New rules for registration of Microbial Biological Control Agents (MBCAs) in EU – a boost for commercialisation?

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As for all plant protection products and active substances, the registration process for Microbial Biological Control Agents (MBCAs) in EU includes two main aspects; scientific data and assessment as well as regulatory requirements to be observed. For many decades, for MBCAs both aspects were repeatedly and deeply criticised by nearly all stakeholders involved – industry, science, politics and certain authorities. Subjects of discussion were manyfold, often also due to opposing interests as, for example, low registration costs and timelines versus comprehensive registration dossiers using the precautionary principle on a strain-specific basis. Both scientific and regulatory aspects limited the commercialisation and market extension for MBCAs.

Regarding scientific data requirements and risk assessments for MBCAs, omissions and inadequacies as well as the neglect of the specifics of biological pest control methods became obvious in 2001 by Directive 2001/36 on the data requirements for A.S. and PPPs. These data requirements were purely designed for the evaluation and registration of chemical pesticides. "New" data requirements for microorganisms set out in Regulations 283/2013 and 284/2013 in 2013 did not change the situation for MBCAs since they were simply copied from the chemical pesticide requirements without adaption to MBCAs. The situation for MBCAs did not significantly change after the introduction of the low-risk pesticide category by Regulation 1107/2009 although it was assumed that this would ease MBCA registrations and foster commercialisation of MBCAs. Whereas for other, non-microbial biopesticides the publication of applicable low risk criteria in Regulation 2017/1432 in 2017, nearly a decade after introduction of the low-risk category, was a huge improvement, for MBCAs the criteria established were still incomplete and final criteria are currently still under development.

One of the most criticised topics in the scientific evaluation of MBCAs in the last decades was the erroneous definition/use of secondary and relevant metabolites, i.e., the definitions applicable for chemicals were used also for microbial metabolites (e.g., Scheepmaker et al. 2019). Beside the specific issue, the overall discussions have shown the urgent need for more specific, scientific-based data requirements for MBCAs. Regulation 283/2013 on the data requirements for active substances for example stated that "such information shall not be required, where […] it is not necessary owing to the nature of the product or its proposed uses, or it is not scientifically necessary, or it is technically not possible to supply. In such a case a justification shall be provided". However, the daily registration work has shown again and again that a strict scientific approach was seldom accepted, instead the regulatory box-ticking approach is used in the scientific evaluation of MBCAs, and regulatory requirements are often placed above scientific argumentation. Köhl et al. (2019), for example, have stated that for the environmental fate assessment, for many microorganisms "the precautionary principle of the risk assessment can be fulfilled by referring to the general microbiological principles of population dynamics in competitive environments". Instead, often strain-specific but conditionally informative information was used. The authors further concluded that "precautionary principles and avoiding any theoretical risk predominates the procedures for MBCAs leading to unnecessary and costly data collection. Switching to 'principles of evidence-based acceptable risks' instead, would allow more restricted data requirements which may have to be adapted whenever new knowledge and technology becomes available or new safety questions are raised".

To handle these past problems "and to better reflect the latest scientific developments and the specificities of micro-organisms, while maintaining a high level of protection of human and animal health and of the environment", the specific criteria for the approval (Regulation 1107/2009), uniform principles (Regulation 546/2011) and data requirements (Regulations 283/2013 and 284/2013) for MBCAs are currently being revised and presumably applicable from Q4 2022 onwards.

Annex II of Regulation 1107/2009 establishing the procedures and criteria for the approval of active substances, for example, was revised to include specific criteria for approval of active substances that are micro-organisms (incl. low risk criteria), differentiating them from chemical active substance approval criteria. The uniform principles for evaluation and authorisation of plant protection products (Regulation 546/2011) have been revised adapting, for example, the decision-making criteria to the characteristics of micro-organisms, such as their pathogenicity and infectivity, rather than focusing on toxicity. Furthermore, the revised decision-making criteria related to environmental fate, now focus on surface and groundwater only. The persistence in the environment in concentrations considerably higher than the natural background levels are not considered an exclusion criterion anymore.

