# A Legal Framework for Plant Biostimulants and Agronomic Fertiliser Additives in the EU

**Report for the European Commission**

**Enterprise & Industry Directorate - General**

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## List of Acronyms

| | |
|---|---|
| **ABSA** | American biological safety association |
| **ANS panel** | Food ingredients and packaging EFSA panel |
| **ANSES** | Agence Nationale de Sécurité Sanitaire de l'Alimentation |
| **BPR** | Biocidal products regulation |
| **BSA** | Brand specific authorisation |
| **BVL** | German Federal Office of Consumer Protection and Food Safety |
| **C/N** | Carbon nitrogen ratio |
| **CA** | Competent authority |
| **CEF panel** | Food Contact Material, Enzymes, Flavourings and Processing Aids EFSA Panel |
| **CLP** | Classification labelling and packaging |
| **COGEM** | GMO Dutch panel |
| **COM** | European Commission |
| **CoP** | Cosmetic products |
| **CRF** | Controlled released fertiliser |
| **CSIRO** | Commonwealth Science and Industrial Research (Australia) |
| **DB** | Database |
| **DG** | Directorate-General |
| **DG AGRI** | Agriculture and rural development Directorate-General |
| **DG ENTR** | Enterprise and Industry Directorate-General |
| **DG SANCO** | Health and Consumers Directorate-General |
| **DG TRADE** | Trade Directorate-General |
| **E.E.I.G** | European Economic Interest Grouping |
| **EBIC** | European Biostimulants Industry Council |
| **EC** | European Community |
| **EC50** | Half maximal effective concentration |
| **ECHA** | European Chemical Agency |
| **ECPA** | European Crop Protection Association |
| **EEA** | European economic area |
| **EFSA** | European Food Safety Authority |
| **EMBRAPA** | Brazilian Agricultural Research Corporation |
| **EPPO** | European plant protection organisation |
| **EU** | European Union |
| **EURL** | European reference laboratory |
| **FeA** | Feed additive |
| **FEEDAP** | Additives and Products or Substances used in Animal Feed EFSA panel |
| **FEFANA** | EU Association of Specialty Feed Ingredients and their Mixtures |
| **FoA** | Food additive |
| **FTE** | Full time equivalent |
| **GHS** | Global harmonisation system |
| **GLP** | Good laboratory practices |
| **GMO** | Genetically Modified Organism |
| **HACCP** | Hazard and Critical Control Points |
| **HCB** | French GMO committee |
| **HPLC** | Liquid chromatographic techniques |
| **HR** | Humidity rate |

| | |
|---|---|
| **IBMA** | International Biocontrol Manufacturers' Association |
| **IFA** | International fertiliser association |
| **IFDC** | International fertilisers development center |
| **IFOAM** | International Federation of Organic Agriculture Movements |
| **IT** | Information Technology |
| **IUCLID** | IT REACH system |
| **IUPAC** | International chemical classification |
| **MFSC** | French term for fertilising materials |
| **MRL** | Maximum residues level |
| **MS** | Member States |
| **MSDS** | Material safety data sheet |
| **N** | Nitrogen |
| **NCA** | National competent authority |
| **NDA panel** | Dietetic Products, Nutrition and Allergies EFSA panel |
| **NFU** | French norms |
| **NOEC** | Non observed |
| **NRA** | National risk assessment agency |
| **OECD** | Organisation for Economic Co-operation and Development |
| **PAH** | Polycyclic aromatic hydrocarbons |
| **PB&AFA** | Plant biostimulant and agronomic fertiliser additives |
| **PBT** | Persistent, bio accumulative and toxic |
| **PCB** | Polychlorinated biphenyls |
| **PCDD** | Polychlorinated dibenzodioxins |
| **PEC** | Predictable environmental concentration |
| **PGR** | Plant growth regulator |
| **pH** | measure of the acidity or basicity of an aqueous solution |
| **PNEC** | Predictable no effect concentration |
| **PPP** | Plant Protection Products |
| **PPR panel** | Plant Protection Products and their Residues EFSA panel |
| **PS** | Plant strengtheners |
| **R&D** | Research and Development |
| **RA** | Risk assessment |
| **RAC** | Regulatory assessment committee |
| **REACH** | Registration, Evaluation, Authorisation and Restriction of Chemical Substances |
| **RM** | Risk management |
| **SDS** | Safety data sheet |
| **SLIM** | Simpler legislation for the internal market |
| **SME** | Small and medium enterprise |
| **SRF** | Slow release fertiliser |
| **SVHC** | Unknown or variable composition, complex reaction products or biological materials |
| **TC** | Third Country |
| **ToR** | Terms of reference |
| **US** | United States |
| **USD** | US dollar |
| **UV** | Ultra violet |
| **WP** | Work package |

# Executive summary

Regulation (EC) No 2003/2003 (the Fertilisers Regulation) lays down rules relating to the placing on the market of fertilisers. It covers only a part of the inorganic (mineral) fertilisers i.e. "*EC fertilisers*" that meet its legal requirements regarding their minimum nutrient content, their safety, and their absence of adverse effect on the environment and as such may circulate freely on the European market.

The Commission has conducted an evaluation of the functioning of the Fertilisers Regulation and, in the light of the outcome of that exercise, extensive preparatory work for a revision of the Fertilisers Regulation took place in 2012-2013, in particular with the objective to extend its cope to other fertilising and related materials, of which plant biostimulants and agronomic fertiliser additives.

At large, these two categories can be distinguished from each other and from fertilising materials by the following main characteristics, related to their functionalities:

- Plant biostimulants act on plant processes, improving nutrition and vigour;
- Agronomic fertiliser additives act on fertilisers and fertilising materials, prior uptake by the plant of the released nutrients, enhancing their efficacy for plant nutrition and reducing losses to the environment.

For the purpose of the future legislation, extended definitions of both categories are elaborated and proposed as outputs of the study.

## Study objectives

The present study aims at supporting the ongoing activities for the revision of the Fertilisers Regulation by proposing appropriate data requirements and efficient administrative procedures to carry out the assessment of risks and efficacy of plants biostimulants and agronomic fertiliser additives (PB&AFA). Arcadia International was commissioned to undertake this study on "a *legal framework for plant biostimulants and agronomic fertiliser additives*" between July 2013 and February 2014.

The objectives of the study were fourfold:

- To examine the main national and international legislations related to the placing of plant biostimulants and agronomic fertiliser additives to the market. **How do Member States and Third Countries currently address the marketing of such type of products?**

- To analyse existing and comparable EU regulatory system which could be found suitable for regulating the marketing of plant biostimulants and agronomic fertiliser additives. **What can be learned from existing and comparable EU legal frameworks? Can any of the existing EU framework fit for the purpose of placing PB&AFA to the EU market?**
- **To study the current & future EU business environment for plant biostimulants and agronomic fertiliser additives**;
- **To develop a proposal for the most appropriate regulatory framework** including data requirements and efficient administrative procedure that should be established in the context of the new Fertilising materials Regulation.

## Methodology

After an initial project scoping, the methodological approach consists of analytical tasks based on deep literature review, interviews with experts, national competent authorities, business and trade associations representatives of PB&AFA sectors, and Commission. These analytical tasks have been followed by a reporting task which brought together the study findings that are presented in this final report.

## The plant biostimulants and agronomic fertiliser additives business and usage by producers' context

**The PB&AFA industry:** The plant biostimulant category is in its relative infancy, but the rapidly increasing level of investment in research is beginning to yield insights into the potential of these products. Its market driven by economic and socio-political factors seems to be growing rapidly (>10% per year). The European Biostimulants Industry Consortium (EBIC) considers that the 2012 EU market value (sales) of plant biostimulants can be estimated at € 400-500 million with potential to grow to more than € 800 million in 2018.

Factors driving this growth of the plant biostimulants sector are multiple:

1. European agricultural and food safety policies have integrated environmental considerations and are promoting the safe use of agricultural inputs. This applies to alternative solutions being, in between others, the use of plant biostimulants and biopesticides that are used under the integrated crop management schemes ;
2. In response to consumer demands for healthy food products with minimal environmental impacts growers are looking for ways to use synthetic chemicals and mineral fertilisers more efficiently. Biostimulants are increasingly seen as a response to these consumer demands for "softer" agricultural practices;
3. The use of plant biostimulants is spreading from some pioneer EU countries (FR, IT, Spain) to a wider number, both within Europe and the rest of the world.

Most of the plant biostimulant companies are small and medium-sized enterprises (SMEs). In total EBIC considers that the EU plant biostimulant sector is composed of about 200-250 companies of which about 90% are SMEs. Additionally, it can be observed an initial consolidation of the sector with entry of

large R&D companies which leads to increase of investment in research for plant biostimulants.

The business situation for agronomic fertiliser additives is diametrically opposite. It is dominated by a small number of international companies which have developed new innovative products that are, mainly, incorporated in commodity fertiliser formulations.

Markets for agronomic fertiliser additives are globalised for several years already. They are nearly mature. The projected average annual growth rate to 2015 is estimated at about 1.5%-2.5% in Western Europe, slightly lower than growth rate in the US (2.0%-3.5%) and in Japan (3.0%-4.5%). Most of the business actors claim to have an important R&D division which is often structured internationally to simultaneously support several markets.

**The experience linked to the use of PB&AFA**: Plant biostimulants and agronomic fertiliser additives have already been used by producers for several years and several decades e.g. dried seaweeds extracts. Historical data on the efficacy of PB and AFA indicate some variability in time and space, which could handicap the trust rising among users and scientists. While PB substances show good efficacy in laboratories in the large majority of cases, this efficacy is not always confirmed in field situations and therefore the PB are not fully recognised by all producers as reliable commodity.

## How do EU MS and Third Country authorities regulate the placing of PB&AFA on the market?

This analysis has been performed by screening eleven regulatory frameworks at both EU MS level (BE, DK, ES, DE, FR, IT, and HU) and international level (Brazil, Canada, South-Africa, and USA). The focus has been placed on plant biostimulants as most of agronomic fertiliser additives are already included in Annex I of the Fertilisers Regulation.

None of the studied regulatory frameworks defines the term "*plant biostimulants*" but substances/products can be placed on the market in all countries covered under the study. PB&AFA are regulated either under the fertiliser acts or the plant protection products acts. In some cases by both schemes (e.g. Canada).

The regulatory processes are highly variable ranging from free access to the market (e.g. UK) to a registration scheme based on pre-market approval (e.g. FR, IT) including notification procedures with data requirements (e.g. BE, DE, IT) or limited data requirements. The majority of the different regulatory schemes ask for a detailed characterisation and identification of the substances but allow the registration of non-fully defined/characterised substances. In several schemes the provision of an analytical method for quality control is not a mandatory requirement.

Toxicological and ecotoxicological data are required by only a few schemes (the ones based on a pre-market approval). However the required tests and studies to be provided by applicants are never listed as such. Safety to human and the environment has to be demonstrated while risk management measures shall be presented whenever necessary but none of the studied regulatory schemes lists the studies requirements. It is of the registrant responsibility to present data to proof safety of its product on an ad hoc basis.

Efficacy has to be demonstrated in all countries. Data requirements are preferably based on field trials data but efficacy can also be demonstrated by results from laboratory testing or other dedicated assays. Belgium and France have established a system which leads to the obligation for applicants to demonstrate field efficacy preferably before granting of authorisation as part of the registration dossier or (and) after registration.

The most demanding schemes as regards data requirement are based on a pre-market approval approach. This appears to entail long (> 1 year) and quite unpredictable examination timing (from application to registration).

