

REGULATORY FRAMEWORK REVIEW

An analysis of regulation of biological plant protection products and other regulated products

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1. INTRODUCTION

Micro-organisms, semiochemicals and botanicals, often referred to as '**biological plant protection products**' are currently under the scope of the Plant Protection Products Regulation (EC) No 1107/2009. Although efforts are being made to accommodate these biological plant protection products under the current legislation (e.g. separate set of data requirements for micro-organisms, provisions for 'low-risk substances') and specific guidance is being developed, it is clear that the **current legislation was designed for chemical active substances**. The data requirements, exposure models and risk assessment strategies, have all been drawn up with synthesised chemical actives of high purity in mind. In addition, criteria appropriate for chemical active substances and plant protection products such as one clear mode of action, an effective killing of the targeted disease/pest, as little as possible effects on non-target organisms, rapid degradation in the environment and no residues are difficult to translate one-on-one to biological plant protection products. What is more, biological plant protection products often do not have a '-cidal' effect, or less strongly than conventional chemical product. Also, rapid degradation in the environment is often not desirable, as they are often designed to settle and persist and continue to demonstrate a benefit. Finally, a combination of biological plant protection products is often required to reach a desired efficacy level in a particular crop/circumstance. Overall, the approach provided for in current PPP legislation can impose an **unnecessarily high and inappropriate regulatory burden** on the approval and authorisation of biological plant protection products, while the level of risk resulting from the use of many biological products is known, documented and considerably lower than for conventional chemical pesticides.

As agriculture is evolving continuously, and developments relating to more sustainable alternatives for chemical control of pests and diseases are being encouraged (cf. Sustainable Use Directive 2009/128/EC and provision relating to IPM), biological plant protection products are becoming more and more important. Over the past years, several chemical control options have been banned or restricted. Therefore, farmers are increasingly experiencing difficulties to control certain pests or diseases. Although new biological plant protection solutions for integrated pest management (IPM) strategies are being developed at a fast pace, their **market entry is slow** as the resources of the evaluating authorities are being depleted by the regulatory requirements for existing products (e.g. active substance renewals and product re-authorisations). Advancements are further hampered by the lack of specific expertise related to biological plant protection products.

The scope of this thought-starter document is to concisely highlight the **regulatory problems** that manufacturers of biological plant protection products are confronted with today when trying to put their products on the market **and importantly, to make proposals** for a **better workflow** under Regulation (EC) No 1107/2009 and/or for a **future legislation** specifically for biological plant protection products.

2. REGULATORY PROBLEMS

A first problem that arises when dealing with **biological plant protection products**, is that there is **no formally agreed definition** in place at EU level, nor at global level. For the purpose of this document, biological plant protection products will include products with active substances that are based on microbials, botanicals, biochemicals of natural origin (and nature-identical if synthesized) or semiochemicals. The FAO/WHO 'Guidelines for the registration of microbial, botanical and semiochemical pest control agents' (WHO/HTM/NTD/WHOPES/2017.05¹) distinguish these products from conventional chemical plant protection products "by a combination of their active substance material and/or nature, and their use". The EC 'Guidance Document on botanical active substances used in plant protection products' (SANCO/11470/2012 - rev. 8 20 March 2014 ²), which has later been used to produce the OECD Guidance Document (ENV/JM/MONO(2017)6³), defines a **botanical active substance** as consisting of "one or more components found in plants and obtained by subjecting plants or parts of plants of the same species to a process such as pressing, milling, crushing, distillation and/or extractions. The process may include further concentration, purification and/or blending, provided that the chemical nature of the components is not intentionally modified/altere d by chemical and/or microbial processes". The EC guidance document on semiochemical active substances and plant protection products (SANTE/12815/2014 rev. 5.2, May 2016 ⁴ defines **semiochemicals** as "substances or mixtures of substances emitted by plants, animals and other organisms that evoke a behavioural or physiological response in individuals of the same or other species". Within the EU, micro-organisms are defined as "any microbiological entity, including lower fungi and viruses, cellular or non-cellular, **capable of replication or of transferring genetic material**" (Reg. (EC) No 1107/2009, Art. 3). Dead micro-organisms (except for viruses) are therefore considered chemical active substances. This is in contrast with the FAO/WHO Guidelines (WHO/HTM/NTD/WHOPES/2017.05), which define a **microbial or a microorganism active substance** as a "microorganism (protozoan, fungus, bacterium, virus or other microscopic self-replicating biotic entity) (...) and any associated metabolites, to which the effects of pest control are attributed. (...) A microorganism active substance may contain **viable and/or non-viable microorganisms**. It can contain relevant metabolites/toxins produced during cell proliferation (growth), material from the growth medium, provided none of these components have been intentionally altered".

It is generally recognized that the current Plant Protection Product Regulation (EC) No 1107/2009 is too one-sidedly focused on '**-cidal**' (**killing**) **control** when it comes to biological plant protection products and therefore, the criteria are unsuitable as an authorization tool for biological plant protection products. Moreover, biological plant protection products often have a complex composition and living organisms often have multiple modes

¹ <http://apps.who.int/iris/bitstream/handle/10665/259601/WHO-HTM-NTD-WHOPES-2017.05-eng.pdf;jsessionid=5C8BFEE5BAF002CFB626900DA6B558BB?sequence=1>

² https://ec.europa.eu/food/sites/food/files/plant/docs/pesticides_ppp_app-proc_guide_doss_botanicals-rev-8.pdf

³ [http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono\(2017\)6&doclanguage=en](http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2017)6&doclanguage=en)

⁴ https://ec.europa.eu/food/sites/food/files/plant/docs/pesticides_ppp_app-proc_guide_doss_semiochemicals-201605.pdf

of action. Therefore, biological plant protection products would benefit from limiting the data requirements and risk assessment practice in line with Regulation (EC) No 1107/2009 to substances and products with direct controlling/killing effect on disease and pest so that they can be evaluated and authorized faster under more appropriate criteria.

