considered necessary. In this case, only a precautionary warning phrase focused on exposure by inhalation for the usual component of living organisms is considered to be necessary. In that case, the following 'precautionary warning phrase' will be added to the label:

  'Contains [name of usual component of living organism]: [name of usual component of living organism] may have the potential to provoke sensitising reactions and allergy or asthma symptoms or breathing difficulties if inhaled'.

  This precautionary warning phrase has been derived from the standard precautionary warning phrase used for all micro-organisms in accordance with the PRAPeR Expert Meeting on micro-organisms in June 2009: 'Contains [*name micro-organism*]: Micro-organisms may have the potential to provoke sensitising reactions'.

- The two precautionary warning phrases are considered as general pre-emptive measures and not as results of a risk assessment. Any risk mitigation measures related to these two precautionary warning phrases do not rule out the MPCP being considered as a 'low-risk' product.[39]

- In general, classification based on the presence of a co-formulant excludes the product's 'low-risk' status, as risk mitigation measures (restriction sentences for conditions for safe use) are needed. This is also valid for the prescription of risk mitigation measures based on the risk assessment.

P.7.4 Additional toxicity information

Corresponding data requirement:	(EU) No 284/2013, Annex, Part B, 7.4
Relevant evaluation criterion:	(EU) No 546/2011, Annex, Part B, 1.5.1
Relevant decision making criterion:	(EU) No 546/2011, Annex, Part B, 2.5.1
Eligible for substantiated waiving:	Yes (see text)

Purpose of this point:
Provide additional information on toxicity of the MPCP containing MPCA-AM to humans.

Conditional/waiving: When the toxicity of the MPCP is sufficiently addressed under the data requirement 7.3 no further information is required besides a justification for not submitting data.

Assessment principle:
The evaluation/risk assessment of additional toxicity information on the MPCP will be based on expert judgement case-by-case.

[39] Currently a discussion at EU level is ongoing if wearing of gloves by the operator during mixing and loading following the precautionary approach regarding sensitisation is considered a generic RMM (basic hygiene) and therefore not affecting the low-risk status of the product.

Testing: if testing is required, then the particular parameters to be investigated and the objectives to be achieved are considered on expert judgement case-by-case.

P.7.5 Data on exposure

Corresponding data requirement:	(EU) No 284/2013, Annex, Part B, 7.5
Relevant evaluation criterion:	(EU) No 546/2011, Annex, Part B, 1.5.1
Relevant decision making criterion:	(EU) No 546/2011, Annex, Part B, 2.5.1
Eligible for substantiated waiving:	No

Purpose of this point:
Provide information or generate data on non-dietary exposure of operator, worker, bystander and residents to the MPCP containing MPCA-AM and the components which may be toxicologically relevant (e.g. metabolites of concern, relevant impurities, safeners, synergists), under the proposed conditions of use, including a realistic worst-case exposure scenario.
Results from exposure monitoring during production and use of the plant protection product shall be submitted.

The information and data referred to in this point shall provide the basis for the selection of appropriate protective measures including personal protective equipment to be used by operators and workers and other appropriate risk mitigation measures (e.g. for bystanders and residents) and to be specified on the label. A risk assessment should be provided (qualitative for the micro-organism regarding sensitisation and quantitative for e.g. metabolites of concern, relevant impurities, safeners, synergists).

Conditional/waiving: In most cases no reference values are set for micro-organisms and therefore no quantitative exposure assessment is required. A qualitative exposure/risk assessment is required for the sensitisation potential of the micro-organism. A quantitative exposure/risk assessment is required for e.g. metabolites of concern or relevant impurities for which a hazard was identified for humans or animals.

Assessment principle:
A risk assessment should be provided for the micro-organism regarding sensitisation as well as for components which may be toxicologically relevant (e.g. metabolites of concern, impurities, safeners, synergists). The exposure assessment for the components which may be toxicologically relevant (e.g. metabolites of concern, relevant impurities, safeners, synergists) shall include a quantitative exposure assessment considering dermal absorption/default data. The risk assessment should be considered as the basis for the selection of appropriate protective measures including personal protective equipment to be used by operators and workers and other appropriate risk mitigation measures (e.g. for bystanders and residents) and to be specified on the label.