**What can be learned for existing and comparable EU legal frameworks? Can any of the existing EU framework fit for the purpose of placing PB&AFA to the EU market?**

The analysis of the existing EU regulatory schemes for comparable products (i.e. cosmetic products, chemical products (REACH), food additives, feed additives, plant protection products, biocides) shows that two types of EU regulation co-exist: REACH and the regulatory frameworks based on a pre-market approval (the food safety frameworks). Each type of approach is tailored to the specificity of the risks in its own area.

The majority of these regulatory frameworks have been developed at earliest in the 1960s and have all been designed to assess safety of chemical substances. These sectorial frameworks are "risk based" approaches that consider the business environment of each sector. The majority of these have developed specific schemes and requirements for non-fully synthetic chemical substances/products which are not perceived by the majority of the stakeholders to be fully satisfactory.

Several substances that are used as PB&AFA are already registered under other EU regulatory frameworks. These substances can be ranged in three categories:

- Substances already registered under REACH for fertiliser and/or other usages;
- Substances already registered/notified at MS level;
- Substances authorised at EU level (e.g. seaweed extracts in cosmetics, feed additives).

In conclusion to this analysis, it can be considered that each of these two main types of regulatory frameworks includes interesting obligations for the drafting of a regulation for PB&AFA but none of these two types of approaches can be considered as fully suitable for PB&AFA for the main following reasons:

- REACH doesn't fully consider the potential risks linked to food and PB&AFA are mainly used in specialty food crops such as fruit and vegetables;
- REACH does not consider microorganisms in its registration process, while biostimulants include a expanding list of microbial products;
- Applying a pre-market approval system with a risk assessment procedure which has primarily been designed for synthetic chemical products would lead to too high costs for applicants (> € 500,000) of products which are often not of synthetic chemical nature (mainly true for PB).

**Which approach to a legal framework for plant biostimulants and agronomic fertiliser additives?**

For the purpose of the future legislation, the initially proposed definitions have been discussed and are slightly amended as proposed:

- A **plant biostimulant** is any substance or microorganism, in the form in which it is supplied to the user, applied to plants, seeds or the root environment with the intention to stimulate natural processes of plants benefiting nutrient use efficiency and/or tolerance to abiotic stress, regardless of its nutrients content, or any combination of such substances and/or microorganisms intended for this use.
- An **agronomic fertiliser additive** is any substance or microorganism, in the form in which it is supplied to the user, added to a fertiliser, soil improver, growing medium with the intention to improve the agronomic efficacy of the final product and/or to modify the environmental fate of the nutrients released by the fertilisers, or any combination of such substances and/or microorganisms intended for this use.

In the above definitions, **substance** means a chemical element and its compounds, as it occurs naturally or by manufacture, including any impurity inevitably resulting from the manufacturing process.

In order to address the specific issues potentially associated with the use of such a wide and varying group of substances, the placing to the market procedure is based on an approach with the obligation for individual or group of similar PB&AFA to be registered in a EU registry before being lawfully placed on the market.

In accordance with existing EU and national regulatory frameworks for similar substances, the applicant company (the registrant) will have to submit a registration dossier that shall include a relevant set of information to a EU Agency (ECHA or EFSA). The registration dossier will have to include the following informations:

- Identification and characterisation of the substance (incl. biological properties when relevant and physico-chemical properties);
- Mode of action and function of the substance;
- Absence of contaminants;
- Manufacturing, quality control, and analytical method(s);
- Toxicology, ecotoxicology, environmental fate, and residues in plants where relevant;
- Demonstrated agronomic efficacy of the concerned claim(s).

Applicants are encouraged to use existing data submitted in other EU regulatory contexts. The future PB&AFA scheme shall allow applicants to use existing data (data sharing and data bridging) as long as technical equivalence is demonstrated in order to avoid repeating studies (especially animal testing) and optimise costs. Registrants shall be allowed to waive certain data when the nature of the registered substances or the absence of exposure of a given environmental compartment is not of concern. Mechanisms for the grouping of substances and grouping of crops for the demonstration of efficacy are proposed to limit the number of applications for similar substances.

In order to secure an optimal registration process, each above-mentioned (group of) requirement has been defined to fit the largest majority of registration cases.

Data requirements for characterisation have been developed to allow registration of non-fully defined substances due to their natural origin. This approach is very much in line with the UVCB[1] approach under REACH and the botanicals under the Plant Protection Products Regulation. Requirements for the provisions of tools for quality control have been developed to cover all types of substances (from well-defined substances for which an analytical method has to be provided to non-well-defined natural extract for which the quality control will relay on a detailed description of the raw material and of the manufacturing process).

For proof of human and environmental safety a 3 tier risk-based approach is proposed to capture the specificities of these wide and varying groups of substances.

Registrants have to demonstrate agronomic efficacy of their products (2 options are discussed) and guarantees product efficacy to producers.

The procedure after submission of the dossier will entail the following potential steps:

- Step 1: Reception of the application dossier by the EU Agency (EFSA or ECHA) which will immediately perform a completeness check. The completeness check will be systematically required for each application and limited to a validation of the correct classification of the substance and a control of the existence of all elements expected for a dossier.
- Step 2: Compliance check will be performed on a limited number of dossiers on the basis of the following rules:
    - For dossiers containing only Tier 1 toxicological and ecotoxicological data: 30% of the total number of dossiers will be randomly selected for compliance;
    - For all other dossiers a compliance check will be automatically performed.

  Additionally it is recommended that at least one dossier per applicant company is selected for compliance. Compliance checks will aim (1) at ensuring that the dossier includes all necessary information and documentation as prescribed by the future Fertilisers Regulation and the relevant guidance documents to be developed, (2) at assessing whether data waivers in tier 1 dossiers are well justified and (3) at conducting deeper analysis of tier 2 and 3 dossiers.
- Step 3: If the completeness check can be cleared by the Agency, the latter will deliver a registration number, which then allows the placing of the plant biostimulant or the agronomic fertiliser additive on the market under the conditions specified by the registrant and reported in a transparent way in the EU registry. The registration will remain valid for a period of 15 years and the data submitted by the applicant will be subject to data protection for the equivalent period of time. Confidentiality will be granted on registrant request. As under similar regulatory framework a data sharing mechanism will be provided for if a second applicant applies for a similar substance.

[1] Unknown or Variable compositions, Complex reaction products and Biological materials

The results of the compliance check could lead either to keep the registration, to require mitigation measures to be mentioned in the Registry, to a request from the Agency to complement the existing information, or finally to a rejection of the application if a non-manageable risk is identified. In the latter case, the substance will be included in the negative list which will be a part of the Fertilisers Regulation and will be amended by delegated/implementing Act.

- Step 4: At any moment after registration was granted and eventually confirmed, the data submitted by applicants as well as their conclusions regarding the safety and/or the efficacy of the PB&AFA may be subject to re-examination by Member State Competent authorities on a voluntary basis in view of changing or confirming the conditions of the existing registration;
- Step 5: If this/these reviewing Member State(s) conclude(s) that there is a need for reconsidering an existing registration, the Agency will be organising a peer-review of the conclusions drawn by this(ese) Member State(s);
- Step 6: The conclusion of the peer-review will be formalised as an opinion of the Agency and submitted to the Commission if its conclusions are putting the existing registration into question. The Commission might then proceed with an adaptation of the negative list provided in one of the Annex of the Fertilisers Regulation through a Commission delegated/implementing Act.

The steps described above strike a balance between a relatively simple administrative approach allowing rapid access to the market for PB&AFA and several safety nets allowing appropriate ways to address unexpected risks or lack of efficacy in a timely manner. This will be addressed both via randomly quality control of the submitted dossier before full registration but also via possibility for post-registration re-assessment by volunteering Member States. At the same time this approach will provide the producers with some guarantee of agronomic efficacy of the registered PB&AFA.

# 1 Introduction

The European Commission intends to revise Regulation (EC) No 2003/2003 of the European Parliament and of the Council of 13 October 2003 relating to fertilisers (the Fertiliser Regulation) pertaining to inorganic fertilisers and to extend its scope to also include:

- Organic fertilisers;
- Soil improvers;
- Liming materials;
- Growing media;
- Plant biostimulants; and
- Agronomic fertiliser additives.

In line with Article 114 of the Treaty, the new legislation pursues two objectives:

- To establish an effective internal market by ensuring the free circulation of and a level-playing field for all categories of fertilising materials and related non-fertiliser materials on the whole EU territory; and
- To support the competitiveness of the different industries falling under the scope of the Regulation while providing for a high level of health, safety, environmental and consumer protection.

More specifically, the new Regulation will aim to:

- harmonise legislation for all fertilisers and related products;
- guarantee the safety of the material placed on the market with regard to human health and the environment;
- ensure efficacy/utility and the ability of farmers to rely on the quality of the products bought;
- facilitate the access to the market of innovative products; and
- To reduce the administrative burden for authorities and for industry.

To date, the Commission has developed several policy options in view of the future revision of the Fertiliser Regulation and has conducted extensive stakeholders' consultations with the intention of developing a regulatory proposal.

The question related to plant biostimulants became quite predominant in the discussions and an EU stakeholders association (i.e. EBIC) has been created to follow the works carried out by the Commission in view of developing EU legislation for this type of products.

In July 2013, Arcadia International was commissioned by DG Enterprise and Industry to undertake a study aiming at contributing to the proposal for an EU legal framework for the placing of plant biostimulants and agronomic fertiliser additives on the market. In this regard, the study will help to support the case for defining and implementing a regulatory framework for the above mentioned products in the overall context of the revision of the Fertiliser Regulation.

## 1.1 Policy background

The first pan-European Fertiliser Regulation regarding the placing on the market of fertilisers in the EU dates back to Directive 76/116/EEC of 18th December 1975[2] (Basic Directive), after which it was amended several times. In the context of the SLIM initiative[3], the Basic Directive and 17 associated Directives on fertilisers were replaced by a unique legal text: Regulation (EC) No 2003/2003 aiming to ensure the free circulation of so-called "*EC fertilisers*"[4] within the EU. Regulation (EC) No 2003/2003 has not brought any substantial changes to the Basic Directive.

The Fertiliser Regulation co-exists with national regulatory frameworks related to the placing of fertilisers on the market. In the large majority of MS, specific legislation has been developed leading to the possibility for individual companies to decide to place inorganic fertiliser on the market under the national label or under the EC label. More information on these national schemes can be found in the previous studies performed by DG ENTR in support to the ongoing revision of the Fertiliser Regulation[5].

Regulation (EC) No 764/2008[6] on mutual recognition aims to allow for a product lawfully marketed in one Member State and not subject to EU harmonisation to be marketed in any other Member State. This Regulation applies to the placing on the market of non-harmonised goods legally present on national markets, including fertilisers (e.g. mineral, organic and organo-mineral fertilisers) and other fertilising materials e.g. growing media, soil improvers, agronomic fertiliser additives and plant biostimulants.

However, several issues have been identified during the last years leading to the conclusions that a fundamental review of the existing legislation on fertilisers was required in order to fully harmonise the EU fertilising materials market(s) including mineral and organic fertilisers, soil improvers, growing media and possibly biostimulants and allow free movements of goods within the EU.