Biological plant protection products may qualify for a kind of **fast-track registration procedure**, as many of the active substances and products are developed to have a **low risk profile**, have a safe history of use, to be formulated in inert materials, and/or to be used at levels similar as those that occur commonly in the relevant environmental compartment. This means that higher tier testing is usually not required. Articles 22 and 47 of Regulation (EC) No 1107/2009 deal specifically with low-risk plant protection substances/products. While the Regulation calls for **prioritizing** their use, in practise it offers no appropriate mechanisms thereto. Although specific criteria (described in Annex II §5 of Regulation 1107/2009, updated in August 2017 by amending Regulation (EU) No 2017/1432) are in place for low risk products, low-risk plant protection active substances have to undergo the same lengthy and cumbersome approval procedures as conventional plant protection active substance, resulting in very low numbers of low-risk active substances – most of them biological – currently available on the EU market. In addition, low risk products should be authorized in 120 days, unfortunately it still takes Member States about one year to complete the procedure. Consequently, on 15 February 2017, the European Parliament adopted with near unanimity a **Resolution1 (2016/2903 (RSP))** calling on the European Commission to submit, before the end of 2018, a specific legislative proposal to establish a fast-track evaluation, approval (a.s.) and authorization (product) process for low-risk plant protection products of biological origin.

Depending on the **mode of action**, a biological input can fall under different legislations. For example, if a product works against abiotic stress, it could be considered to fall under the fertilizer legislation as biostimulant once the revised Regulation (EC) 2003/2003 will come into force, but if a product works against biotic stress (such as induced resistance) or against a pest or a disease, it falls under the Plant Protection Products Regulation (EC) No 1107/2009. This is problematic, given the vast difference in data requirements and assessments between both procedures. The more since the **claim** determines which legislation will apply, and not the **intrinsic properties** of the substance and the **exposure profile** of the product.

In addition, Regulation (EC) No 1107/2009 is based on the **hazard principle**, which is not suitable for biological plant protection products. For example, thousands of substances can be potentially synthesized by one micro-organism, and it can never be excluded that one of them will fall under the hazard principles. Therefore, the regulatory procedure for biological plant protection products should be risk-based such that the probability of a risk to men and environment can be determined when the product is used for crop protection. In this context, it is worth referring to the '**precautionary principle**' as explained in Commission Communication COM(2000)

1 final⁵, which embeds the appraisal of exposure by “quantitatively **or qualitatively** evaluating the probability of exposure to the agent under study.” Other than that, one of the aims of the Communication is to “avoid unwarranted recourse to the precautionary principle, as a disguised form of protectionism”.

Nowadays, it is becoming more and more recognized that the current procedures of authorising a plant protection product through Regulation (EC) No 1107/2009 **slows down innovation** when it comes to biological crop protection products. For example, from fundamental research it is becoming increasingly clear that the microbiome (also called the ‘2nd genome’) plays an essential role in the health of every plant. The microbiome is the microbial community of many types of microorganisms within the plant (endophytes), around leaves and roots that - with the right composition - in symbiosis with the plant through all kinds of mechanisms can form a shield against attacks of diseases and pests. Research also makes it clear that through biological induction from external factors the microbiome of a plant can be optimized in a certain growing condition, so that it can exert its protective effect. If such biological plant protection products for influencing the microbiome would become available, there is **no appropriate legislation for evaluation of these tools**. As a consequence, the availability of such products on the market will be slowed down.

3. LESSONS FROM OTHER EU LEGISLATIONS

Based on experience with other EU chemicals legislations that are based on risk assessment, certain aspects that could be a source of inspiration for a future legislative framework for biological plant protection products, are discussed below. This includes legislative text, guidance documents, procedures etc. The following five regulatory frameworks have been selected as a scope for this document and will be discussed in further detail. Aspects of other chemical legislations (e.g. veterinary medicines, food additives, ...) could be relevant as well but have not been included because they can be linked to aspects of the five selected relevant regulatory frameworks discussed below.

- Medicinal Products Regulation (Regulation (EC) No 726/2004)
- Feed additives Regulation (Regulation (EC) No 1831/2003)
- REACH Regulation (Regulation (EC) 1907/2006)
- Biocidal Products Regulation (BPR) (Regulation (EC) No 528/2012)
- Cosmetic Product Regulation (Regulation (EC) No 1223/2009)

⁵ <https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52000DC0001&from=EN>

3.1. MEDICINAL PRODUCTS REGULATION

In the EU, a medicinal product for human use may be authorized either by the European Commission through a centralized procedure (resulting in a single marketing authorization for the whole of the European Union + Iceland, Norway and Liechtenstein) or by national competent authorities through a national authorization procedure (authorizing the use in their own territory). In contrast to the Plant Protection Products Regulation, there is no separate approval/authorisation stage for the active substance and the product: only the products receive a marketing authorization.

The centralized procedure is laid down in Regulation (EC) No 726/2004. Some medicinal products fall within the 'mandatory scope' of the Annex of this regulation and are obliged to use the centralized procedure for submitting their marketing authorization application:

- products derived from biotechnology,
- orphan medicinal products, and
- medicinal products for human use which contain an active substance authorized in the Union after 20 May 2004 and which are intended for the treatment of AIDS, cancer, neurodegenerative disorders or diabetes.

For medicinal products falling under the 'optional scope' of the Annex of Regulation (EC) No 726/2004, applications for the following categories may, at the request of the applicant, be accepted for assessment under the centralized procedure:

- products that contain an active substance not authorized before 20 May 2004,
- products constituting a significant therapeutic scientific or technical innovation, or
- products for which an EU authorization would be in the interest of patients.

Procedural aspects and timelines

Companies wishing to market a medicinal product that is eligible for the centralized authorization procedure, submit their application directly to the European Medicines Agency (EMA). The EMA is responsible for the validation and scientific evaluation of the application via the Committee for Medicinal products for Human Use (CHMP). Each European Member State has one representative on the CHMP and one alternate. They carry out a scientific assessment of the application and give a recommendation on whether the medicine should be authorized or not. This starts with the appointment of a Rapporteur and a Co-Rapporteur in the CHMP which are normally chosen in accordance with their field of expertise (therapeutic area). They act as a bridge between the European system and their national assessment teams.

The complete evaluation procedure for new marketing authorization applications is limited to 210 days (see figure below), subject to extensions if additional questions need to be addressed. After submission of the application, the Rapporteurs are responsible for preparing two independent Assessment Reports, which the committee will consider. All comments from the CHMP are summarized in a List of Questions which is sent to the applicant. At this point there's a 'clock stop' allowing the applicant to provide the necessary answers. Once the response is submitted, the secondary evaluation starts which is ended by creation of a Joint Assessment Report by the Rapporteurs. An additional 'clock-stop' may occur after day 180, when the CHMP has adopted a List of Issues to be (orally) addressed by the Applicant. This leads to a final CHMP Opinion.