Risk assessment to the micro-organism:
In the absence of appropriate test methods all micro-organisms are currently assumed to have the potential to cause sensitisation reactions in humans. Therefore, the use of adequate PPE for operators has to be considered where appropriate. Operator exposure may occur during mixing/loading and application. As skin is an effective barrier for micro-organisms, external skin exposure will not lead to systemic exposure and skin protection equipment is not necessary from a risk assessment point of view. In case of a powder formulation (but not for liquid formulations or granule formulation which are nearly dust-free) RPE is required for the

operator during mixing and loading of the MPCP. No substantial inhalation exposure to the micro-organism is be expected during spray application, as the product is diluted. Therefore, no respiratory protection equipment is considered necessary during application.

Risk assessment to metabolites of concern:
According to the Regulation (EU) No 546/2011:

'Metabolism is inherent of all living organisms. If secondary metabolites that are known to be hazardous to humans or other non-target organisms have been identified during the assessment of the micro-organism, the evaluation of a plant protection product containing this micro-organism shall include an assessment of the risk due to exposures to such metabolites expected from the intended use.'

The exposure assessment for metabolites of concern for which a hazard has been identified for human or animal health should consider both the presence of the metabolite in the product and in situ production (see sections A.6.1 and A.7.2). Exposure resulting from the presence of the metabolite of concern in the product can be assessed in the same way as for chemical plant protection products. The level of the metabolite in the product can be used as input parameter in the model. This would address the risk to the operator, bystander, resident, and worker. Since generally no specific dermal absorption values will be available, default values should be used. Exposure resulting from *in situ* production of the metabolite of concern can be assessed by an alternative approach as explained in the metabolite guidance in step 14: '*…the concentration of metabolite formed under production promoting conditions which can be used as a maximum for metabolite production. Examples of such conditions favourable for metabolite production may be laboratory conditions which can be justified to be conditions which maximize the formation of the metabolite (e.g., nutrient-rich medium), or during interaction of the microorganisms with the target or host organism. Information on population dynamics of the microorganism in the relevant environmental compartment can then be used to infer information on the maximal metabolite production in the relevant environmental compartment upon application and to which the relevant non-target organisms (i.e., the organism for which the hazard is identified) might be exposed.'*

For further guidance, please refer to Annex II of the 'Guidance on the risk assessment of metabolites produced by micro-organisms used as plant protection active substances, SANCO/2020/12258.

P.7.6 Available toxicological data relating to non-active substances

Corresponding data requirement:	(EU) No 284/2013, Annex, Part B, 7.6
Relevant evaluation criterion:	(EU) No 546/2011, Annex, Part B, 1.5.1
Relevant decision making criterion:	(EU) No 546/2011, Annex, Part B, 2.5.1
Eligible for substantiated waiving:	No

Purpose of this point:
Provide information on each co-formulant, safener and synergist present in the MPCP.

All available information of each co-formulant, safener and synergist present in the MPCP will be evaluated and be used for classification and labelling. The criteria used for classification and labelling of a mixture are described in the ANNEX of Regulation (EC) No 1272/2008.

P.7.7 Supplementary studies for combinations of plant protection products

Corresponding data requirement:	(EU) No 284/2013, Annex, Part B, 7.7
Relevant evaluation criterion:	(EU) No 546/2011, Annex, Part B, 1.5.1
Relevant decision making criterion:	(EU) No 546/2011, Annex, Part B, 2.5.1
Eligible for substantiated waiving:	Yes (see text)

Purpose of this point:
Provide information on the synergistic or additive toxicological effects of the combination of plant protection products.

Conditional/waiving: In certain cases it may be necessary to carry out additional studies for combination of plant protection products where the product label includes requirements for use of the MPCP with other PPP and/or with adjuvants as a tank mix. However, MPCP are hardly used in combination with other PPP and/or with adjuvants, therefore in most cases a statement to indicate that the MPCP will not be used in combination with other PPP and/or adjuvants will be sufficient to address this data requirement.

Assements principle:
The evaluation/risk assessment of combination of PPP and/or adjuvants will be based on expert judgement case-by-case.

Testing: if testing is required, then the particular parameters to be investigated and the objectives to be achieved are considered on expert judgement case-by-case.

P.8 RESIDUES IN OR ON TREATED PRODUCTS, FOOD AND FEED

Most of the data and information on residues is generated at active substance level under the data requirements of section 6 of part B set in Annex to regulation (EU) No 283/2013. The applicant is requested to provide justification that the data and information provided in the active substance assessment report is already sufficient for a risk assessment for the plant protection product. If not, the route of assessment as provided by the data requirements (EU) No. 283/2013 can be followed to provide a new risk-envelope assessment (Chapter A.6 of this evaluation manual). Please also refer to the Commission Communication concerning Part B of the Annex to (EU) No 283/2013 (Official Journal of the European Union, 2023/C 202/03)[40] and to Part B of the Annex to (EU) No 284/2013 (Official Journal of the European Union, 2023/C 202/03)[41] as relevant guidance documents are listed for the residue section.