Issues that have been identified during the last years are as follows:

- At present only mineral products are classified as 'EC fertilisers', while organic, organo-mineral, soil improvers, growing media and biostimulants are governed by national legislations and internal market is expected to be established via applicability of the principles of the Regulation (EC) No 764/2008 on mutual recognition. However, MS are reluctant to accept mutual recognition for national fertilisers, as they are not convinced that the requirements in other MS related to public safety, health or the environment are equivalent to their own requirements leading to potential

[2] Council Directive 76/116/EEC of 18 December 1975 on the approximation of the laws of the Member States relating to fertilisers.
[3] SLIM: Simpler legislation for the internal market. The SLIM initiative was launched in May 1996 and it was targeted to identify ways in which Single Market legislation could be simplified.
[4] EC fertilisers meaning mineral fertilisers that meet the requirements of the Regulation for their nutrient content, their safety, and the absence of adverse effects on the environment.
[5] Available at: http://ec.europa.eu/enterprise/sectors/chemicals/documents/specific-chemicals/fertilisers/index_en.htm#h2-8
[6] Regulation (EC) No 764/2008 of the European Parliament and of the Council of 9 July 2008 laying down procedures relating to the application of certain national technical rules to products lawfully marketed in another Member State and repealing Decision No 3052/95/EC

market distortions and technical barriers for trade of fertilising products with the EU;

- Most stakeholders and national Competent Authorities are interested in extending the scope of the current Regulation (EC) No 2003/2003 to include not yet covered mineral fertilisers, organic fertilisers, organo-mineral fertilisers, soil improvers, growing media, and possibly biostimulants;
- Application of Regulation (EC) No 764/2008 might lead to administrative burden as many MS are reluctant to apply de facto the mutual recognition principles to fertilisers;
- Timeline for the inclusion of new fertilisers types for "EC fertilisers" in Regulation (EC) No 2003/2003 is considered as too long and current procedures as cumbersome by a large majority of the producers and authorities;
- The current provisions of Regulation (EC) No 2003/2003 are not always fully addressing the safety and environmental concerns (e.g. presence of heavy metals in mineral fertilisers);
- In the absence of harmonised rules for organic and organo-mineral fertilisers as well as for growing media and soil improvers, a level playing field for product safety and protection of the environment is not achieved (more affirmative sentence).

## 1.2 Study objectives

The study contributes to the proposal of the Commission for an EU legal framework for the placing on the market of plant biostimulants (PB) and agronomic fertiliser additives (AFA).

In more details, the objectives of the study are to:

- **Analyse existing regulatory systems** for plant biostimulants and agronomic fertiliser additives in the EU, Member States and Third Countries; and
- **Develop a proposal for the most appropriate regulatory framework** that should be established in the context of the revised Fertiliser Regulation.

In particular, the study aims to elaborate on the relevant data requirements and administration of a registration process for these two sub-categories.

## 1.3 Methodology

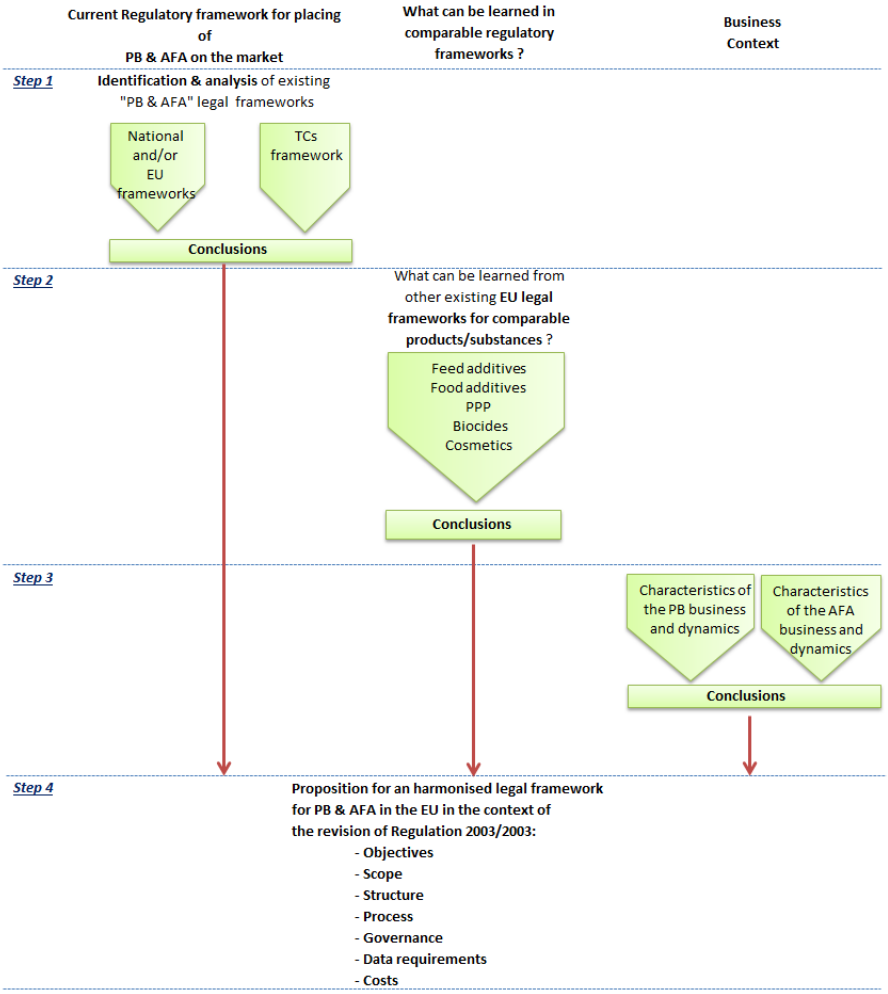
The study methodology entails three main tasks:

- **Task 1** consists in 3 subtasks. First a review of existing regulatory frameworks at EU, at Member States and at international levels, which apply to chemical substances/microorganisms comparable to the ones used as plant biostimulants (**sub task 1.1**) and agronomic fertiliser additives (**sub task 1.2**) is carried-out. The aim is in particular to describe data requirements as well as administrative procedures established by these regulations with regard to risks assessment for human health and the environment, as well as the assessment of the efficiency/efficacy of these products. A comparison of the average time and related costs (for both authorities and applicants) needed for granting

access to the market has also to be performed. Eventually, an estimate of expected market volumes in the EU for typical plant biostimulants or agronomic fertiliser additives (range from "*low volume*" to "*high volume products*") has to be provided (**sub-task 1.3**); i.e. the turnover that a company could expect after successful introduction of such substances/mixtures on the market. As the plant biostimulants and agronomic fertiliser additives markets are currently developing, the data collection for sub task 1.3 aims at estimating potential business size and future development to be expected in this field for the coming decades.

- **Task 2** consists in proposing the most appropriate set of data to be required in a future EU legislation concerning plant biostimulants and agronomic fertiliser additives in order to evaluate in a proper way the risks associated with their use, as well as their efficiency/efficacy. Under this task a distinction has to be made between chemical and microbial biostimulants when defining the most suitable data requirements. This distinction does not in principle apply to agronomic fertiliser additives as they are in the majority of cases (but not always) of chemical nature. A tiered approach and opportunities for waiving certain data based on appropriate justification is discussed in the analysis. An estimation of the costs associated with the recommended set of data is provided and compared to the expected turnover as determined under Task 1.3.
- Under **Task 3**, the study team recommends a policy option with regard to the submission and evaluation of the proposed data set and describes (1) the main principles of the procedure (processes, requirements, expected timing) (2) the actors to be involved and their respective role (applicant companies, administrative/scientific bodies, Member States competent authorities, Commission, etc.).

**Figure 1 Overall project workflow**




## 1.4 Structure of this report

This report is structured as follows:

- Section 2 provides a general overview of the policy and business context of the plant biostimulant and agronomic fertiliser additives (PB&AFA). discusses first the current national and international regulatory frameworks for products comparable to PB&AFA and then describes the existing EU registration regulatory framework for food safety and for chemicals;
- Section 3 lists data requirements for applicants for PB&AFA and presents the proposed regulatory process and. Then costs for implementation and managing the proposed regulatory approach are discussed.

Annexes provide supporting documents and detailed results of Task 1 are presented in an Excel DB that is part of the final deliverable of the study and will be made available when the present report is published.

# 2 Context

This section summarises preliminary facts and evidences required to set-up the scene before drafting the regulatory process for PB&AFA and listing data requirements for the designed process. It starts by presenting the definitions to be used as well as the scope of the future regulation. Any regulation has to be placed in its business context which is then described. Then we present how PB&AFA are currently placed to the market at national level and in Third Countries. The section ends with a presentation of comparable EU regulatory frameworks with the aim of identifying relevant and accurate provisions for the building of the PB&AFA regulation.

## 2.1 Preliminary definitions and scope of the future regulation

The Terms of Reference of the study define plant biostimulants and agronomic fertiliser additives as follows:

- **Plant biostimulant** means a material which contains substance(s) and/or microorganisms whose function when applied to plants or the rhizosphere is to stimulate natural processes to benefit nutrient uptake, nutrient efficiency, tolerance to abiotic stress and/or crop quality, independently of its nutrient content;
- **Agronomic fertiliser additive** means any substance added to a fertiliser, soil improver or growing medium to improve the agronomic efficacy of the final product or modifying the environmental fate of the nutrients released by the fertilisers[7].

These preliminary definitions raise several comments:

1. As such, the definitions are not clear about whether they cover the products in the form they are supplied to the user, or the components of the products;
2. The terms "*material*" and "*substance*" need to be clarified, or alternative terms should be proposed, in order to avoid possible confusions with the uses of these terms in relevant regulations, like the REACH, PPP and biocide regulations;
3. Further amendments can be proposed to fit into the actual and potential uses of plant biostimulants, i.e. application of plant biostimulants to "*plants or the rhizosphere*", as indicated, appears to be too restrictive (the rhizosphere is a limited part of the root environment only, and "plants" in the common sense do not comprise seeds which are worth mentioning explicitly);
4. "*Crop quality*", indicated in the definition of plant biostimulants, is a poorly defined, hence potentially very broad, concept. Overlaps with the effects of plant growth regulators (PGRs), regulated as PPP in the EU, are obvious and challenge the proposed definition of plant biostimulants in the future regulation.

[7] Additives can also be used to improve the manufacturing, processing, preparation, treatment, packaging, transport or storage of fertilisers without any direct agronomic effects. These are referred to as 'technological additives', as opposed to 'agronomic additives', and are not subject to this study.

In line with these considerations, this report will propose and justify amended definitions in section 3.1.1 and clarify some of the issues raised on the nature of the registered items in the future regulation in section 3.3.2.

The future legislation aims at regulating the placing of PB&AFA on the market. Therefore the concept and definition of "*placing on the market*" is fundamental for the application of the future legislation and for the exact definition of its scope.

Several EU regulatory frameworks provide definitions of placing on the market. Specific definitions have been created to adjust to sectorial needs. In the context of this study, definitions as listed in Regulation (EC) No 765/2008 of the European Parliament and of the Council of 9 July 2008 setting out the requirements for accreditation and market surveillance relating to the marketing of products and repealing Regulation (EEC) No 339/937 can be considered.

Regulation 765/2008 defines the term "*placing on the market*" in Article 2(2), which reads as follows:

> "'*Placing on the market' shall mean any supply of a product for distribution, consumption or use on the Community market in the course of a commercial activity, whether in return for payment or free of charge*".

In addition, Article 2(1) of Regulation (EC) No 765/2008 introduces a definition of the term "*making available*". The provision is worded as follows:

> "'*Making available on the market' shall mean the first making available of a product on the Community market* ".

The Guide to the implementation of directives based on the New Approach and the Global Approach ("Blue Guide")[8] states that the placing on the market takes place when the product is transferred from the stage of manufacture with the intention of distribution or use on the Community market.

"*Placing on the market*" has to be clearly differentiated from the "*use*" which is allowed after the "authorisation" of the product. "*Authorisation*" means an administrative act by which the competent authority authorises the placing on the market of a product in its territory[9].