Within 15 days a draft implementing decision is sent by the Commission to the Standing Committee on Medicinal Products for Human Use, allowing for its scrutiny by EU countries. They have 15 days to return their linguistic comments, and 22 days for substantial ones. Once a favourable opinion is reached, the draft decision is adopted via an empowerment procedure. The adoption of the decision should take place within 67 days of the opinion of the EMA. The decision is subsequently published in the Community Register.

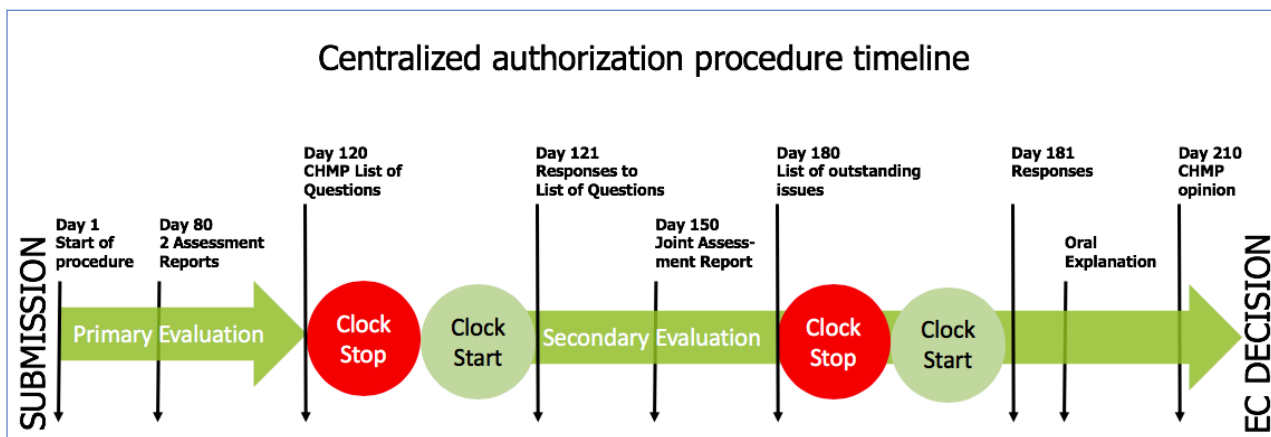


Figure 1: Centralized authorization procedure timeline

Support and early market access

The legislation contains a number of provisions aimed at fostering patient's early access to new medicines that address public health, such as:

- the **accelerated assessment procedure**⁶: This procedure applies to medicinal products of major public health interest and in particular those that are therapeutically innovative. The evaluation time is reduced from 210 to 150 days.

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http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000955.jsp&mid=WC0b01ac05809f843a

- the **conditional market authorisation**⁷: In the interest of public health, applicants may be granted a conditional marketing authorization for such medicines where the benefit of immediate availability outweighs the risk of less comprehensive data than normally required, based on the scope and criteria defined in legislation and guideline. Such authorisations are valid for one year on renewable basis.
- the **compassionate use opinion**⁸: This allows the use of an unauthorized medicine. The EMA provides recommendations through the CHMP, but these do not create a legal framework. Compassionate use programmes are coordinated and implemented by Member States, which set their own rules and procedures. These programmes are only put in place if the medicine is expected to help patients with life-threatening, long-lasting or seriously debilitating illnesses, which cannot be treated satisfactorily with any currently authorised medicine. The medicine must be undergoing clinical trials or have entered the marketing-authorisation application process and while early studies will generally have been completed, its safety profile and dosage guidelines may not be fully established.

Furthermore, EMA has launched the **PRIME scheme**⁹, which is a set of tools comprising legislative and development support. Already during the development of a medicinal product, and based on preliminary clinical data and evidence that it addresses an unmet medical need, applicants can request support under the PRIME scheme. This may include assistance in determining whether the product is eligible for the accelerated assessment procedure, a dedicated contact person, early appointment of a rapporteur, reinforced support from the CHMP, the SAWP ([Scientific Advice Working Party](#)) or another relevant scientific committee.

In addition, there are a number of other development support activities:

- The **Innovation Task Force (ITF)** is a forum for informal early dialogue with applicants, in particular SMEs and academic sponsors, to proactively identify scientific, technical and regulatory issues related to emerging therapies and technologies.
- The **Micro-, Small- and Medium-sized-Enterprise (SME) Office** facilitates communication with SMEs through dedicated personnel within the Agency, provides administrative and procedural assistance, monitors applications and organizes workshops and training sessions for SMEs.

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http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000925.jsp&mid=WC0b01ac05809f843b

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http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000293.jsp&mid=WC0b01ac058007e691

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http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000660.jsp&mid=WC0b01ac058096f643

- **Scientific advice and protocol assistance** is provided, whereby the Agency provides advices to a company on the appropriate tests and studies for the development of a medicine, based on specific questions from companies. While PRIME is open to all companies on the basis of preliminary clinical evidence, applicants from SMEs and academia generally have less experience with the regulatory framework and therefore would benefit from earlier scientific and regulatory advice. They may also request fee waivers for scientific advice.
- The **Adaptive Pathways** approach is a scientific concept of medicines development and data generation for medicines in areas of high medical need where collection of data via traditional routes is difficult and with potential for a gradual extension of the target population and possibility to collect and use real-world data. It is based on three principles:
 - iterative development, which either means:
 - approval in stages, beginning with a restricted patient population then expanding to wider patient populations;
 - confirming the benefit-risk balance of a product, following a conditional approval based on early data (using surrogate endpoints) considered predictive of important clinical outcomes;
 - gathering evidence through real-life use to supplement clinical trial data;
 - early involvement of patients and health-technology-assessment bodies in discussions on a medicine's development.

Provisions for biological products ('biosimilars')

Biological medicines contain an active substance from a biological source, such as living cells, organisms or proteins. So-called 'biosimilar' medicinal products are biological medicines that are highly similar to another already approved biological medicine (the 'reference medicine'). By demonstrating biosimilarity, a biosimilar can rely on the safety and efficacy experience gained with the reference medicine. Developers of biosimilars are required to demonstrate through comprehensive comparability studies with the 'reference' biological medicine 1) that their biological medicine is highly similar to the reference medicine notwithstanding natural variability inherent to all biological medicines; and 2) that there are no clinically meaningful differences between the biosimilar and the reference medicine in terms of safety, quality and efficacy. This allows avoiding the unnecessary repetition of clinical trials already carried out with the reference medicine. The safety of biosimilars is monitored through pharmacovigilance activities once they are on the market, in the same way as for any other medicines.