P.9 FATE AND BEHAVIOUR IN THE ENVIRONMENT

Most of the fate and behaviour assessment is performed on active substance assessment level under the data requirements set in Annex to the regulation (EU) No 283/2013. The

[40]. Communication from the Commission concerning Part B of the Annex to (EU) No 283/2013 setting out the data requirements for active substances in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market (Official Journal of the European Union, 2023/C 202/03).

[41] Communication from the Commission concerning Part B of the Annex to (EU) No 284/2013 setting out the data requirements for active substances in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market (Official Journal of the European Union, 2023/C 202/02).

applicant is requested to provide justification that the data and information provided in the active substance assessment report is already sufficient for a risk assessment for the plant protection product. If not, the route of assessment as provided by section 7 of the data requirements (EU) No. 283/2013 can be followed to provide a new risk-envelope assessment (the A-part of this evaluation manual).

P.10 EFFECT ON NON-TARGET ORGANISMS

Scope
According to the Introduction (vii) to Chapter 10 of (EU) 284/2013:

> *" The information provided for the plant protection product, together with other relevant information, and that provided for the micro-organism (including possible metabolites of concern as identified in point 2.8 of Part B of the Annex to Regulation (EU) No 283/2013) shall be sufficient to:*
>
> *— specify the hazard symbols, the indications of danger and relevant risk and safety phrases or the pictograms, signal words, relevant hazard and precautionary statements for the protection of the environment to be mentioned on packaging (containers),*
>
> *— permit an evaluation of the short- and long-term risks for non-target species – populations, communities, and processes as appropriate,*
>
> *— permit an evaluation whether special precautions are necessary for the protection of non-target species"*

Data waiving
For all the non-target organisms groups, Chapters 10.1 to 10.5 of of (EU) 284/2013 mention that "*The same information submitted on the micro-organism (and/or on a plant protection product containing that active substance with respect to a representative use), as detailed in points* [ed.8.1-8.6], *8.7 and 8.8 of Part B of the Annex to Regulation (EU) No 283/2013 shall be provided for the plant protection product subject of the application, unless the applicant can:*

> *— justify the applicability and relevance of the outcome of the assessment made on the same data submitted for the micro-organism approval (and/or for a plant protection product containing that active substance with respect to a representative use),*
>
> *— predict the effects of the plant protection product on the basis of the data available for the co-formulants (e.g. qualitative and quantitative composition), as well as for the micro-organism and possible metabolites of concern (based on data submitted in accordance with Section 8 of Part B of the Annex to Regulation (EU) No 283/2013 for the approval of the micro-organism(s) in the plant protection product), or"*

As metioned as well under section A.8, it is not considered necessary to conduct studies with the non-target organisms if the applicant can justify based on the data submitted under the section environmental occurrence of the micro-organisms that no exposure on non-target organisms to PPP will occur.

Hazard testing
Therefore, in addition to the points mentioned in the section A.8, the following points are important when considering the effects of the PPP on the non-target organisms:

- Based on these requirements, it is considered necessary that a justification should be provided in the case the applicant wishes to waive studies with the formulation. Data on formulation is not required if the formulation is the micro-organism , for example rice grains coated with the micro-organism.
- When co-formulants are present, waiving of formulation testing based upon the fact that the co-formulants are inert and thus non-hazardous is not accepted. For example, in the 10 days oral chronic bees study, certain additives can increase the mortality and even reduce the feed consumption of bees [42]. In other cases,, co-formulants may have physical mechanisms of action relevant for some non-target organism groups. The focus NTOs for physical mechanisms of action are bees, foliar and soil arthropods, and soil meso- and macro-fauna[43,44]. However, aquatic organisms may also suffer from physical MoAs, and should be addressed on a case-by-case basis, depending upon the ingredient and the physical/chemical properties thereof. In all cases vertebrate testing is to be stringently avoided. Further justification might include a reference to the EFSA conclusion comparing the current application rates/predicted exposure levels to the application rates/predicted exposure levels in the EFSA conclusion, if these co-formulants are registered as plant protection products. For oily co-formulants (or actives), a physical mode of action via suffocation is generally considered to be possible. For example, for oil dispersion (OD) formulations, physical effects on NTAs and bees are expected, please refer to the FAO/WHO for definitions of different type of formulations (https://www.fao.org/publications/card/en/c/CB8401EN/). For conventional chemicals, Chapter 7 of the Ctgb Evaluation Manual (version 2.4) presents the approaches for testing and risk assessment for oily active substances and for products with a high concentration of oily components. The pertinent excerpt from the Evaluation Manual is included here, and considered to be equally applicable to pesticides based upon micro-organisms and containing oily components:

  "*it is noted that oily active substances generally have a physical mode of action, i.e., insects are killed because an oil film is formed on their body, which prevents them from breathing. The available NTA studies usually are performed with exposure to dried residues. The tested exposure scenarios therefore reflect introduction of species after the product has dried, which is relevant for organisms hiding under leaves or entering from off-field areas. The studies do not cover the direct effect of the application, i.e., when arthropods are oversprayed or come in contact with the wet oil spray, which based on the mode of action are considered the routes of exposure with the highest risk. The standard studies in fact can be considered as 'aged residue' studies (i.e., with an ageing time of 1-2 hrs). For the in-field risk assessment, this is acceptable, however for the off-field risk assessment aged residue studies are not acceptable. Therefore, for oily active substances the relevance of the submitted studies may be a point of discussion in the risk assessment for non-target arthropods. The consequence for the risk assessment will be a case-by-case decision, ranging from an uncertainty analysis to the request for new studies (e.g., lab studies with overspray, or field studies). It should be noted that the same line of reasoning may apply to: - other a.s. with a mode of action aimed at suffocation of the target organisms, and - products with a high percentage of oily components*".

[42] Bluhm, W. *et al*. (2017) Limited solubility of test items in regulatory honey bee (*Apis mellifera*) testing: potential use of solvents, solubilizers and viscosifiers with aqueous sucrose solution. Poster SETAC Europe 2017.
[43] Straw E. A. *et al.* (2022) "Inert" ingredients are understudied, potentially dangerous to bees and deserve more research attention, Proc. R. Soc. B 289: 20212353.
[44] Karise R. and Mänd M. (2015) Recent insights into sublethal effects of pesticides on insect respiratory physiology, Insect Physiology, 2015:5, 31-39.

- If one or more of the co-formulants is classified, and this/these co-formulant(s) is/are present at relevant levels in the formulation according to the CLP Regulation, this/these co-formulant(s) will contribute to the classification of the PPP.

According to point 4.1 of Annex I of Regulation (EC) 284/2013, in the case that a study conducted with another formulation than the one to be authorized is submitted, a bridging statement should be provided in order to assess if the formulation are comparable. For this the Guidance document on the assessment of the equivalence of technical materials of substances regulated under Regulation (EC) No 1107/2009 (SANCO/10597/2003 – rev 10.1, July 2012) can be used.

If adverse effects are observed in the studies used for the risk assessment and additionally the risk is unacceptable, additional information is needed on the exposure or the hazard characterisation' (e.g., field trials).

Risk assessment
In regards to the evaluation of impact of the micro-organism and PPP on non-target organisms, (EU) 546/2011 specifies which information should be considered when evaluating the risk to non-target organisms:

> *"— micro-organisms are living organisms capable of replication that may be naturally present in high numbers in the environment, and the specific micro-organism under assessment may already be occurring in relevant European environments at a relevant taxonomic level,*
>
> *— the biological properties and the mode of action of a micro-organism are the first and crucial step in the evaluation process, because they define which are the relevant aspects and elements on which the evaluation should focus, and also which aspects are not relevant for a robust informed decision making,*
>
> *— extensive information on the micro-organism under assessment (at the relevant taxonomic level) may be available in the public domain (e.g. history of use, peer-reviewed scientific literature). Best use of this information shall be made. Where applicable, regulatory experimental studies may be needed to determine the specific properties of the micro-organism under evaluation.*

Metabolism is inherent of all living organisms. If secondary metabolites that are known to be hazardous to humans or other non-target organisms have been identified during the assessment of the micro-organism, the evaluation of a plant protection product containing this micro-organism shall include an assessment of the risk due to exposures to such metabolites expected from the intended use".