According to the indications made by the Commission the scope of the future legislation is limited to the placing on the market and does not apply to the use of an authorised product.

## 2.2 Industry description, business dynamics and future opportunities

According to findings from research and advisory services, the use of plant biostimulants and agronomic fertiliser additives in agriculture offers significant opportunity for farmers. Improved root and shoot growth, better stress

[8] Published by the European Commission (1999), see http://ec.europa.eu/enterprise/policies/single-market-goods/files/blue-guide/guidepublic_en.pdf, in particular page 18.

[9] Regulation (EC) No 1107/2009 of the European Parliament and of the Council of 21 October 2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC .

resistance, better root growth potential, improvement of nutrient uptakes, and reduction in nitrogen levels of fertilisation are some of the possibilities that these compounds connote to sustainable agriculture.

The use of products to promote plant growth and vigour is not really new as some of these products, e.g. seaweeds, have been used by farmers for many decades before their use was significantly reduced as a result of the preference given to synthetic fertilisers during the Green Revolution. Historically, biostimulants were applied to high-value crops: mainly greenhouse productions, orchards (grapes, citrus, stone fruits, apples, pears) open-field vegetables (tomatoes, salads, etc.) and horticultural products (flowers and ornamentals).

Farmers were encouraged to use chemical products to further increase productivity as the efficacy to cost ratio was much greater. In some countries regulations were encouraging farmers to use chemical fertilisers by the mean of direct subsidies when buying chemical fertilisers.

Since the reform of the Common Agricultural Policy in 1992 ("*the MacSharry Reform*") environmental consequences have been taken into considerations and the sector for alternative products has emerged at the same time that producers of plant nutrients were looking for ways to improve nutrient use efficiency and plant protection producers are looking for alternatives to traditional synthetic chemistry.

Plant biostimulants and agronomic fertiliser additives sectors appear to be quite specific, with few similarities despite the fact that they are both often incorporated into regular fertilization practices in order to boost plant nutrition. Therefore we present these two business sectors separately.

## Market overview for plant biostimulants

Although plant biostimulants were originally popularised in organic agriculture, they are increasingly moving into conventional agriculture. Plant biostimulants first moved into specialty crops, e.g. high-value agricultural and horticultural productions, and are increasingly being introduced into conventional crop production to respond to economic and sustainability imperatives.

Several studies have been undertaken on the growth of the plant biostimulants market in recent years, either by market research firms or by agriculture industry organisations. In many cases, widely divergent statistics have been offered for the size and value of this market as not all research uses the same criteria to define the market. Overlaps exist with mainly biopesticides and liquid fertilisers. Despite these differences, however, the growth of the plant biostimulants market is concluded by most studies.

The biostimulants market seems to be growing rapidly, driven by economic and socio-political factors. The European Biostimulants Industry Consortium (EBIC) considers that the 2012 EU market value (sales) of biostimulants can be estimated at € 400-500 million. EBIC carried out informal surveys within its members in late 2011 and early 2013 to better estimate the size of the European plant biostimulants markets. EBIC also reported that more than 6.2 million hectares in the EU are treated with biostimulants (about two applications of biostimulants per year on 3 million hectares).

According to the survey responses received by EBIC in 2011, the EU market is growing at 10% or more per year, with future growth predicted at the same

levels (market forecast of € 800 million in 2018). For EBIC, another sign of market growth is the number of new users which is rapidly increasing even if no statistics can be reported. Because plant biostimulants have not been widely used in the past, many growers are testing them on a limited area for one or two seasons before scaling up their use.

EBIC further highlights that the factors driving this continued growth are multiple:

4. European agricultural and food safety policies have integrated environmental considerations and are promoting the safe use of agricultural inputs. This applies to alternative products being plant biostimulants or biopesticides that are used under the integrated crop management schemes including integrated pest management;
5. In response to consumer demands for healthy food products with minimal environmental impacts growers are looking for ways to use synthetic chemicals and mineral fertilisers more efficiently and effectively. Biostimulants are therefore increasingly seen as a way to improve the return on their investment in other inputs and as a way to respond to consumer demands for "softer" agricultural practices;
6. Recent high and volatile prices for agricultural inputs like fertilisers have created incentives for farmers to optimise the efficiency of input use;
7. Plant biostimulants use is spreading from some pioneer countries to a wider number, both within Europe and the rest of the world. Related to this, biostimulants companies are expanding their professional networks and connecting with new global distributors that are helping them target previously inaccessible markets; and
8. The biostimulants sector has developed new innovative products targeting specific agronomic needs, thus attracting new customers.

EBIC member companies currently have biostimulants products on the market in several countries. EBIC added that "*despite the small size of many biostimulants producers, they already have significant cross-border activity".* As shown in the following table, the national home market is a minority of the current market for EBIC member companies.

**Table 1 EBIC member companies business areas**

| Company Identifier | Company Size | Home market (in %) | Other EU countries (in %) | Non-EU countries (in %) |
|---|---|---|---|---|
| Company 1 | Medium | 25 | 50 | 25 |
| Company 2 | Medium | 35 | 25 | 40 |
| Company 3 | Medium | 40 | 50 | 10 |
| Company 4 | Medium | 70 | 25 | 5 |
| Company 5 | Medium | 35 | 25 | 40 |
| Company 6 | Small | 30 | 0 | 70 |
| Company 7 | Large | 1 | 2 | 98 |
| Company 8 | Medium | 75 | 10 | 15 |
| Company 9 | Small | 50 | 30 | 20 |
| Company 10 | Small | 20 | 20 | 60 |
| Company 11 | Large | 20 | 30 | 50 |
| Company 12 | Large | 15 | 18 | 67 |

*Source: EBIC*

With regard to employment, EBIC considers difficult to provide a highly reliable estimation of the total number of jobs in the plant biostimulant industry. Most of the biostimulant companies are small and medium enterprises (SMEs)[10] less than 250 employees. The respondents of the 2011 and 2013 EBIC surveys together employs about 2,000 staff in Europe and every respondent reported a growing employment trend for their company in Europe. In total EBIC considers that the EU plant biostimulant sector is composed of about 200-250 companies of which about 90% are SMEs.

Two additional key criteria have to be taken into consideration to assess the development of the plant biostimulant sector: consolidation of the sector and level of investment in research.

The plant biostimulant category is in its relative infancy, but the rapidly increasing level of investment in research is beginning to yield insights into the potential of these products. A recent study by PiperJaffray[11] estimates the global plant biostimulants market to be approximately $ 1 billion and see it growing at about 20% annually per year. The same study indicates that the largest regional market for bio-based products (including plant biostimulants and biopesticides) is North America, currently accounting for around 40% of sales. Europe, Asia and Latin America, represent 25%, 20% and 10%, respectively. PiperJaffray indicates that there are a couple of significant explanations for these trends. First, growers in North-America and Western Europe are generally about 5-10 years ahead of developing country growers in the new product adoption cycle. Second, most biological developers and distribution networks are situated in developed countries. Finally, middle-class demand for organic foods, residue-free produce and overall wellness has been much stronger in developed countries. "*While developed countries will still continue to be the volume drivers of biologicals in coming years, with the USA leading sales of biopesticides and plant biostimulants and Europe leading demand growth for both group of products, trends in developing agriculture powerhouses such as Brazil, eastern Europe and China are aligning to allow more industry growth to be tackled on*".

Biopesticides/biostimulants are attracting greater interest as core options in crop protection programmes, with a number of recent high profile acquisitions by major R&D based companies. According to industry players, consolidation will further expand.

**Table 2 Large agrochemical companies move into the biological industry**

| Year | Acquirer | Company | Type of alignment | Acquisition price in USD |
|---|---|---|---|---|
| 2012 | BASF | Becker Underwood | Acquisition | 1.02 billion |
| 2009 | BASF | AgraQuest | Strategic partnership | |
| 2013 | Bayer | Prophyta | Acquisition | N/A |
| 2012 | Bayer | AgraQuest | Acquisition | 500 million* |
| 2009 | Bayer | AgroGreen | Acquisition | N/A |
| 2011 | DuPont | AgraQuest | Strategic partnership | |
| 2007 | DuPont | Marrone Bio | Strategic partnership | |
| 2013 | Monsanto | Agradis | Acquisition | N/A |

[10] Less than 250 employees

[11] PiperJaffray, Industry note, *"Agriculture: Biological crop chemistry primer: green shoots through green products; August 27, 2013.* Reproduced by courtesy of the authors.

| Year | Acquirer | Company | Type of alignment | Acquisition price in USD |
|---|---|---|---|---|
| 2012 | Monsanto | Alnylam | Strategic partnership | |
| 2011 | Monsanto | Beelogics | Acquisition | N/A |
| 2012 | Novozymes | EMD(Merck) | Acquisition | N/A |
| 2011 | Syngenta | Pasteuria Bioscience | Strategic partnership | N/A |
| 2013 | Syngenta | Isagro | Strategic partnership | |
| 2012 | Syngenta | Pasteuria Bioscience | Acquisition | 123 million* |
| 2012 | Syngenta | Devgen | Acquisition | 523 million |
| 2012 | Syngenta | Novozymes | Strategic partnership | N/A |
| 2013 | *Makhteshim* | ChileAgro Solutions | Acquisition | N/A |
| 2013 | Bayer | Stoller-China | Strategic partnership | N/A |

*Source: PiperJaffray, Industry note, "Agriculture: Biological crop chemistry primer: green shoots through green products"*; August 27, 2013

In addition to these alliances, the recent published strategic partnership between Novozymes BioAg and Monsanto is another key relevant indicator of the ongoing of large traditional R&D groups' strategy to invest in bio-based agricultural inputs businesses.

*On 10 December 2013, Novozymes and Monsanto Company announced a long-term strategic alliance to transform research and commercialisation of sustainable microbial products that will provide a new platform of solutions for growers around the world. The BioAg Alliance will allow the companies to leverage employees, technologies and commercial assets in the companies' agricultural biologicals portfolios (biopesticides and plant biostimulants). The result will be a comprehensive research, development and commercial collaboration to help farmers globally meet the challenge of producing more with less in a sustainable way – for the benefit of agriculture, consumers, the environment and society at large.*

As momentum grows, the level of applied knowledge around biostimulant technologies is increasing as well. EBIC considers that R&D efforts can be estimated at between 5% to 10% of the total sales, but some reinvest an even higher share in innovation. Many companies have between 10% and 33% of their staff involved in R&D activities with a few companies slightly below that range.

EBIC 2011 survey results indicate that: "*In addition, respondents of the 2011 survey reported almost 150 R&D partnerships with universities and other public research institutes. While most of these are in Europe, they also include partners in Australia, Brazil, Canada, Chile, Ghana, Mexico, New Zealand, Turkey and the United States. It generally takes 2-5 years to bring new products to market, a significant investment considering how little protection there is to prevent copies/reverse engineering of biostimulant products. Several companies reported in 2011 that less than 10% of their products are patentable (and some even said none can be patented). A handful of others report that 60% or more of their products contain some patented element, although this does not mean the product as a whole is protected by patent. In many cases, it is a specific aspect of the production process that is patented".*

## Market overview for agronomic fertiliser additives

There is a common understanding that the current fertiliser additives are indiscriminately grouped in two categories with very different functions. A first category, i.e. the technological additives, covers additives that modify the physical characteristics of the final fertiliser product aiming at improving the manufacturing, handling and application of fertilisers. The other category, which should be clearly separated from the previous one, covers performance-enhancing additives (i.e. agronomic fertiliser additives) that use fertiliser technology to improve nutrient use efficiency. These performance-enhancing additives covers additives that modify the release of nutrients from commercial fertilisers, but are not restricted to this category of effects as other performance-enhancing additives act on the stability of the nutrient, e.g. by protecting them from chemical and biological degradation in soils.