As mentioned above, products derived from biotechnology, including biosimilars, are obliged to follow the centralized procedure and are consequently evaluated by the CHMP. The same regulatory timeline of 210 days applies.

Provisions for herbal medicinal products

In the EU, three types of applications for herbal medicinal products are available, depending on the level of experience with the product. These are described in Directive 2001/83/EC and amending Directive 2004/24/EC:

- **A standalone application:** The results of pharmaceutical tests, non-clinical tests and clinical trials need to be submitted. This type of application applies e.g. in case of a new herbal substance/preparation.
- **Well-established use application:** Results of non-clinical and clinical trials are replaced by detailed references from published scientific literature if the applicant can demonstrate that the active substances have been in well-established medicinal use within the EU, for at least 10 years, with recognised efficacy and an acceptable level of safety.
- **Traditional use registration:** A simplified registration procedure allows registration without requiring tests and trials on safety and efficacy, provided that there is sufficient evidence of the medicinal use over a period of at least 30 years, including at least 15 years in the EU. The efficacy is considered plausible on the basis of long-standing use and experience. Non-clinical tests are not necessary, where the herbal medicinal product on the basis of the information on the traditional use proves not to be harmful in specified conditions of use. However, even a long tradition (within or outside the EU) does not exclude the possibility that there may be concerns with regard to the product's safety, and therefore the competent authorities are entitled to ask for all data necessary for assessing the safety.

In addition, **EU herbal monographs** are established by the EMA's Committee on Herbal Medicinal Products (HMPC). They contain the scientific opinion of the HMPC on safety and efficacy data concerning a herbal substance and preparations thereof, intended for medicinal use. Interested parties are invited to propose substances for assessment, to respond to calls for scientific data at the beginning of an assessment and to comment on draft monographs during public consultations. Public participation is an important way for members of the HMPC to obtain a complete set of bibliographic references and scientific data for a given assessment and shows the Agency's commitment to **transparency and openness** in line with EU legislation. The HMPC evaluates scientifically all available information including non-clinical and clinical data but also documented long-standing use and experience in the EU and, if available, outside the EU. The monograph can be taken into account by Member States when examining an application. Any decisions not to accept the content of the monograph should be duly justified, considering the important role of the monographs to bring harmonisation to this field.

3.2. REGULATION ON ADDITIVES IN ANIMAL NUTRITION

Feed additives are products used in animal nutrition for purposes of improving the quality of feed and the quality of food from animal origin, or to improve the animals' performance and health, e.g. enhanced digestibility of the feed materials. Feed additives are only allowed to be put on the market after a scientific evaluation

by the European Food Safety Authority (EFSA), demonstrating that the additive has no harmful effects on human and animal health and on the environment. Regulation EC 1831/2003 deals with the use of additives in animal nutrition while Regulation EC 429/2008 details the rules for implementation of Regulation EC 1831/2003.

Procedural aspects

Applicants need to submit (1) an application to the European Commission, (2) a technical dossier directly to EFSA, (3) three reference samples of the feed additive to the European Union Reference Laboratory. Following the receipt of a technical dossier by the applicant, an acknowledge of receipt is sent to the applicant. In parallel the European Commission sends a request to EFSA to carry out the risk assessment. EFSA then carries out a completeness check to verify that the details submitted by the applicant comply with Regulation EC 1831/2003 and Regulation 429/2008. Once the dossier is complete, the application is declared valid and EFSA can start its scientific assessment, which is done by its Panel on Additives and Products or Substances used in Animal Feed. EFSA assesses the feed additive in terms on safety, quality and efficacy. EFSA must endeavour to give an opinion within six months of receipt of a valid application. This time limit may be extended if EFSA needs to request additional information from the applicant. EFSA's work ends with the publication of a scientific opinion. The Commission will prepare a draft implementing Regulation to grant or deny authorization within 3 months of receipt of EFSA's opinion. The draft regulation is presented in the Standing Committee on the Food Chain and Animal Health (SCoFCAH) Section "Animal Nutrition" and Member States vote on the proposal. Authorizations are granted for use in feed intended for specific animal species or categories, and for specific conditions of use.

The Regulation covers the following feed additive categories:

- Technological additives (e.g. preservatives, antioxidants, emulsifiers, stabilising agents, acidity regulators, silage additives)
- Sensory additives (e.g. flavourings, colorants)
- Nutritional additives (e.g. vitamins, minerals, aminoacids, trace elements)
- Zootechnical additives (e.g. digestibility enhancers, gut flora stabilizers)
- Coccidiostats and histomonostats

There are two types of authorisations:

1) Authorisations issued to a holder of authorisation

Those are granted for additives belonging to the categories "Zootechnical additives" and "Coccidiostats and histomonostats" as well as additives consisting of, containing or produced from genetically modified organisms (GMOs)

2) Authorisations not issued to a holder of authorisation

Those are granted for additives belonging to the categories "technological additives", "sensory additives" and "nutritional additives"

Both types of authorisations are valid for 10 years throughout the EU and the European Economic Area (EEA). Those authorisations shall be renewable for a 10-year period. An application for renewal shall be sent to the Commission at least 1 year before the expiry date of the authorisation.

Feed additives may be put on the market and used only for the purpose stated within the granted authorisation. All authorised feed additives are listed in Annex I of the European Commission's [Register of Feed Additives](#). The Register of Feed Additives provides information about animals for which the additive has been authorised and the relevant conditions for use. Certain restrictions may include setting maximum permitted levels or for use in drinking water.

Differentiation in data requirements

Feed additives can e.g. be micro-organisms or botanicals (which consist of different constituents). Registration requirements are not the same for the different types of feed additives. For example, wherever needed and appropriate a distinction is made in the data requirements for feed additives based on chemical substances, botanicals and micro-organisms. These feed additives of different origin are presented as 3 streams of data requirements throughout the annexes of Regulation (EC) No 429/2008. As a consequence, this legislation contains elements which could be of interest for the evaluation of biological plant protection products. In addition, the expertise of EFSA's Panel on Additives and Products or Substances used in Animal Feed should be shared with the EFSA Panels involved in the scientific assessment of active substances of biological plant protection products.

Qualified Presumption of Safety (QPS)

In 2007, EFSA's Scientific Committee recommended that a Qualified Presumption of Safety (QPS) approach should be implemented across EFSA (EFSA, 2007¹⁰). This should apply equally to all safety considerations of biological agents that EFSA assesses. The Scientific Committee also set out the overall approach to follow and established the first list of proposed biological agents for QPS status. The QPS list is reviewed by EFSA's Panel on Biological Hazards (BIOHAZ). New biological agents recommended for QPS status are regularly added to the 2013 QPS list through a Panel statement.