Regulations 283/2013 and 284/2013 were updated to include several MBCA-related definitions and provide clarity on when which set of data requirements applies: a) Data requirements specified in Part A apply to semiochemicals, extracts from biological material, a purified metabolite produced by a micro-organism as well as a metabolite that is not purified from a producing micro-organism if the micro-organism is not capable of replication or to transfer genetic material. Data requirements specified in Part B apply to micro-organisms, either as a single strain or as a qualitatively defined combination of strains (classically termed "microbial consortia") as well as a combination of micro-organism(s) and one or more metabolites produced by the micro-organism(s) that are claimed to be part of the plant protection action. However, this applies only when the application of the metabolite(s) purified from the micro-organism would not cause the claimed plant protection action alone.

The possibility to commercialise microbial consortia, which are very often significantly more effective and adaptive and thus commercially more interesting, could be a huge step in bringing the regulatory process closer to the scientific reality and the agricultural practice. In addition, products based on microbial consortia allow, for example, for the development of patentable formulations enabling a better protection of investments.

The focus of the revision of the data requirements has shifted form the box-ticking approach to a scientific evaluation approach based upon the biological properties of the MBCA. This makes possible to use this information in a weight of evidence approach to demonstrate that adverse effects are not to be expected if products are used according to Good Agricultural Practise. This allows for scientific justification of study waivers e.g., in the case of toxicity, residues or ecotoxicity. For example, studies to determine the potential infectivity and pathogenicity of the micro-organism shall be performed, unless the applicant demonstrates that infectivity and pathogenicity to humans/mammals are not expected, using

information on the biological properties (e.g., mode of action, growth requirements and relationship to human and non-target organism pathogens, also using information retrieved from reliable public sources). Generally, this could significantly reduce study costs and ease the commercialisation of MBCAs. It is, however, currently open for speculation and interpretation what type of information will be accepted as sufficient evidence to "demonstrate that effects are not to be expected" by authorities. No toxicity or genotoxicity data is required for microorganisms; however, it should be addressed for possible metabolites of concern in a separate section.

From the regulatory point of view, the adapted scientific data requirements for MBCAs and the resulting incentives fostering commercialisation have no deeper impact since, e.g., registration timelines etc. have not changed. The lack of additional regulatory incentives is, for example, highlighted by the declaration of The Netherlands in the SCOPAFF (Standing Committee on Plants, Animals, Food and Feed, Section Phytopharmaceuticals) meeting of 27-28 January 2022. The Netherlands stated that "we [The Netherlands] support the current proposals for the assessment on micro-organisms which will improve the dossiers and the assessments. Although we see that these proposals will increase the quality of the dossiers, we do not expect them to significantly accelerate the approval process for micro-organisms because the regulatory procedure remains unchanged, and a significant amount of data is still requested. In our view this was one of the goals of the review, because micro-organisms are essential and needed on the market to make the agricultural transition which we strive to. We would therefore like to emphasise that further action is needed to accelerate the approval process for micro-organisms. We would especially like to call out for further action in order to accommodate the group-assessment of micro-organisms and to initiate the development of the necessary guidance document for harmonization".

The opinion of the Netherlands is to be fully supported. This is especially true since, as already indicated above, regulatory incentives such as reduced registration fees often apply only for low-risk active substances. On the other hand, additional new general regulatory requirements must be considered which also have a strong impact on the registration process for MBCAs, especially since some of them, again, are not adapted to MBCAs.

For example, for all active substances, including micro-organisms, the use of the IUCLID (International Uniform Chemical Information Database) software for dossier submission is mandatory from March 2021 onwards. The use of IUCLID is one of the major changes in plant protection introduced by entry into force of the Transparency Regulation 2019/1381. Within this scope, the complete dossier including studies will be made publicly available with only a few exceptions of confidential information that are in line with Article 63 of Regulation 1107/2009. Moreover, applicants must notify all studies conducted for active substance approval from 27th March 2021 onwards. The competent authority will not accept non-notified studies (if they were conducted later than the 27th of March 2021) nor will accept that notified studies are not used in a dossier without a proper justification. Unfortunately, dossiers based on scientific justifications and public literature are currently not well reflected in the dossier structure of ICULID, which was originally developed for chemicals.