In short, the risk assessment should take into consideration the following information:
- Mode of action and other biological properties
- Survival and dispersal of the active micro-organism in the environment
- Its ecological niche
- The natural background level of the active micro-organism, where it is indigenous
- Where relevant, other authorised uses of the plant protection product in the area of envisaged use containing the same active substance or which give rise to the same residues
- Studies on toxicity, pathogenicity and infectivity

No Guidance Document for the environmental risk assessment of micro-organisms has been established in EU-context. During expert meetings on general issues on the risk assessment for micro-organisms in 2007 and 2009 (the 'List 4 meeting' and PRAPeR M2 resp.) it was agreed that initial off-crop exposure densities in soil and water could be determined using the worst-case approach, (see fate section for further considerations).

For any given environmental compartment, the risk characterisation should, when possible, contain a comparison of the predicted exposure with the available effect values from effect studies with the micro-organism. However, when such a comparison is made no assessment factors are available to decide whether the risk is acceptable or not. The assessment factors used for chemical substances are not validated for micro-organisms, and are only used for relevant metabolites/toxins, according to the decision criteria in (EU) 546/2011.
Therefore, in most cases the risk assessment for the micro-organism will consist of a qualitative or semi-quantitative evaluation of the likelihood that an adverse effect will occur under the expected conditions of exposure. For these reasons, it is recommended to use the approach of PRAPeR M2 and derive a margin of safety (i.e., MoS) by comparing the endpoint with estimated exposure. Based on this evaluation it can be decided whether the risk is acceptable or not using a weight-of-evidence considering the mode of action, information on the ecology of the micro-organism in question and the assumptions used for the calculating the exposure.

For further guidance please refer to the OECD 67 (OECD, ENV/JM/MONO (2012)1).

P.10.1 Effects on terrestrial vertebrates

Corresponding data requirement:	(EU) No 284/2013, Annex, Part B, 10.1
Relevant evaluation criterion:	(EU) No 546/2011, Annex, Part B, 1.7.1
Relevant decision making criterion:	(EU) No 546/2011, Annex, Part B, 2.7.1
Eligible for substantiated waiving:	Yes (see the section above on data waiving)

Purpose of this point:
Provide information on the infectivity and pathogenicity of the PPP containing MPCA-AM to birds, mammals, amphibians and reptiles.

Conditional/Waiving: See the section above and as well on data waiving under section A.8.

Testing: if testing is required, then consider the Commission Communication concerning Part B of the Annex to (EU) No 284/2013 (Official Journal of the European Union, 2023/C 202/02) section 10.

According to Chapter 10.1 of (EU) 284/2013, "
If generation of data is required based on the provisions laid down under this point, relevant studies shall be performed and they shall provide LD50 values and include gross pathological findings. The studies may be conducted on the species used in the studies referred to in point 8.1 of Part B of the Annex to Regulation (EU) No 283/2013".

Considerations related to testing: See the section on "Consideration related to testing" under section A.8.1.

Risk assessment/Risk evaluation:

a) Risk due to the micro-organism and its potential to infect and multiply in the host: The use of the chemical Guidance for the risk assessment for birds and mammals (EFSA 2009) is considered less relevant for assessing solely the effects of micro-organism, since exposure parameters in this Guidance (e.g. DT50, RUD) are based on chemical databases. Consider the recommendation provided under "Scope" and refer to (EU) No 546/2011, Annex, Part B, 1.7.1 (a).
b) Risk due to toxic effects of PPP, refer to (EU) No 546/2011, Annex, Part B, 1.7.1 (b).

Decision-making: Based on the information provided by the applicant, the Member State should conclude on whether there might be unacceptable effects on terrestrial vertebrates following the intended use of PPP containg the MPCA-AM. According to the (EU) No 546/2011, Annex, Part B, 2.7.1, no authorisation shall be granted:

(a) if the micro-organism is pathogenic to terrestrial vertebrates,

(b) in case of toxic effects of the plant protection product, if the acute and short-term toxicity/exposure ratio for terrestrial vertebrates is less than 10 on the basis of LD50 (acute dietary risk assessment) or the long-term toxicity/exposure ratio is less than 5, unless it is clearly established through an appropriate risk assessment that under field conditions no unacceptable impact occurs, directly or indirectly, after use of the plant protection product in accordance with the proposed conditions of use.