The QPS approach can be used for pre-market safety assessment of notified biological agents by all EFSA's Scientific Units and Panels. The aim of QPS is to harmonize risk assessment and allow risk assessors to focus on the biological agents with the greatest risks or uncertainties.

The QPS approach is currently used for microorganisms in the three broad categories within which the majority of species notified to EFSA fall: bacteria, yeasts and viruses. The microorganisms are intentionally used at

¹⁰ EFSA Journal (2007) 587, 1-16. Introduction of a Qualified Presumption of Safety (QPS) approach for assessment of selected microorganisms referred to EFSA.

different stages into the food chain, either directly or as a source of food and feed additives or food enzymes, or as plant protection products.

If a defined taxonomic unit does not raise safety concerns or if any possible concerns can be excluded, the QPS approach can be applied and the taxonomic unit can be recommended to be included in the QPS list. Biological agents included in the QPS list usually undergo a simplified assessment by EFSA.

For example, for certain types of feed additives based on microorganisms, toxicological studies are not required if:

- enzymes are produced by microorganisms considered by EFSA to qualify for the QPS approach to safety assessment (or rarely from a commercial strain (lineage) of micro-organism with a substantial history of documented safe use);
- enzymes are produced by genetically modified micro-organisms (GMMs) for which the recipient strain is considered by EFSA to qualify for the QPS approach to safety assessment, and for which the molecular characterisation of the enzyme does not give rise to concern;
- the micro-organism is considered by EFSA to qualify for the QPS approach to safety assessment or when its biology is sufficiently well known to allow pathogenic/toxigenic strains to be excluded by direct testing.

In some cases additional specifications (“qualifications”) may have to be met which will require a separate assessment. Biological agents not considered suitable for QPS will undergo a full safety assessment by EFSA.

The QPS approach is equally applicable to the assessment of botanicals or botanical preparations for which an adequate body of knowledge exists (e.g. from the same plant variety) and therefore without the need for further testing (EFSA, 2014¹¹). However, the particularity of botanicals that may be presented in a wide variety of forms or whose morphology and chemical composition may be markedly affected by geographical and environmental factors, makes the possibility to establish the QPS status at high taxonomic levels quite limited.

3.3. REACH REGULATION

The REACH Regulation (EC) No 1907/2006 - which applies to all chemical substances imported or manufactured in the EU - contains some concepts that may be relevant to active substances of biological origin, and in particular to botanical active substances and micro-organisms/enzymes. Chemical substances shall not be manufactured in the European Community or placed on the market unless they have been registered under the REACH Regulation. Member states are responsible for enforcement of the REACH Regulation by a system of official controls. Registration costs depend on company-size of the registrant, with lower fees for SMEs.

¹¹ EFSA Journal 2014;12(3):3593. Scientific opinion on a Qualified Presumption of Safety (QPS) approach for the safety assessment of botanicals and botanical preparations.

Procedural aspects and data requirements based on quantity

Under the REACH regulation, applicants need to submit a registration dossier to the European Chemicals Agency (ECHA). The data requirements on physico-chemical, environmental fate, ecotoxicological and toxicological substance properties for the dossier depend on the quantity of product that is imported or manufactured per year and per registrant (legal entity) in the EU. There are four tonnage bands for registration: 1-10 tonnes, 10-100 tonnes, 100-1000 tonnes and >1000 tonnes per year. The higher the tonnage, the more data requirements apply. Registration is not required if the tonnage is <1 ton. All registrants of a same substance shall participate in a substance information exchange forum (SIEF) to ensure proper data exchange and to avoid unnecessary testing. Therefore, in practice, the data requirements for a specific substance are determined by the registrant with the highest tonnage band. Depending on substance properties, some data requirements may be waived, e.g. aquatic toxicity data are not required for substances that are highly insoluble in water, or a biodegradation study is not required for inorganic substances. Standard options for data waiving are foreseen in the REACH Regulation and must be justified case by case. An exposure and risk assessment is only needed for substances >10 t/y that are identified to be hazardous for man or environment. A drawback of lower data requirements for low tonnage substances is that higher assessment factors are used for the derivation of safe threshold concentrations (Predicted No Effect Concentrations, PNEC, for the environment and Derived No or Minimum Effect Levels, DNEL or DMEL, for human health) when less (eco)toxicity data are available.

ECHA has signed some sectorial agreements providing a cooperation framework for improving the data in the registration dossiers for specific groups of substances, e.g. for metal compounds and inorganic substances (<https://echa.europa.eu/-/echa-and-eurometaux-agree-on-framework-for-cooperation>).

Evaluation

Registration dossiers are not necessarily evaluated by ECHA or member state competent authorities; however, they need to be updated by the applicant on a timely basis. ECHA may examine any registration dossier to verify compliance with the REACH regulation. No lower than 5 % of the total received dossiers for each tonnage band is selected for such a dossier evaluation. In addition, a complete substance evaluation can be performed. The prioritisation of substance evaluation is mainly based on an assessment of the risk for man and environment considering hazards, exposure and tonnage. ECHA compiles a draft Community rolling action plan which covers a period of three years and specifies substances to be evaluated each year. Substances shall be included if there are grounds for considering (either on the basis of a dossier evaluation carried out by ECHA or on the basis of any other appropriate source, including information in the registration dossier) that a given substance constitutes a risk to human health or the environment. The actual substance evaluations are carried out by the member state competent authorities. Hazardous substances may be listed for authorisation and/or restriction of their uses.

Substance identity

When a company wants to register a new substance, it must provide a complete substance identity profile (SIP) to ECHA, which will compare it to existing registrations in order to appoint the company to an existing SIEF for that substance or to confirm that the substance not yet has been registered. A 'substance' under REACH can either be a monoconstituent, a multiconstituent or a UVCB (unknown or variable composition, complex reaction products or of biological materials). These are defined as follows:

- In a **mono-constituent** substance, one main constituent is present at a concentration of at least 80% and the impurities count for less than 20% of the composition of the substance.
- In a **multi-constituent** substance, each of the several main constituents is present at a concentration of between 10% and 80%. The impurities count for less than 10%. A multi-constituent substance is named as a "reaction mass of the main constituents" present in the substance.
- A **UVCB substance** has many different constituents, some of which may be unknown. The composition can be variable or difficult to predict. UVCB substances are often not fully identifiable and therefore you need to provide a description of the manufacturing process and other types of information, such as a boiling range. In general, the name of a UVCB substance is usually a combination of the starting materials and process.