The International Fertilizer Industry Association (IFA) has developed several definitions which are currently being used by industry, as follows:

- Fertiliser technology: substances that improve the efficacy of the final product;
- Slow or controlled-release fertiliser: A fertiliser containing a plant nutrient in a form which delays its availability for plant uptake and use after application or which extends its availability to the plant significantly longer than a reference rapidly available nutrient fertiliser;
    - Slow-release fertiliser (SRF): nutrient-containing compounds that decompose over an extended time by biological or chemical means into plant-useable nutrient forms;
    - Controlled-release fertiliser (CRF): nutrients coated by hydrophobic polymers or matrices to restrict the dissolution of the nutrient and therefore extending the release of available nutrients;
- Stabilised nitrogen fertiliser: A fertiliser to which is added a substance which extends the time the nitrogen component remains in the soil in the urea-N or ammoniacal-N form;
- Nitrification inhibitor: A substance that inhibits the biological oxidation of ammoniacal-N to nitrate-N;
- Urease inhibitor: A substance that inhibits hydrolytic action on urea by the enzyme urease.

Chelating and complexing agents which are not recognised by IFA as agronomic fertiliser additives are however already included in the Annex I to the Fertiliser Regulation and it is assumed from indications given by the Commission that these categories of products described above will be considered in the future EU legislation.

According to the International Fertilisers Development Center (IFDC), there are very few reports and market data to describe the specific business related to agronomic fertiliser additives.

The most comprehensive recent one is the presentation made by AgIndustries Research & Consulting presented at the International Conference on slow and controlled release (CRFs) and slow released fertilisers (SRFs) in 2013[12].

[12] Available at http://www.fertilizer.org/ifa/HomePage/LIBRARY/Conference-papers/Agriculture-Conferences/2013-IFA-New-Ag-International-Conference

According to this report, the key characteristics of the market for the above-mentioned products are:

- Markets for CRFs and SRFs are globalised for already several years:
- The United States, Western Europe and Japan have historically been the 3 largest world regional markets for CRFs. The US CRFs market (700,000 tons) is almost 5 times larger than the Western European market (150,000 tons), based on product volume, and nearly 13 times larger than the Japanese market (about 50,000 tons);
- In the EU, the CRFs market distribution reads as follows (2009 data):
  - 61% of the total volumes go to professional markets (BtoB);
  - 29% to consumers (hobby market)(BtoC); and
  - 10% directly to farmers.
- The projected average annual growth rate to 2015 is about 1.5%-2.5% in Western Europe, slightly lower than growth rate in the US (2.0%-3.5%) and in Japan (3.0%-4.5%);
- The global market for N stabilisers and SRFs is developing rapidly:
  - US consumption of SNFs amounted to an estimated 3,381,000 metric tons of nitrogen in 2010;
  - SNFs consumption in Western Europe totaled an estimated 129,000 metric tons in 2009;
  - Nitrification inhibitor-stabilised fertilisers are widely used in Japan; however consumption data are not available.

It can be observed that business is dominated by a small number of large companies (e.g. BASF, Kock, Dow, Everis (ICL), SKW in Germany) which have developed new innovative products that are added to commodity fertiliser formulations.

Significant events in the world market for AFA since 2010 have been observed:

- Formation of a manufacturing and marketing alliance between Koch Fertiliser Trading SARL and Agrotain International, followed by the launch in April 2010 of Koch Advanced Nitrogen (urea stabilized with NBPT) in the UK;
- Kock Agronomic services' October 2011 acquisition of Agrotain International's N stabiliser and SNF assets;
- Launch of several new products :
  - Arborite AG: NBPT-based urease inhibitor product,
  - Nexen: new SNF by Koch.

Agronomic fertiliser additives are often incorporated into regular fertilisation practices in a supplementary way that boosts nutrition. Value creation come from premium that the fertiliser manufacturers can add on the price of the commodity fertilisers. For example, BASF is keeping most of its additives for its own fertiliser business and in these cases do not sell them to any third commercial partners. For BASF, the annual added sale revenue is estimated at € 18 million[13].

[13] Information provided during an interview with an industry representative

Most of these actors have an important R&D sector which is often structured internationally to support several markets (e.g. Kock has 10 R&D international staff for the development of new agronomic fertiliser additives and Everis in between 10 and 15 high qualified R&D staff).

This introduction to the plant biostimulants and fertiliser additives markets clearly highlights that we are facing two very different sectors in many criteria as summarised in Table 3 below.

**Table 3 Comparison between the EU plant biostimulants and the agronomic fertiliser additives business sectors**

| Criteria | Plant biostimulants | Agronomic fertiliser additives |
|---|---|---|
| Market trend (estimated annual growth rate) | > 10% | 1.5-2.5% |
| Business maturity | Low | High |
| Business structure | Ongoing consolidations | Mature |
| R&D investment | Medium to high | Medium |
| Type of industry | Mainly SMEs | Mainly large companies |
| Business perimeter | Often local to national | Regional to international |
| Number of industry players | High (>200) | Low |
| Marketing approach | Twofold:<br>- Marketing of stand-alone products<br>- Incorporation into fertilisers to optimise nutrient uptake | |

## 2.3 How are plant biostimulants and agronomic fertiliser additives currently placed to the market at EU/MS level? At international level?

This section summarised the current situation regarding the placing of plant biostimulants and agronomic fertiliser additives on the market at national level in the EU and at international level in Third Countries.

The description of the national regulatory frameworks is concentrating on plant biostimulants as most of the AFA are already included in the Fertiliser Regulation 2003/2003. The term "*agronomic fertiliser additives*" is not defined per se in the current Fertiliser Regulation but some types of additives have been added (M4, M5 and M9) to Annex I of the Regulation.

Today, the Regulation lists the following agronomic fertiliser additives:

- Chelating agents: list E.3.1 of Annex I of Regulation (EC) No 2003/2003;
- Complexing agents: list E.3.2 of Annex I of Regulation (EC) No 2003/2003;
- Nitrification inhibitors: list F1 of Annex I of Regulation (EC) No 2003/2003;
- Urease inhibitors: list F2 of Annex I of Regulation (EC) No 2003/2003.

The procedure for introducing a new type of fertiliser to Annex I so that it can be marketed as an "*EC fertiliser*" is defined in Article 31 of Regulation (EC) No 2003/2003 and further specified in a non-binding guidance document produced

by the Commission[14] in co-operation with Member States experts. The guidance document describes the content of the technical file to be submitted including information relating to health and safety, REACH registration data, information on the agronomic effects, the methods of use and the efficacy of the product and a proposal for an internationally recognised method for analysis of the specific product. The procedure also requires that the application with the technical file is submitted to one of the Member States that will act as rapporteur to the Working Group on Fertilisers on the basis of the tests and review conducted at the national level. Finally, the Fertilisers Working Group (with participation of the Member States and industry) is the main body where issues are raised and discussed, proposals for solutions and necessary revisions are formulated and where an agreement on a proposal to include new fertilisers types in Annex I is made. The Working group meets normally twice a year[15].

The analysis has been performed by considering several EU MS mainly BE, DE, ES, FR, IT and HU and four Third Countries (TCs) (Brazil, Canada, South-Africa, and the USA). The selection of these countries has been made to secure that the main types of regulatory schemes would be described.

As an introduction, the following elements should be considered:

- The term "*Plant biostimulants*" is not defined in any of the regulatory framework under analysis; therefore our analysis has been performed by considering comparable products and products that will fall as plant biostimulant under the future EU Regulation;
- "*Agronomic fertiliser additives*" is solely defined in the French legislation (NFU 44-204 standard which has been made compulsory under Articles L255-1 to L255-11 of the "*Code Rural*").

The description of the national and TC regulatory schemes aims at highlighting the main similarities and differences of the schemes and should not be perceived as an exhaustive description of each of them. Additionally this analysis aims at identifying interesting features that could be considered in the building of the future EU regulatory framework for PB&AFA.

The descriptions of the different schemes are sorted by level of data requirements (low to high requirements) (from simple notification to registration approaches).

## The Belgian regulatory scheme

The legislation related to the placing on the market of plant biostimulants ( or associated to this type of products) takes place in the context of the "Arrêté Royal du 28 Janvier 2013" in which a category concerning "*other fertilisers*"[16] has been created. Other fertilisers can be fertilisers, growing media, soil improvers, and other products of which plant biostimulants.

[14] Communication from the Commission, Guide to the compilation of a technical file on application to designate a fertiliser as 'EC fertiliser' http://ec.europa.eu/enterprise/sectors/chemicals/files/fertilizers/2009_02_03_new_guidance_final_en.pdf

[15] Source: Evaluation of Regulation (EC) 2003/2003 relating to Fertilisers - Final Report – CSES available at : http://ec.europa.eu/enterprise/sectors/chemicals/files/fertilizers/final_report_2010_en.pdf

[16] Definition: « tout produit auquel est attribué une action spécifique de nature à favoriser la production végétale » free translation : « any product that acts specifically in order to improve crop production »

Applicants have to notify the national authority (Service Public Fédéral Santé publique, Sécurité de la Chaîne alimentaire et Environnement DG Animaux, Végétaux et Alimentation, Service Pesticides et Engrais, hereinafter "SPF")) that it wants to place on the market a new fertilising material that do not fall under the scope of the existing categories. This notification should be as complete as possible but there is no defined guidance documents regarding the required composition of the dossier. The national authority examines the dossier and grants the authorisation (called "*dérogation*") by communicating the applicant the registration code/number when the dossier is considered complete and when no unacceptable safety issue has been identified. However, in the large majority of cases, the SPF asks the applicant for additional questions and for the provision of additional information on a dossier by dossier basis. In these cases, authorisation is granted when SPF considers that enough information has been submitted to assess that the product would not pose any significant safety or environmental issues.

SPF does not ask the applicant to provide toxicological and ecotoxicological data. However applicants are required to provide information proving the efficacy of the product by mean of field trials data or/and laboratory tests results or/and by providing scientific literature evidences (in this case applicants are requested to provide field results after approval is granted).

The mode of action of the product intended to be placed on the market has to be described by the applicant. It is being used to analyse whether or not the product is a plant protection product.

On average the SPF receives 250 new dossiers per year of which about 10 of these can be considered as plant biostimulants products. SPF applies a flat fee system of € 1,500 per dossier (one single payment at application).

## The Danish regulatory scheme

The Danish AgriFish Agency (DAA) is the National Authority in charge of the questions related to placing on the market of specific fertilisers category in which plant biostimulants can be placed.

Like the current Fertiliser Regulation, the Danish Order on Fertiliser and soil improvers etc. has no separate category for plant biostimulants. Hence, they have been registered as soil improvers under national legislation. We do not have very many products registered, which could be categorised as biostimulants; our estimate is about 15. Traditionally, they are not used very much in Denmark and if so, mostly by organic farmers. We have recently had an increasing number of requests regarding biostimulants and applications for registration. As some of those contain ingredients or are described as having properties interfacing with plant protection products, we have started a collaboration with the Danish Environmental Protection Agency (the DEPA) handling the requests.

If the product is not categorised as a soil improver (in which case it would be the responsibility of the AgriFish Agency), nor clearly as a plant protection product (which falls under the responsibility of the DEPA), the general chemicals legislation applies, belonging to the DEPA's area of expertise.

If this does not require registration (e.g. dried sea weeds extracts), the product can freely be placed on the Danish market.