Another difficulty in the approval of micro-organisms as active substance is the mandatory EFSA-compliant literature review. According to Commission Regulation 283/2013, an EFSA-conform literature search is a prerequisite in dossier preparation and is required to provide an overview of public literature related to the active substance, metabolites and breakdown or reaction products and plant protection products containing the active substance and dealing with side-effects on health, the environment and non-target species. For micro-organisms, information at the relevant taxonomic level (e.g., strain, species, genus) and an explanation on why the chosen taxonomic level is considered relevant for the addressed data requirement shall be provided. These literature searches usually result in a large number of publications, making the evaluation of literature quite complex and thus cost intensive. Moreover, it is often difficult to obtain proper information from literature since the identity of used micro-organisms are often not well described. Additionally, reclassifications or renaming of species and strains complicate the task even more. However, the literature search for micro-organisms includes additional difficulties, namely the handling of secondary/relevant metabolites. The authorities request information on secondary metabolites of potentially concern produced by the micro-organism of interest (present in the MBCA as well as in situ production). As it is mostly not known which secondary metabolites are potentially produced on strain level, authorities often request to consider all known secondary metabolites produced on genus level if it cannot be excluded that they may be produced by the micro-organism of interest, frequently referring to genome-based evidence. Although in recent years, more and more genomes have been sequenced, the identification of secondary-metabolism related gene clusters, are lagging behind, making it impossible to exclude the production of certain secondary metabolites based upon genome sequence data. Authorities also request to perform EFSA compliant literature searches for secondary metabolite groups independent of the micro-organism of interest, e.g., adverse effects of volatile organic compounds. Such requests are not appropriate and not considered within the scope of the requirements. Consequently, further literature searches on the effects of an extended list of potentially produced secondary metabolites are needed, leading to an even higher load of publications that must be considered. Therefore, a proper search strategy and a scientifically sound justification for choosing the correct taxonomic level and/or the relevant secondary metabolites is mandatory.

All in all, the upcoming regulations are a significant boost for commercialisation of MBCAs, especially combined with additional rules such as the low-risk categorisation as well as some national incentives regarding MBCA registration and use. Possibilities for registration and availability of products based on microbial consortia as well as a broader availability of MBCA-products in general can pave the way for a wider use of such products, also in field crops, shifting the current focus on cash crops to additional agricultural crops. It is important to highlight that the new regulations described in this article are only a part of the current efforts to modernise EU agriculture. In this context, the European Green Deal, The Biodiversity and Farm to Fork Strategies as well as the Sustainability Goals additionally foster the use of MBCAs, e.g., by the requirements to reduce the use of chemical pesticides significantly by 2030 or the mandatory introduction and strengthening of Integrated Pest Management opening huge possibilities for the commercialisation of MBCAs. It is important to highlight that the driving force behind this ongoing modernisation of the EU agriculture is based on economic considerations triggered by the loss of pollinators, soil fertility, losses due to climate change as the heat and drought wave 2022 in the EU impressively shows. In addition, the COVID pandemic as well as the war in Ukraine have shown how vulnerable the agricultural sector and food supplies are. Thus, the current political processes described above aim to make the food sector more resilient in any aspect. As MBCAs are a major instrument to achieve many of these goals, it is very likely that we will see additional actions taken to support and foster commercialisation of MBCAs in the near future. As these respective triggers are not restricted to the EU but apply on a global scale, similar changes can be expected in further countries worldwide.

Due to the current discussions and significance of biostimulant products, with many of them based on micro-organisms, it must be mentioned in this context, that further complications may arise in future due to the borderline-cases between plant protection and biostimulant actions of a micro-organism as well as the plant protection requirements regarding, for example, identity. As the differentiation between biopesticides, regulated under plant protection law, and biostimulants, regulated under EU or national fertiliser laws, is not a scientific but a regulatory one and a specific micro-organism may exert both biostimulant and plant protection actions, this aspect is not to be neglected in commercialisation of MBCAs as well as micro-organism based biostimulants. However, at the current stage, no general assumptions are possible and decisions have to be based on a case-to-case basis.

Of course, all these significant changes on national as well as international level have a huge impact on the commercialisation, including R&D, registration, scientific evaluation, distribution and marketing of MBCAs. Therefore, it is of uttermost importance to develop the commercialisation strategy of a MBCA-based product on suitable and tailored concepts considering the full scope of current and future developments, including climate-based crop shifts, Integrated Pest Management, Precision- and Digital Farming or Organic Agriculture. In any case, the initiated changes as well as the current political and public will foster the commercialisation of MBCAs more than at any time before. AP