Active substances in biological plant protection products can often be considered UVCBs or multi-constituents. It is particularly challenging to define their substance identity and to verify substance sameness. The ECHA Guidance for identification and naming of substances under REACH and CLP (Version 2.1; May 2017)¹² provides detailed guidance on this topic.

Examples registered under REACH are: 'Reaction mass of (2E)-3,7-dimethylocta-2,6-dien-1-ol and (2Z)-3,7-dimethylocta-2,6-dien-1-ol' (a multi-constituent substance containing mainly geraniol and nerol), 'Saccharomyces cerevisiae, ext.' (a UVCB consisting of yeast proteins, carbohydrates, minerals, salts etc.), 'Essential oil of Spearmint obtained from the aerial part of *Mentha spicata* and/or *Mentha cardiaca* (Lamiaceae) obtained by distillation' (a UVCB consisting of ca. 15 identified compounds).

Exemptions for substances of natural origin

Annex V (§9) of the REACH Regulation contains a list of substances obtained from natural sources which are exempted from registration as registration is deemed inappropriate or unnecessary for these substances in accordance with article 2(7)b of the REACH Regulation. These substances are: vegetable fats, vegetable oils, vegetable waxes; animal fats, animal oils, animal waxes; fatty acids from C6 to C24 and their potassium, sodium, calcium and magnesium salts; glycerol.

¹² https://echa.europa.eu/documents/10162/23036412/substance_id_en.pdf/ee696bad-49f6-4fec-b8b7-2c3706113c7d

However, a regular REACH registration applies when these natural substances have been chemically modified, e.g. neutralized, or when they are classified (except if flammable or skin/eye irritant) or considered persistent and bioaccumulative (PBT/vPvB). The types of biological substances registered under REACH are diverse and comprehend plant extracts, oils, fatty acids and enzymes.

It should be noted that whole living or dead organisms (e.g. yeast, freeze-dried bacteria) or parts thereof (e.g. body parts, branches, leaves, flowers) are not considered as substances, preparations or articles in the sense of REACH.

Data requirements and risk assessments

Different industry consortia are active with regards to biologicals and compliance with REACH. Some examples of REACH consortia for specific biological substances are:

- EU Federation of Essential Oils (EFEO)
- Enzymes REACH Consortium
- The REVODS Consortium (REACH consortium for vegetable oils and derived substances)

Different types of complex substances give rise to different challenges, in terms of interpretation of the data requirements (scope for data waiving, suitability of study methodologies etc.), performance of exposure calculations and risk assessments. Several consortia have therefore compiled guidance documents specific to their type of substances. E.g. EFEO together with IFRA has compiled 'Guidelines on Substance Identification and Sameness of Natural Complex Substances (NCS) under REACH and CLP' (EFEO & IFRA, 2015¹³) and 'Guidelines on the Environmental Assessment of Natural Complex Substances (NCS)' (EFEO & IFRA, 2016¹⁴). The Enzymes REACH Consortium has written a document on the 'Safety evaluation of technical enzyme products with regards to the REACH legislation (ERpC, 2009¹⁵) and an 'Enzyme REACH Consortium Guidance: How to populate IUCLID 5 Section 1 and test material information in Section 4 - 7 for enzymes' (ERC, 2013¹⁶).

If considered useful, detailed information on specific REACH registration strategies can be gathered from these and other industry consortia.

¹³http://www.efeo.eu/fileadmin/user_upload/REACH/EFEO_IFRA/Dokument_5_August_2015/23628_GD_2015_08_14_GUIDELINES_ON_SUBSTANCE_IDENTIFICATION_AND_SAMENESS_OF_NATURAL_COMPLEX_SUBSTANCES_NCS_UNDER_REACH_AND_CLP.pdf

¹⁴http://www.efeo.eu/fileadmin/user_upload/REACH/EFEO_IFRA/Dokument_26_May_2016/eco_tox_essential_oil_guidance_en.pdf

¹⁵<http://www.enzymes-reach.org/sites/default/files/201310/Safety-evaluation-of-technical-enzyme-products-with-regard-to-REACH.pdf>

¹⁶<http://www.enzymes-reach.org/sites/default/files/201312/how-populate-IUCLID-5-section-1-and-test-material-info-in-section-4-7-for-enzymes-ERC-guidance-OCT-2013.pdf>

3.4. BIOCIDAL PRODUCTS REGULATION

Also under the Biocidal Products Regulation (BPR), specific provisions apply for substances or products from biological origin.

Simplified authorisation procedure

Articles 25 to 28 of the BPR specify the so-called '**simplified authorisation procedure**'. A biocidal product is eligible for this simplified procedure if all the following conditions are met:

- a) all the active substances contained in the biocidal product appear in Annex I and satisfy any restriction specified in that Annex;
- b) the biocidal product does not contain any substance of concern;
- c) the biocidal product does not contain any nanomaterials;
- d) the biocidal product is sufficiently effective; and
- e) the handling of the biocidal product and its intended use do not require personal protective equipment.

Annex I includes active substances like plant extracts, pheromones, oils, viruses and food additives. Applicant can request to become listed in Annex I. When the simplified procedure is applicable, the efficacy and stability of the product need to be demonstrated. However, no risk assessments are required. Nevertheless, not all biocidal products containing active substances from biological origin can apply for this simplified procedure (e.g. pyrethrins).

Data requirements and risk assessments

At the active substance level, specific data requirements for micro-organisms are set, different from the ones for chemical active substances (this is also the case in Regulation (EC) No 1107/2009). Annex II specifies the data requirements for micro-organisms under Title 2. ECHA has published a 'Guidance on Active Micro-organisms and Biocidal Products, Version 2.1' (ECHA, 2017¹⁷) on how to interpret the data requirements for active substances and products.