If the product is categorised as a soil improver, or any other product regulated by the Danish Order on Fertiliser and soil improvers etc., companies are required to register their product with the AgriFish Agency. The register is made public online; earlier a hard copy is made available. DAA asks for data regarding the contents – all ingredients making up minimum 1 % have to be labelled – and documentation for the agronomic efficacy according to Danish conditions (e.g., soil type, abiotic factors). According to the Order on payment a registration fee is charged, plus a yearly fee according to the amount of product ant type sold.[17]

As for Belgium the Danish approach is not requiring to provide toxicological nor ecotoxicological data. In some limited cases (e.g. sea weed extracts with no chemical products being used during the process, notification is voluntary and not mandatory). The fee level is lower than for (about €300-500 per notification payable when submitting the application).

## The Spanish regulatory scheme

The current national legislation that includes plant biostimulants is the "ORDEN APA/1471/2007" regulating the placing on the market of "*otros medios de defensa fitosanitaria*"[18] (called "*fitofortificantes*"). This legislation was developed and overseen by the "fertiliser section" till end of 2011 before it moved into the "agrochemical section" of the Ministry of Agriculture.

Under the current regulation, commercial products that have been notified can immediately be placed on the market without waiting for any approval. This approach had led to a large number of products being sold. A new royal decree is being prepared to correct the shortcomings of the current situation and should be issued by early 2014.

The definition being used in the existing Orden does not clearly identify whether or not plant biostimulants as being defined under Section 2.1 would fall under the scope of this legislation. The current definition reads as follows:

"*Products included in this scope of application are the organisms of biological control, the traps and other means or devices for the control of pests, as well as the products that could favour that the crops develop vigour or resistance in front of the adverse effects related to pathogen attacks, or environmental conditions, or allow mitigate in another manner the devastations that they could cause, and other products…".* This definition clearly includes a range of products affecting both biotic and abiotic stress.

In the new legislation, the name of this product group will be simplified to "*MDF: medios de defensa fitosanitaria*" but the question whether or not plant biostimulant (as defined at EU level) will be included in the scope of the legislation remains open.

The draft royal decree calls for two types of products, those requiring authorisation before commercialisation and those simply requiring notification before commercialisation (the current situation but with some changes to the notification process). Notification requirements will include data to justify the safety of products and the claims and registration fees will apply. Notification

[17] The Orders can be found at http://erhvervsstyrelsen.dk/productcontactpoint.dk/database/0/13/0/[1]Fertilisers[1]Agriculture[1][1][1][1][1][1][1][1][1][1]

[18] Free translation: "other means for crop protection"

dossiers will have to be submitted to one autonomous community and marketing will start immediately without awaiting for any authorisation.

Authorisation by the Ministry of Agriculture – subdireccion General de Sanidad e Higiene Vegetal y Forestal (MAGRAMA) will apply to a range of product categories, among which "*plant extracts and others*" and "*certain fertilisers*" (based on a list of raw materials yet to be published).

MAGRAMA will have 3-6 months (depending on the product in question) to grant or refuse authorisation for a product that is not eligible for commercialisation immediately after notification. In case MAGRAMA does not publish an opinion before the deadline, the product is automatically approved for sales.

Data requirements are listed in Article 2 of the new draft decree and can be listed as follows:

- List of raw materials;
- Characterisation methods or identification methods (depending on type);
- Analytical methods;
- Analysis of active components;
- Presence/absence of contaminants (list to be defined);
- Physico-chemical and technical properties by a third accredited laboratory applying ISO 17025 standard;
- Safety information and toxicology obtained through Good Laboratory Practices (GLP) (no list defined);
- Ecotoxicity and environmental fate information (no list defined);
- Field trials (4 crops * 3 growing cycles) conducted by official authorised entity; and
- For micro-organisms, each of them must correspond to a pure strain that is identified and characterised, which does not come from a species that is pathogenic to people, crops, animals, flora or fauna.

Data requirements will be retroactive in the spirit of providing a level playing field. Data will have to be submitted for products already on the market within 12 months, unless there is a justifiable reason to extend the period to 2 years (e.g. to conduct adequate field trials).

The Spanish industry representatives[19] have estimated that this approach will lead to regulatory costs ranging from € 30,000 to more than € 100,000. The number of applications to be submitted under the new scheme has not yet been estimated by the national industry.

## The German regulatory scheme

The German Federal Office of Consumer Protection and Food Safety (BVL) has developed a regulatory framework for "*plant strengtheners*" (PS) that corresponds to plant biostimulants as defined under Section 2.1.

[19] AEFA: Associacion Espanola de Fabricantes de Agronutrientes

A detailed description of this category, the notification procedure, the data requirements and the list of plant strengtheners is clearly presented on the BVL website[20].

The segmentation between PS and PPP on one hand and PS and fertilisers on the other are also clearly mentioned.

The approach is based on a notification to BVL that leads to an automatic authorisation. In case there are indications that the notified product does not fulfil the definition of plant strengtheners or may cause harmful effects on human and animal health, groundwater or the environment, BVL prohibits the placing on the market of the product by informing the notifier in writing.

Commercial products containing more than 5% of seaweed extracts cannot be considered as PS. In the majority of cases they are classified as PPP or as Plant Aids (under the national Fertiliser Acts).

BVL insists that notifications include a detailed description of the characteristics of the product even if BVL doesn't list requirements. That allows identifying whether or not a safety and/or environmental risk could be anticipated. In more than 90% of cases, BVL request additional information to the notifier but this approach does not suspend the marketing authorisation.

BVL does not require the mandatory furniture of an analytical/quality method in all cases.

Between March 2012 and July 2013, about 300 notifications have been submitted by BVL. About 15% of these have been rejected mainly due to poor submitted datasets and wrong categorisation (BVL is of the opinion that the systems leads to difficulties differentiating between PS and PPP). About 1.5 Full Time Equivalent (FTE) is dedicated to the processing of notification dossiers. This is considered as not sufficient by BVL.

Fees for notification are low: € 400. This is explained by the fact that most of applicants are small SMEs (more than 100 companies are listed in PS register).

## The Italian regulatory scheme

Italy has a national fertiliser legislation called Decreto Legislativo 75/2010[21] which covers fertilisers groups not covered by Regulation (EC) No 2003/2003 and in particular products that could fall under the plant biostimulant category as defined under Section 2.1. The national authority in charge of fertilisers is the Ministry of Agriculture ("*Ministero delle politiche agricole alimentari e forestali*").

Plant biostimulants can be considered as falling in the product category called "*Prodotti ad azione Specifica*" (specific action products) as defined under Annex 6 of the Decree. Annex 6 list three different sub-categories (each including sub-sub categories):

[20] See: http://www.bvl.bund.de/EN/04_PlantProtectionProducts/03_PlantResistanceImproversAndAdjuvants/01_PlantStrengtheners/PlantProtectionProducts_PlantStrengtheners_node.html

[21] Decreto legislativo 29 aprile 2010, n. 75 (So n. 106 alla Gu 26 maggio 2010 n. 121) Riordino e revisione della disciplina in materia di fertilizzanti, a norma dell'articolo 13 della legge 7 luglio 009, n. 8

- Products acting on fertilisers (including inhibitors of urease, nitrification);
- Products acting on the soil; and
- Products acting on the plant in which plant biostimulants are listed.

Registration applies to add a new designation type to the Annex 6 of the regulation. The register lists 7 designation types for PB&AFA and commercial products are not registered by authorities.

New type designations are inserted after a company submits a dossier (according to Annex 10 of the decree) containing the following details:

- Production methods, raw materials used;
- Final product composition, physico-chemical nature, heavy metal content;
- Analytical method for quality control;
- Biological contaminants if relevant;
- Material Safety Data Sheet (MSDS) according to Regulation (EC) No 1907/2006, if relevant;
- Toxicity data (no list of tests provided);
- Ecotoxicity and environmental fate data (no list of tests provided);
- Agronomic information (crops, application method, effects).

The compilation of a dossier costs about € 30,000 to 50,000. The dossier is assessed by a special commission, appointed by the Ministry. Typical assessment time is 12-18 months, but varies a lot depending on the quality of the dossier. It is to be noted that currently the Commission has been dissolved, so the situation is frozen.

When a new designation type is created and inserted in the register, any company can market similar products (same approach than for the Fertiliser Regulation).

## The Hungarian regulatory scheme

The legal basis of the Hungarian scheme is the "*Decree 36/2006 (V.18.) FVM*" of the Ministry of agriculture and rural development on the authorisation, storage, marketing and use of yield enhancing substances.

Yield enhancing substances covers chemical, mineral and organic fertilisers, composts, worm composts, soil improvers, soil conditioner preparation, microbiological preparations, group of products, plant conditioner preparation.

Plant biostimulants could be ranged under the category of plant conditioner preparation as its definition reads as follows:

> "*Plant conditioner preparation: means a preparation manufactured from organic or inorganic materials with favourable influence on the growth, yield and general conditions of plants and which have an effect on plant life cycles primarily by influencing the nutrient supply*".

Article 3 of the Decree indicates that: "*Yield enhancing substances may be placed on the market or used if:*

*a) they have favourable effects on the soil and cultivated crops supported by tests and studies, in case of technically reliable use they do not have any harmful effect on plants, soils, human or animal health or any unacceptable risk to the environment and nature,*

*b) they have an authorisation for placing on the market and use of yield enhancing substances (hereinafter: authorisation) granted by the Central Agricultural Office (hereinafter: competent authority).*

*Authorisation for yield enhancing substances is granted for commercial products and may also be granted as product family. The provisions of other legislation on the authorisation of plant protection products shall also apply to yield enhancing substances containing plant protection products."*

Data requirements for plant conditioner preparation are as follows:

- Physical, chemical description of the product including the complete composition of the preparation, name of active substances, basic materials;
- Field of uses and doses of applications provided by the manufacturer;
- Description of the manufacturing technology;
- Presence of heavy metals (quantification required on 3 samples);
- Testing results of organic contaminants. The requirements are only listed in case waste is being used (then testing results of total polycyclic aromatic hydrocarbons (PAHs) content, benz(a)pyrene content, mineral oil content, polychlorinated biphenyls (PCBs) content and polychlorinated dibenzodioxins (PCDDs) content have to be reported);
- Test verifying biological efficacy: 3-6 field trials or under greenhouse for each crop group. These efficacy trials may be carried out by the competent authority or an organisation accredited for this field, of Hungary or of the EEA Member States by respecting the provisions of the European and Mediterranean Plant Protection Organisation on Good Agricultural Practice and the relevant test methodology. The tests made in the EEA Member States may be accepted if they were carried out under Hungarian or comparable agro-ecological conditions (climatic, agricultural, environmental and pedological) as well as plant health conditions. Field trials for non-crop-specific preparations may be substituted by pot tests, while trials carried out for crop groups may be substituted by tests for cultivation sectors;
- Microbiological tests;
- MSDS of the preparation, in accordance with the provisions of Act on chemical safety;
- In case of yield enhancing substance containing hazardous substance, under provisions of the CLP legislation, demonstration of the behaviour of hazardous materials in soils, their effects on sub-surface waters[22];
- If waste was (also) used for the production of plant conditioner preparation, additional ecotoxicological (*Daphnia*-test, fish test, algal test) and other tests may also be required, depending on the quality of the waste.

[22] Detailed requirements are listed per group of products in Decree 36/2006. The list is too large to be reported here.

Authorisation is valid for ten years and can be renewed.