P.10.2 Effects on aquatic organisms

Corresponding data requirement:	(EU) No 284/2013, Annex, Part B, 10.2
Relevant evaluation criterion:	(EU) No 546/2011, Annex, Part B, 1.7.2
Relevant decision making criterion:	(EU) No 546/2011, Annex, Part B, 2.7.2
Eligible for substantiated waiving:	Yes (see the section above on data waiving)

Purpose of this point:
Provide information on the infectivity and pathogenicity of the PPP containing MPCA-AM to fish, aquatic invertebrates, algae and aquatic macrophytes.

Conditional/Waiving: See the section above and as well on data waiving under section A.8.

Testing: if testing is required, then consider the Commission Communication concerning Part B of the Annex to (EU) No 284/2013 (Official Journal of the European Union, 2023/C 202/02) section 10.

According to Chapter 10.2.1 of (EU) 284/2013, in case of investigating the effects on fish, "*If generation of data is required based on the provisions laid down under this point, relevant studies shall be performed and they shall provide LD50 values, and shall include gross pathological findings. The studies may be conducted on the species used in the studies referred to in point 8.2.1 of Part B of the Annex to Regulation (EU) No 283/2013*".
For aquatic invertebrates, algae and aquatic plants, in case the data requirement cannot be waived, generation of data is required.

Considerations related to testing: See the section on "Consideration related to testing" under section A.8.2.

Risk assessment/Risk evaluation:

a) Risk due to the micro-organism and its potential to infect and multiply in the host: the risk assessment scheme described in the Guidance on tiered risk assessment for plant protection products for aquatic organisms in edge-of-field surface waters (EFSA Journal 2013; 11(7):3290) is considered less relevant for assessing solely the effects of micro-organism. Consider instead the recommendation provided under "Scope" and refer to (EU) No 546/2011, Annex, Part B, 1.7.2 (a).
b) Risk due to toxic effects of PPP, refer to (EU) No 546/2011, Annex, Part B, 1.7.2 (b).

Decision-making: Based on the information provided by the applicant, the Member State should conclude on whether there might be unacceptable effects on aquatic organisms following the intended use of PPP containg the MPCA-AM. According to the (EU) No 546/2011, Annex, Part B, 2.7.2, no authorisation shall be granted:

(a) if the micro-organism is pathogenic to aquatic organisms, unless it is clearly established through an appropriate risk assessment that under field conditions no unacceptable impact on aquatic organism populations would occur after use of the plant protection product in accordance with the proposed conditions of use; or

(b) in case of toxic effects of the plant protection product if the:
— toxicity/exposure ratio for fish and Daphnia is less than 100 for acute exposure and less than 10 for long- term exposure, or

— algal growth inhibition/exposure ratio is less than 10,

unless it is clearly established through an appropriate risk assessment that under field conditions no unacceptable impact on exposed species occurs, directly or indirectly, after use of the plant protection product in accordance with the proposed conditions of use.

P.10.3 Effects on bees

Corresponding data requirement:	(EU) No 284/2013, Annex, Part B, 10.3
Relevant evaluation criterion:	(EU) No 546/2011, Annex, Part B, 1.7.3
Relevant decision making criterion:	(EU) No 546/2011, Annex, Part B, 2.7.3
Eligible for substantiated waiving:	Yes (see the section above on data waiving)

Purpose of this point:
Provide information on the infectivity and pathogenicity of the PPP containing MPCA-AM to bees.

Conditional/Waiving: See the section above and as well on data waiving under section A.8.

Testing: if testing is required, then consider the Commission Communication concerning Part B of the Annex to (EU) No 284/2013 (Official Journal of the European Union, 2023/C 202/02) section 10.

According to Chapter 10.3 of (EU) 284/2013, in case the data requirement cannot be waived, generation of data is required.

Considerations related to testing: See the section on "Consideration related to testing" under section A.8.3.

Risk assessment/Risk evaluation:

a) Risk due to the micro-organism and its potential to infect and multiply in the host: the risk assessment schemes described EPPO Series PP 3 Environmental Risk Assessment Scheme for Plant Protection products – Chapter 10: Honeybees (first published in 1993, the latest revision in 2010) and according to the first tier of the EFSA Guidance Document on the risk assessment of plant protection products on bees (*Apis mellifera*, *Bombus spp*. and solitary bees) (EFSA Journal 2013;11(7):3295) are considered less relevant for assessing solely the effects of micro-organism. Consider instead the recommendation provided under "Scope" and refer to (EU) No 546/2011, Annex, Part B, 1.7.3 (a).
b) Risk due to toxic effects of PPP, refer to (EU) No 546/2011, Annex, Part B, 1.7.3 (b).