Also for other types of biocides from biological origin, guidance is available:

- Report on "How to deal with extracts and oils of plant or animal origin? (18th meeting of representatives of Members States Competent Authorities, 2005)¹⁸

¹⁷ https://echa.europa.eu/documents/10162/23036412/biocides_guidance_micro_organisms_en.pdf/4d028d38-6d3c-4f2d-80f7-3aa2118ca49a

¹⁸ https://echa.europa.eu/documents/10162/16960215/bpd_guid_addendum-tngs-data_requirements_pt18_pt19_oils_and_extract_en.pdf/69428f80-0991-4522-8cb1-830b6d002e83

- Guidance for waiving for pheromones for inclusion in Annex I/IA of Directive 98/8/EC (18th meeting of representatives of Members States Competent Authorities, 2005)¹⁹
- Guidance documents on data requirements for naturally occurring substances used as attractants/repellents (18th meeting of representatives of Members States Competent Authorities, 2005)²⁰

In addition to the above, the biocidal products regulation foresees in the derogation from the requirements in specific cases (cf. Article 55). It also includes general rules for the adaptation of the data requirements (Annex IV, e.g. based on exposure considerations).

3.5. COSMETIC PRODUCT REGULATION

In the EU, cosmetic products fall under Regulation (EC) No 1223/2009. Cosmetic products can only be made available on the market if they are safe for human health when used under normal or reasonably foreseeable conditions of use.

A so-called '**responsible person (RP)**' must ensure compliance of the cosmetic product with the regulation. The RP can either be the manufacturer, the importer, the distributor or a person mandated to act as RP. The RP is a.o. responsible for verifying that the product is manufactured according to GMP (good manufacturing practice) and must maintain a **product information file (PIF)**, which contains product information, a safety assessment etc. The PIF must be readily accessible to the member state competent authority. In case of non-conformity, the RP immediately needs to take corrective measures.

The **safety assessment** of the cosmetic product included in the PIF needs to be carried out **by a so-called 'safety assessor'**, i.e. a person with specific qualifications similar to pharmacy, toxicology or medicine.

Prior to placing the product on the market, the RP needs to submit a **notification** via the Cosmetic Product Notification Portal (CPNP) of the Commission. This notification includes information on the product, the RP, the location of the PIF, the member state(s) where the product is marketed, the label etc. The label must comply to specific rules set out in the regulation.

The **safety assessment** of cosmetic products is **based on the ingredients**. There are lists with **prohibited substances** (Annex II), **restricted substances** (Annex III) and **positive lists** with allowed colorants (Annex IV), preservatives (Annex V) and UV-filters (Annex VI). The product safety report must gather all relevant data on the ingredients, the manufacturing process, impurities, conditions of use, as well as risk assessments. The

¹⁹ https://echa.europa.eu/documents/10162/16960215/bpd_guid_addendum-tnsg-data_requirements_pt19_pheromones_en.pdf/e18e5e11-551b-4037-b5d1-43d566bac046

²⁰ https://echa.europa.eu/documents/10162/16960215/bpd_guid_addendum-tnsg-data_requirements_pt19_naturally_occurring_substances_en.pdf/dc7bfd37-9da3-40ac-a11b-3a4696d2aec5

CosIng (cosmetics ingredients and substances) **database** is a valuable tool to access information on the ingredients.

Placing products on the market is not allowed if **animal testing** was performed on the final product, or if it was performed on one or more ingredients after a validated alternative testing method has become available.

4. LESSONS FROM OTHER JURISDICTIONS

United States

In the US, biological plant protection products are called 'biopesticides' and they are defined as certain types of pesticides derived from natural materials as animals, plants, bacteria and certain minerals. They fall into three major classifications: **biochemical pesticides, microbial pesticides and plant-incorporated protectants** (PIPs). New biopesticides are often registered in less than a year (compared with an average of more than three years for conventional pesticides). And although less data are required for registration, US Environmental Protection Agency (US EPA) always conducts a rigorous review to ensure that registered biopesticides do not harm people or the environment.

EPA²¹ has determined that pest control organisms such as **insect predators, nematodes and macroscopic parasites** are exempt from registration. Also, pheromones and identical or substantially similar compounds labelled for use only in pheromone traps and pheromone traps in which those chemicals are the sole active ingredient are not subject to registration.

To determine if a substance can be registered as a biochemical pesticide and may be assessed under a reduced data set, US EPA makes an initial distinction between natural substances that have a **toxic and a non-toxic mode of action** against a target pest. If it has a toxic mode of action, US EPA considers it to be a conventional chemical pesticide and it will be assessed for safety to human health and the environment as any synthetic chemical. US EPA also makes a further distinction between **toxicity and lethality** since many biochemical pesticides can have a lethal mode of action against a target pest without being toxic. Such distinction is currently not in place for biological plant protection products at EU-level...

US EPA applies a **tiered assessment approach** for both biochemical and microbial pesticides which is similar to the approach proposed by the OECD guidance document on botanical active substances used in plant protection products (ENV/JM/MONO(2017)6). Based on taxonomy and/or current knowledge of the source, different groups can be distinguished leading to different requirements especially for analytical methods and regulatory approaches:

²¹ <https://www.epa.gov/pesticide-registration/pesticide-registration-manual-chapter-3-additional-considerations>

- Group 1: active substances that are - with current knowledge - known to have no unacceptable effects on humans, animals and the environment and are based on materials with known specifications (e.g. food grade)
- Group 2: active substances based on a material with an established specification and for which the taxonomy and current knowledge indicated that the active substance may contain components of possible concern for humans, animals and/or the environment. In this case, these components should be identified and quantified.
- Group 3: active substances that are not based on a material with an established specification. In this case, complete identification and characterization is in principle needed.

As long as biological plant protection products need to be registered under Regulation (EC) No 1107/2009 based on hazard principle and no specific legislation is available, this kind of tiered approach to hazard assessment could be considered for all biological plant protection products and not only for botanicals.

Australia

The Australian Pesticides and Veterinary Medicines Authority (APVMA) has established a guideline for the regulation of '**biological agricultural products**'²² which allows for these products to be evaluated on a case-by-case basis. APVMA defines 'biological agricultural products' as "products where the active constituent comprises or is derived from a living organism (plant, animal, micro-organism, etc.), with or without modification. This includes many products that are commonly referred to as 'botanicals', 'organics' or 'herbals'".

However, certain classes of product are specifically exempted from registration. Amongst others, these include soil ameliorants and fertilisers. In addition, plant growth-stimulating products that are not for pest control or specific growth regulation are not regarded to be biological agricultural products. They are covered under State/Territory fertiliser regulations and do not need to be registered by the APVMA. On the other hand, products based on plant hormones must be registered.