## The French regulatory scheme

Rules for placing plant biostimulants and agronomic fertiliser additives on the market are included in the fertiliser acts called "*matières fertilisantes et support de cultures*" (MFSC). This regulatory framework includes all types of fertilisers, growing media, liming materials, soil improvers and any other MFSC. The legal basis is Article L255-1 to L255-11 of Code Rural.[23]

All MFSC in their form of commercial products require a pre-market approval ("*homologation*") but about 90% of the commercial products are exempted from registration when an history of safe use has been demonstrated. In these cases, standards (similar approach than the current one in the Fertiliser Regulation) have been created (i.e. the NFU[24] standards).

Most agronomic fertiliser additives as defined under Section 2.1 are included in several standards and therefore no registration of commercial products is required.

For plant biostimulant as defined under Section 2.1, a standard (NF U 44-204) has been introduced in September 2011 to cover plant biostimulants when added to fertilising materials. Commercial products can be placed on the market if the label or any other commercial document specifies that the product fulfils the requirements of the standard.

For all other plant biostimulants (e.g. used alone and not in addition to fertilisers) a full registration process applies. This approach is rather similar to the Hungarian one and it applies to individual commercial product with the possibility to apply for product families and on group of crops.

A detailed methodological guidance is available[25]. All requirements are fully described in details to the exception of the requirements for proving safety and efficacy of the product. Applicants are required to prove safety and efficacy of their product but no detailed information on the required test data is provided (case by case approach). It is of the responsibility of the applicant to provide enough information in its application dossier to prove safe use of the product (health & environmental safety).

Programme 108[26], a testing protocol that covers a large number of criteria (heavy metal content, nutrient content, physico-chemicals properties, and microbiological analysis), has to be performed for any application. Only a few laboratories are accredited to run this test.

Fees of € 6,000 have to be paid when submitting the application for the first time. Fees are less important in several cases (e.g. renewal, second application of the same substance, modifications of the product composition, modification of the claim, etc.). The total cost for producing all required information and for compiling the registration dossier ranges from € 20,000 to > € 50,000. While the registration process is expected to take one year, it has been observed that in

[23] www.legifrance.gouv.fr
[24] NFU: Norme Française (French Norm)
[25] Available at : http://www.anses.fr/fr/content/documents-dinformation-pour-les-dossiers-sur-les-mati%C3%A8res-fertilisantes-et-supports-de
[26] Available at http://www.cofrac.fr/fr/documentation/index.php?fol_id=58

the majority of cases more than two years were necessary to complete the registration process.

The list of registered products is reported in the French catalogue available at http://e-phy.agriculture.gouv.fr/. It contains about 120 entries of which less than 15 can be considered as plant biostimulants.

### Third Countries regulatory schemes

The analysis of the description of some Third Countries regulatory frameworks for plant biostimulants and agronomic fertiliser additives do not lead to the identification of major differences in comparison to the EU approaches.

**In the USA** registration of PB&AFA takes place in the context of the fertilisers' acts[27]. Since there is no federal fertiliser law for the placing of fertiliser products on the market[28], the registration of plant biostimulants (as well as fertilisers) are regulated at state level. State regulations for fertilisers are generally developed and administered by state agriculture departments.

Such regulations primarily address efficacy claims and composition statements of the active ingredients displayed on fertiliser labels. Most states have fertiliser regulations requires registration and/or licensing of each brand and grade of fertiliser by the person whose name appears on the label before the product may be distributed.

None of the stakeholders that have been consulted during the study have indicated any specific requirement or process for plant biostimulants or agronomic fertiliser additives. The state legal schemes are based on notification systems in which basic information on product composition and agronomic efficacy have to be submitted by applicants. Fees are low (< USD $ 1,000 and variable across states) and the regulatory processes seem to be fast (authorisation is generally granted within a 6-9 months period)[29].

**In Canada,** the "*Fertilisers Act and Regulations*" requires that all regulated fertiliser and supplement products must be effective and safe for humans, plants, animals, and the environment. They must also be properly labelled. The mandate of the Canadian Food Inspection Agency (CFIA)'s Fertiliser Program covers a wide range of products sold for agricultural, commercial, and home and garden purposes. Products include farm fertilisers, micronutrients, lawn and garden products as well as supplements such as water holding polymers, microbial inoculants, and composts.

The Canadian fertiliser Act contains a definition related to "supplements" that could be considered as being PB&AFA which reads as follows: *"any substance or mixture of substances, other than a fertiliser, that is manufactured, sold or represented for use in the improvement of the physical condition of soils or to aid plant growth or crop yields".*

Supplements, subject to the authority of the "*Fertilisers Act and Regulations"*, are products that claim to aid crop yields. They include, but are not limited to, products that:

[27] See http://www.aapfco.org/
[28] Federal legislations are in place regarding the production, use and disposal of fertilisers
[29] Source: stakeholder interviews

- Enhance root or vegetative development;
- Break dormancy;
- Induce early germination or sprouting;
- Condition soil; and
- Contain vitamins with growth regulating properties.

Most supplements are subject to registration and require a comprehensive pre-market assessment prior to their sale in Canada. Products that are exempt from registration are still subject to regulation and must meet all the prescribed standards at the time of sale. Companies that manufacture these products may approach the CFIA and request a voluntary pre-market assessment to verify that their products meet the requirements.

The CFIA's pre-market assessment consists of a detailed, science-based evaluation of product safety information, efficacy, and labelling. To assess a product, the Agency requires that supporting information, which varies in scope depending on the nature of the product, is submitted. The basic supporting information includes the product label, the manufacturing method, and a complete list of ingredients and source materials.

For certain supplements, additional information such as a detailed description of the physical and chemical properties of each ingredient, results of analytical tests that show freedom from biological and chemical contaminants, a toxicological data package derived from either laboratory studies or scientific publications, or data supporting product efficacy may be required.

Efficacy assessments of fertiliser and supplement products can range from simple calculations, ensuring that the product delivers a sufficient amount of nutrients to satisfy plant needs, to highly complex statistical analysis of performance data generated from field or greenhouse trials. In all instances, the efficacy claims that appear on a product label must be supported by scientifically valid information and the product benefits must be substantiated in a clear and definite way. A variety of factors are considered by CFIA evaluators when evaluating product performance including product application rates, nutritional requirements of the target crop, usage pattern, frequency of application, current agricultural practices, appropriate statistical methods, research trial designs, and Canadian climate and soil conditions.

Plant growth regulators may be subject to the authority of either the "*Fertilisers Act"* or the "*Pest Control Products Act"*, or both, depending upon the interpretation of the definitions in the two acts.

Products containing only growth regulators, which carry mixed claims, are subject to registration under the *Pest Control Products Act* contingent upon acceptance of the supplement claims under the *Fertilisers Act*. All other products with mixed claims are subject to registration under the *Fertilisers Act*.

According to stakeholders contacted during the study, the national competent authority seems to ask for more data when it relates to the registration of new supplements (PB&AFA) the data requirements. Trends are to ask for more toxicological and ecotoxicological evidences to the applicants.

**In South-Africa** according to "*Fertilizers, Farm Feeds, agricultural remedies and stock remedies Act 36 of 1947[/SAPL4]"* applicants are required to submit an

application to the Ministry of Agriculture which includes basic toxicological, ecotoxicological and efficacy testing results. Any approved new product is listed in the national Register. There exists three product-types under which approved product will be listed.

Most often, products are listed under the fertiliser product-category, as macro-nutrients, or micro-nutrients. Minimum requirements are needed for specific nutrients. If the product analysis fulfils minimum requirements, no further data is required. Biostimulants are often enriched with nutrients to fulfil these requirements.

Products may be listed as biostimulants where the active is seen as an extract that does not need to be quantified. Statistical significant trial data per crop needs to be submitted to support label agronomic claims.

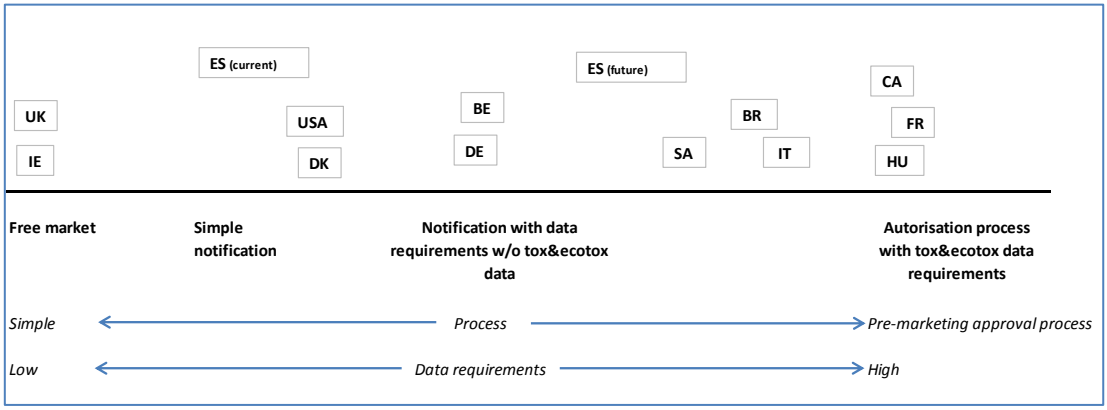
Finally, products may be listed as pesticide, usually under the category of plant growth regulators. In that case, the specific plant growth regulators need to be specified and quantified. Additionally the statistically significant trial data needs to be submitted per crop to support label claim.

Applicants have to decide which information it considers necessary to submit. However, toxicology and ecotoxicology data might also be required by authorities, depending on the source of the plant biostimulant that may indicate a potential risk and on a case by case basis. If the source is known to be a food source, with no toxic inserts being added, these tests are normally waved. There is no predefined list of tests to be submitted.

**Brazil** approach is very similar to that of Hungary where individual plant biostimulants products have to be registered based on the fertiliser acts. Data requirements are dossier specific. National competent authorities are used to ask for more information to applicants. These requirements include more and more toxicological and ecotoxicological evidences.

The description of these regulatory national schemes shows that several regulatory approaches exist ranging from no intervention (free access to the market) to a pre-market authorisation on individual commercial products.

**Figure 2 EU & TC regulatory processes for placing of PB (and AFA) on the market**




*Source: compiled by Arcadia International*

The main conclusions of this analysis in support to the definition of a legal framework for PB&AFA can be found in the introduction part of Section 3.

In more details, when considering a plant biostimulant the following processes, data requirements and costs apply:

**Table 4 Registration process and data requirements for placing of PB on the market at EU and TC levels**

| Item | EU | | | | | | | Third Countries | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | BE | DE | DK | ES[30] | FR | IT | HU | BR | CA | SA | USA |
| **Process** | | | | | | | | | | | |
| Simple notification | | | Yes | Yes | | | | | | | |
| Notification with provisions of data | Yes | Yes | | | | | | | | Yes | Yes |
| Data assessment/review | Yes | Yes | No | No | Yes | | Yes | Yes | Yes | Yes | |
| Registration | | | | | Yes | | Yes | Yes | Yes | | |
| Time to authorisation | Short | Short | Short | Short | >1year | >1year | >1year | >1year | >1year | Short | Short |
| | | | | | | | | | | | |
| **Data requirements** | | | | | | | | | | | |
| Characterisation & identification | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Analytical method | No | No | No | No | No | Yes | Yes | Yes | Yes | No | No |
| Manufacturing process | Yes | Yes | No | No | Yes | Yes | Yes | Yes | Yes | No | No |
| Toxicity data | No | No | No | No | Yes | Yes | Yes | Yes | Yes | No | No |
| Ecotoxicity data | No | No | No | No | Yes | Yes | Yes | Yes | Yes | No | No |
| Environmental fate data | No | No | No | No | Yes | Yes | Yes | Yes | Yes | No | No |
| Efficacy data | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Labelling requirements | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| | | | | | | | | | | | |
| **Fees (in €)** | | | | | | | | | | | |
| | 1,500 | 400 | 200 | | 6,000 | 3,000 | | | | | |
| **Average costs (in €)** | | | | | | | | | | | |
| *For applicant*[31] | <10,000 | <10,000 | <2,000 | <2,000 | >30,000 | >30,000 | >20,000 | >15,000 | >15,000 | <10,000 | <10,000 |

[30] Current situation
[31] Initial costs only. Cost for providing additional data not included

## 2.4 What can be learned from comparable EU regulatory frameworks?

This section presents the results of Task 1 which was aims at reviewing several existing regulatory frameworks at EU level which apply to chemical substances/microorganisms comparable to the ones used as plant biostimulants and agronomic fertiliser additives. According to the ToR of the study, the aim is in particular to describe the data requirements as well as the administrative procedures established by these regulations with regards to risk assessment for human health and the environment, as well as the assessment of the efficiency/efficacy of these products. A comparison of the average time and related costs (for both authorities and applicants) needed for granting access to the market shall also be performed.