Decision-making: Based on the information provided by the applicant, the Member State should conclude on whether there might be unacceptable effects on bees following the intended use of PPP containg the MPCA-AM. According to the (EU) No 546/2011, Annex, Part B, 2.7.3, no authorisation shall be granted:

a) if the micro-organism is pathogenic to bees under the proposed conditions of use, unless it is clearly established through an appropriate risk assessment that under field conditions no unacceptable impact is expected to occur to the populations of bees after use of the plant protection product in accordance with the proposed conditions of use; or

b) in case of toxic effects of the plant protection product, as defined in the decision-making principles of point 2.5.2.3 of Part A.

P.10.4 Effects on non-target arthropods other than bees

Corresponding data requirement:	(EU) No 284/2013, Annex, Part B, 10.4
Relevant evaluation criterion:	(EU) No 546/2011, Annex, Part B, 1.7.4
Relevant decision making criterion:	(EU) No 546/2011, Annex, Part B, 2.7.4
Eligible for substantiated waiving:	Yes (see the section above on data waiving)

Purpose of this point:
Provide information on the infectivity and pathogenicity of the PPP containing MPCA-AM to non-target arthropods other than bees.

Conditional/Waiving: See the section above and as well on data waiving under section A.8.

Testing: if testing is required, then consider the Commission Communication concerning Part B of the Annex to (EU) No 284/2013 (Official Journal of the European Union, 2023/C 202/02) section 10.

According to Chapter 10.3 of (EU) 284/2013, in case the data requirement cannot be waived, generation of data is required " *Analyses might include further studies on additional species, or higher tier studies such as studies on selected non-target organisms using the formulated plant protection product. The choice of non-target arthropods test species playing an important role in integrated pest management may be based on several factors, such as biological properties of the micro-organism and the intended use (e.g. crop type)"*

Considerations related to testing: See the section on “Consideration related to testing” under section A.8.3.

Risk assessment/Risk evaluation:

a) Risk due to the micro-organism and its potential to infect and multiply in the host: the risk assessment schemes described in the Guidance Document on Terrestrial Ecotoxicology (Sanco/10329/2002 rev 2 final), which follows the recommendations of the ESCORT 2 workshop are considered less relevant for assessing solely the effects of micro-organism. Consider instead the recommendation provided under “Scope” and refer to (EU) No 546/2011, Annex, Part B, 1.7.4 (a).
b) Risk due to toxic effects of PPP, refer to (EU) No 546/2011, Annex, Part B, 1.7.4 (b).

Decision-making: Based on the information provided by the applicant, the Member State should conclude on whether there might be unacceptable effects on non-target arthropods other than bees following the intended use of PPP containg the MPCA-AM. According to the (EU) No 546/2011, Annex, Part B, 2.7.4, no authorisation shall be granted:

a) if the micro-organism is pathogenic to arthropods other than bees, unless it is clearly established through an appropriate risk assessment that under field conditions no unacceptable impact is expected to occur to the populations of arthropods other than bees after use of the plant protection product in accordance with the proposed conditions of use; or

b) in case of toxic effects of the plant protection product, as defined in the decision-making principles of point 2.5.2.4 of Part A, unless it is clearly established through an appropriate risk assessment that under field conditions there is no unacceptable impact on arthropods other than bees after use of the plant protection product in accordance with the proposed conditions of use. Any claims for selectivity and proposals for use in integrated pest management systems shall be substantiated by appropriate data.

P.10.5 Effects on non-target meso- and macro-organisms in soil

Corresponding data requirement:	(EU) No 284/2013, Annex, Part B, 10.5
Relevant evaluation criterion:	(EU) No 546/2011, Annex, Part B, 1.7.5
Relevant decision making criterion:	(EU) No 546/2011, Annex, Part B, 2.7.5
Eligible for substantiated waiving:	Yes (see the section above on data waiving)

Purpose of this point:
Provide information on the infectivity and pathogenicity of the PPP containing MPCA-AM on non-target meso- and macro-organisms in soil

Conditional/Waiving: See the section above and as well on data waiving under section A.8.

Testing: if testing is required, then consider the Commission Communication concerning Part B of the Annex to (EU) No 284/2013 (Official Journal of the European Union, 2023/C 202/02) section 10.

Considerations related to testing: See the section on “Consideration related to testing” under section A.8.5.