Applicants must always check with APVMA that their product is regarded by APVMA as a 'biological agricultural product' before adopting reduced data requirements. There are 4 major groups:

- Group 1: biological chemicals (pheromones, hormones and growth regulators, enzymes and vitamins)
- Group 2: plant and other extracts
- Group 3: microbial agents (bacterial, fungi, viruses, protozoa)
- Group 4: other living organisms (microscopic insects, plants and animals plus some organisms that have been genetically modified)

²² <https://apvma.gov.au/node/11196>

²³ [Balog et al., 2017. Differences in the progress of the biopesticide revolution between the EU and other major crop growing regions. Pest. Manag. Sci. 2017 Nov; 73\(11\): 2203-2208](#)

The APVMA recognises the need for **flexibility in determining the data requirements** for biological agricultural products, therefore they should not be considered as absolute requirements but rather as guidelines. If certain data are not considered necessary, relevant scientific arguments for their omission must be put forward. Data requirements are put forward for '**biologically derived chemicals**' (combining group 1 and 2) and for '**organisms**' (combining group 3 and 4). Although several EU Members States (for example The Netherlands, UK, France, ...) try to implement a comparable flexibility for the approval of active substance for biological plant protection products, the assessment procedure often stalls due to data gaps that are difficult to address, even if relevant scientific arguments have been put forward. As a consequence, biological plant protection products do not enter the EU market because the approval or the renewal of approval of the active substance is not obtained due to too strict and irrelevant data requirements.

Canada

In Canada, biopesticides are generally considered to be of lower risk; however, there is no working definition of low risk. Biopesticides can be divided in 3 groups:

- Microbials: naturally occurring and genetically modified bacteria, alga, fungi, protozoa, viruses and related organisms
- Semio-chemicals: naturally occurring chemicals used for communication by insects
- Non-conventional pest control products: naturally occurring substances (other than pheromones/semiochemicals) representing diverse chemistries including botanical essential oils, plant extracts, commodity chemicals, food ingredients, preservatives, inert materials, certain inorganic salts used as fertilizers.

Products considered as 'non-conventionals' must have some, but not all, of the following characteristics: low inherent toxicity to non-target organisms, low potential for use to result in significant human or environmental exposure, not persistent in the environment, widely available to the public for other uses with history of safe use, pesticidal action that is not the result of toxicity to the target organisms (e.g. repellents, desiccants, smothering), unlikely to select for pest resistance.

All pesticides, including biopesticides, available for use in Canada are regulated by Health Canada's Pest Management Regulatory Agency (PMRA). The PMRA carries out health, environment and value assessments on all pesticides prior to their registration. Data requirements for biopesticide assessment are generally similar to those for conventional pesticides. Reduced risk pesticides aren't given a break on data requirements but are given an expedited review for registration in Canada.

India, Brazil, China

Compared to the EU, other major parts of the world have a much higher number of biological plant protection products available on their market. According to Balog *et al.* (2017)²³, the total number of biopesticide products

reached around 1000 in India. India follows the consensus adopted by the USA that biopesticides cannot be toxic (and if they are toxic, they need to be registered as a conventional pesticide). In Brazil, the biopesticide sector has increased by two orders of magnitude over the past five years, with some 100 active ingredients registered. Also in China, the number of registered biopesticides (i.e. microbial pesticides, botanical pesticide, biochemical pesticide, natural enemy and pest-resistance GMO crops) has seen an increase of more than 15% over the past five years (while growth of chemical products was around 3%). In contrast to EU, countries like India, Brazil and China emphasize in their regulatory approach more on the beneficial effects of biopesticides.

5. CONCLUSION

This document provides a summary of pieces of legislation, guidance documents and procedures available under other EU chemicals legislations, as well as other jurisdictions, that could be useful in establishing a EU framework for the evaluation of biological plant protection products. A concise overview is presented below.

Biological plant protection products cannot be considered harmless or without risk, just by referring to their natural origin. A solid regulatory framework that ensures safety for men and environment is required. However, such framework should allow for swift market access also, and the data requirements, risk assessment procedures and timelines, should be proportionate to the risk they potentially represent. The current regulation dealing with plant protection products, including those of biological nature, is not sufficiently adapted to substances of natural origin. Specific provisions are foreseen in the legislation for low-risk substances and products. Nevertheless, the criteria for low-risk are hazard-based, not risk-based. Furthermore, the procedures do not allow for prioritization or fast-tracking of substances/products with a low risk profile. Consideration should also be given to the fact that companies developing biological plant protection products are often SMEs lacking the necessary resources (financial and/or in terms of regulatory experience) to venture the process of active substance approval and product authorisation under Regulation (EC) No 1107/2009, of which the outcome is very uncertain. In addition, return on investment is often limited, given that most biological plant protection products are intended for niche markets. Besides that, applicants would benefit from receiving coherent advice during the R&D and dossier preparation phase, increasing the predictability of the outcome of the regulatory process if the advice is adhered to. To that end, expertise currently available at different (units of) regulatory bodies within the EU should become accessible to applicants.

Interesting building blocks and best practices from other legislations relevant for regulating biological plant protection products

EU Medicinal Products Regulation	Provisions to facilitate early market access if there is a major public health interest: <ul style="list-style-type: none"> • Accelerated assessment procedure • Conditional market authorisation • Compassionate use opinion
	Legislative and development support to prospective applicants in the form of the 'PRIME scheme', the Innovation Task Force, the SME Office, the scientific advice and protocol assistance, the Adaptive Pathways
	Specific provisions for biological products (biosimilars) and herbal medicinal products
	Centralized group of experts doing assessments for substances and products, and providing advice to applicants (e.g. SAWP)
EU Feed Regulation	Distinct data requirements for chemical substances, botanicals and micro-organisms
	The presence of relevant expertise at EFSA
	The Qualified Presumption of Safety (QPS) concept to set priorities by distinguishing between micro-organisms that have a history of safe use and those which could represent a risk. This concept is - to some extent - also applicable to botanicals.
EU REACH	Data requirements based on quantity
	Specific guidance on substance identity (mono-constituents, multi-constituents, UVBCs)
	Exemptions for substances of natural origin
	Specific guidance developed by consortia (e.g. on essential oils, enzymes, ...)
Biocidal Products Regulation	Simplified authorisation procedure for specific substances of natural origin
	Specific data requirements and guidance for micro-organisms
	Derogations from the requirements in specific cases
Other jurisdictions (US, Australia, ...)	Distinction between natural substances based on toxic / non-toxic mode of action, and based on toxicity vs. lethality.
	Tiered approach based on existing knowledge about botanicals
	Data requirements adapted to nature of the active substance, as well as flexibility in applying the data requirements
	Supportive regulatory climate vis-à-vis biopesticides