Risk assessment/Risk evaluation:

a) Risk due to the micro-organism and its potential to infect and multiply in the host: the risk assessment schemes described in the Guidance Document on Terrestrial Ecotoxicology (Sanco/10329/2002 rev 2 final)are considered less relevant for assessing solely the effects of micro-organism. Consider instead the recommendation provided under “Scope” and refer to (EU) No 546/2011, Annex, Part B, 1.7.5 (a).
b) Risk due to toxic effects of PPP, refer to (EU) No 546/2011, Annex, Part B, 1.7.5 (b).

Decision-making: Based on the information provided by the applicant, the Member State should conclude on whether there might be unacceptable effects non-target meso- and macro-organisms in soil following the intended use of PPP containg the MPCA-AM. According to the (EU) No 546/2011, Annex, Part B, 2.7.5, no authorisation shall be granted:

a) if the micro-organism is pathogenic to meso- and macro-organisms in soil, unless it is clearly established through an appropriate risk assessment that under field conditions no unacceptable impact on soil meso- and macro-organism populations occurs after use of the plant protection product in accordance with the proposed conditions of use; or

(bin the case of toxic effects of the plant protection product, if the acute toxicity/exposure ratio for meso- and macro-organisms in soil is less than 10 or the long-term toxicity/exposure ratio is less than 5, unless it is clearly established through an appropriate risk assessment that under field conditions no unacceptable impact on soil meso- and macro-organism populations occur after use of the plant protection product in accordance with the proposed conditions of use.

P.10.6 Effects on non-target terrestrial plants

Corresponding data requirement:	(EU) No 284/2013, Annex, Part B, 10.6
Relevant evaluation criterion:	(EU) No 546/2011, Annex, Part B, 1.7.6
Relevant decision making criterion:	(EU) No 546/2011, Annex, Part B, 2.7.6
Eligible for substantiated waiving:	Yes (see the section above on data waiving)

Purpose of this point:
Provide information on the infectivity and pathogenicity of the PPP containing MPCA-AM on non-target terrestrial plants.

Conditional/Waiving: See the section above and as well on data waiving under section A.8.

Testing: if testing is required, then consider the Commission Communication concerning Part B of the Annex to (EU) No 284/2013 (Official Journal of the European Union, 2023/C 202/02) section 10.

Considerations related to testing: See the section on “Consideration related to testing” under section A.8.6.

Risk assessment/Risk evaluation:

a) Risk due to the micro-organism and its potential to infect and multiply in the host: the risk assessment schemes described in the Guidance Document on Terrestrial Ecotoxicology (Sanco/10329/2002 rev 2 final) are considered less relevant for

assessing solely the effects of micro-organism. Consider instead the recommendation provided under "Scope" and refer to (EU) No 546/2011, Annex, Part B, 1.7.6 (a).

b) Risk due to toxic effects of PPP, refer to (EU) No 546/2011, Annex, Part B, 1.7.6 (b).

Decision-making: Based on the information provided by the applicant, the Member State should conclude on whether there might be unacceptable effects on non-target terrestrial plants following the intended use of PPP containg the MPCA-AM. According to the (EU) No 546/2011, Annex, Part B, 2.7.6, no authorisation shall be granted:

"If the micro-organism has an herbicidal mode of action or it is closely related to a known plant pathogen, and there is a possibility of terrestrial plants being exposed to the micro-organism according to the consideration done under point 1.6, no authorisation shall be granted if the micro-organism is pathogenic to, or the plant protection product has toxic effects on, terrestrial plants. This criterion applies unless it is clearly established through an appropriate risk assessment that, under field conditions, no unacceptable impact on non-target terrestrial plant populations occurs after use of the plant protection product in accordance with the proposed conditions of use".

P.10.7 Additional toxicity studies

Corresponding data requirement:	(EU) No 284/2013, Annex, Part B, 10.7
Relevant evaluation criterion:	(EU) No 546/2011, Annex, Part B, 1.7.1-1.7.6
Relevant decision making criterion:	(EU) No 546/2011, Annex, Part B, 2.7.1-2.7.6
Eligible for substantiated waiving:	Not applicable

Purpose of this point:
According to (EU) 284/2013, ANNEX II, Part B, 10.7 "*Further data may be submitted or additional toxicity studies performed, if tests required in points 10.1 to 10.6 have shown adverse effects in one or more non-target organisms and the risk is considered not acceptable. The type of study to be performed shall be chosen based on the effects and the affected non-target organism(s) observed in the studies required in points 10.1 to 10.6 and during efficacy testing, and may have to include also further studies on additional non-target species*".