On the basis of a proposal by the study team, the Commission validated the following list of regulatory framework to be analysed:

- **REACH (chemical products):** Registration is a requirement on industry (manufacturers/importers) to collect and collate specified sets of information on the properties of those substances they manufacture or supply at or above 1 ton per year. This information is used to perform an assessment of the hazards and risks that a substance may pose and how those risks can be controlled. The amount of data required is proportionate to the amount of substance manufactured or supplied.
- **Plant protection products (PPP):** Registration of PPP in the EU has been in place for more than 20 years now. The core legislation regulating the approval of PPPs on the EU market is Regulation (EC) No 1107/2009, directly applicable in Member States. Based on the predominance of health and environment protection over agricultural production, it sets EU-wide requirements for their placing on the market. Active substances are registered at EU level and corresponding commercial products at MS or zonal level. As the majority of plant biostimulants are of non-synthesised chemical nature, the study has focused on the analysis of the registration process for botanicals, plant extracts and low risky PPP products as well as for basic substances[32].
- **Biocides (BPR):** All biocidal products require an authorisation before they can be placed on the market and the active substances contained in that biocidal product must be previously approved based on the requirements of the Biocidal Products Regulation (BPR, Regulation (EU) No 528/2012). There are, however, certain exceptions to this principle. For example, existing active substances for which the review has not yet been achieved as well as biocidal products containing these active substances can be placed on the market while awaiting the final decision on the approval of the active substances. Provisional product authorisations for new active substances that are still under assessment are also allowed on the market.

[32] Regulation 1107/2009 introduces the new category of "*basic substances*" which are described in recital as "*active substances, not predominantly used as plant protection products but which may be of value for plant protection and for which the economic interest of applying for approval may be limited*". On this basis, specific provisions are set to ensure that such active substances, as far as they do not have an immediate or delayed harmful effect on human and animal health nor an unacceptable effect on the environment, can be legally used in the EU after having been approved as "*basic*" under Regulation 1107/2009.

- **Cosmetics products (CoP):** Free movement of cosmetic products in the internal market is permitted if they comply with the new Regulation (EC) No 1223/2009 (entry into force on 11 July 2013). A responsible person established in the Community shall be designated for each product placed on the market that shall ensure compliance with requirements relating to human health, safety and consumer information. They shall maintain a product information file accessible to public authorities. The Annexes of this Regulation give a list of prohibited substances (Annex II) or restricted substances (Annex III) with respect to use in cosmetic products. Certain colorants (other than those in Annex IV), preservatives (other than those in Annex V) and UV-filters (other than those in Annex VI) are also prohibited.
- **Food additives (FoA):** Food additives are substances added intentionally to foodstuffs to perform certain technological functions, for example to colour, to sweeten or to help preserve foods. All EU food additives are identified by an "E" number and must be authorised before they can be used in foods. Authorisation by risk managers follows a thorough safety assessment carried out by EFSA. Once authorised, these substances are compiled in an EU list of authorised food additives, which also specifies their conditions of use.
- **Feed additives (FeA):** Feed compounds can be freely marketed in the EU after being listed in an EU register. Individual commercial products are approved (holder authorisation) on the basis of a pre-marketing approval process managed by EFSA for risk assessment and by the SANCO standing Committee on animal health for risk management. All technological, sensory and nutritional additives have no holder-specific authorisations (they are registered based on the active substance they contain and not individually). Authorisations for zootechnical additives, for coccidiostats, histomonostats, as well as for additives consisting, containing or produced from GMOs are "holder-specific authorisations" (proprietary)[33].

This analysis has been based on a deep literature review (i.e. review of individual guidance documents for each registration process completed by interview(s) with relevant policy makers and business operators when required).

Results have been compiled in an Excel Database which will be published together with the present report the analysis of which is presented below.

### 2.4.1 General information

#### *2.4.1.1 Distribution of responsibilities and the actors*

The majority of the EU regulatory frameworks under analysis are under the responsibility of DG SANCO with the exception of the Biocides Products Regulation which is under the authority of DG ENV and REACH under the co-responsibility of DG ENTR and DG ENV. All regulatory approaches are based on clear distinction of risk assessment versus risk management, as follows:

[33] See definition in Regulation (EC) No 1831/2003 of the European Parliament and of the Council of 22 September 2003 on additives for use in animal nutrition

**Table 5 Distribution of responsibilities**

| European Legislations | Risk assessment responsible | Drafting of opinion (supporting decision) | Risk management responsible |
|---|---|---|---|
| REACH registration | Not applicable | ECHA | DG ENTR / DG ENV |
| REACH authorisation | ECHA | ECHA | DG ENTR / DG ENV |
| PPP | EFSA | EFSA | DG SANCO |
| BPR | ECHA | ECHA | DG ENV |
| CoP | DG SANCO | | DG SANCO |
| FoA | EFSA | EFSA | DG SANCO |
| FeA | EFSA | EFSA | DG SANCO |

*Source: Compiled by Arcadia International*

The EU legal procedures related to placing materials on the market engaged two specific EU bodies, authority in charge of the risk assessment (the risk assessor) and the body in charge of delivering the authorisation (the risk manager). Regulatory processes require the adoption of a scientific opinion by a risk assessor (EFSA or ECHA) that will be the scientific basis for the adoption of an EU authorisation by the risk manager.

This implies that the authority in charge of risk assessment acts as the sole responsible for the adoption of a scientific opinion (independence of risk assessment from risk management). This split of responsibilities between risk assessment and risk management has been identified in each regulatory framework studied.

In the specific area of pesticides (PPP and BPR), the authorisation procedure is partly decentralised and Member States play a major role in the preliminary scientific assessment of applications for authorisation. In these cases, applications for new active substances are being filed at MS level (rapporteur Member State, "RMS") which is performing the first evaluation of the data package submitted by the applicant and EFSA is performing a peer-review of the RMS before providing conclusions to the risk manager.

ECHA is fully dedicated to REACH and biocides regulatory processes (and Prior Information Consent-PIC Regulation[34] as well). EFSA performs scientific assessment of applications[35] submitted by applicants that want to obtain an authorisation to put a regulated product on the market.

[34] Regulation (EC) No 689/2008 Publication made in accordance with Article 23 of Regulation (EC) No 689/2008 of the European Parliament and of the Council of 17 June 2008 concerning the export and import of dangerous chemicals

[35] The sectors interested by authorisation applications to EFSA are the following 19:

1. Plant Protection Products: active substances (PPP)
2. Maximum Residues Levels (MRL[35] ) of PPP
3. Genetically Modified Organisms (GMO)
4. Flavourings
5. Smoke flavourings
6. Extraction solvents
7. Food enzymes
8. Food contact materials
9. Food additives
10. Nutrient sources

Under the REACH authorisation process of substances of very high concern (SVHC) (annex XIV of REACH) that may cause some risks, a complete risk assessment is performed by ECHA that delivers an opinion and the regulatory committee of the Commission adopt a decision which is being published in the Official Journal of the EU.

All EU authorities for risk assessment and risk management are supported by experts' panels and standing committees, respectively.

**Table 6 Support to EU authorities in charge of risk assessment and risk management**

| European Legislations | Expert groups | Committees |
|---|---|---|
| REACH | Not applicable | Regulatory Committee of Commission |
| REACH authorisation | • Risk Assessment Committee (ECHA-RAC)<br>• Socio-Economic Analysis Committee (ECHA-SEAC)[36] | |
| PPP | EFSA - PPR[37] Panel | DG SANCO – Standing Committee (incl. MS representatives |
| BPR | ECHA - Biocidal products committee-BPC | DG ENV - Regulatory Committee |
| CoP | DG SANCO - Scientific Committee on Consumer Safety ("SCCS") | DG SANCO – Standing Committee (incl. MS representatives |
| FoA | EFSA-ANS[38] panel | DG SANCO – Standing Committee (incl. MS representatives |
| FeA | EFSA-FEEDAP[39] panel | DG SANCO – Standing Committee (incl. MS representatives |

11. Feed additives
12. Transmissible Spongiform Encephalopathy (TSE) tests
13. Animal by-products
14. Antimicrobial treatments
15. Health claims
16. Novel foods
17. Infant formulae
19. Food allergies (exemption from labelling)

[36] The ECHA-SEAC Committee is in support of ECHA in formulating an opinion and is considering socio-economic criteria therefore this Committee could also be considered as part of Risk Management. ECHA calls this activity: technical risk management. In some other areas where socio-economic committees exits (e.g. GMO in the NL-COGEM or in France–HCB they are placed under RA bodies)

[37] The Panel on Plant Protection Products and their Residues

[38] The Panel on Food Additives and Nutrient Sources Added to Food

[39] The Panel on Additives and Products or Substances used in Animal Feed

#### 2.4.1.2 Structure of the legislations

The structure of the legislations analysed in this study and the way they have been defined are based on two different approaches:

- For all legislations under the responsibility of DG SANCO and DG ENV, the structural approach is based on the use of products/substances. Regulation are first organised per intended use regardless of the nature of the product. Each regulatory framework (PPP, BPR, FoA, FeA, CoP, etc….) includes a sub-categorisation of products/substances for which individual requirements for registration purposes may be asked. For example the PPP Regulation segments the active substances in 17 categories (insecticides, fungicides, etc…). The Feed Additives Regulation is composed of six different categories of use. This sub-categorisation has been designed in a flexible manner that allows modifications and re-organisation if/when required to adapt to scientific progress and the registration of new types of products.

  These legislations are based on a clear Risk Assessment and Risk Management approach in which the two activities are clearly separated and performed by different bodies.. In the majority of cases the products/substances are only placed on the market after a scientific review/analysis of the possible adverse effects of the product to food and human safety and to the environment (pre-market approval). Most commonly a risk assessment is mandatory. An exception to this approach is observed under the Cosmetic Regulation for which the authority in charge of risk assessment[40] is under the authority of DG SANCO and is not included in any of the independent EU agency.

- In the single case of REACH under the co-responsibility of DG ENTR and DG ENV a registration and authorisation procedures coexist. As the large majority of chemical substances are already marketed, a registration approach has been set-up in order to draw up an inventory of individual substances covered by the Regulation. For the most risky substances (e.g. SVHC) (based on their CLP classification)[41] an authorisation process applies during which a complete safety assessment is performed. Restrictions of use of these more risky substances can apply.

This concept of risk assessment (RA)/risk management (RM) is only about 15-20 years old. In 1997, the Commission Communication on Consumer Health and Food Safety[42] stressed the importance attached to securing the food safety and health of consumers. The risk assessment approach forms the foundation of scientific advice with regard to consumer health. Scientific risk assessment offers the regulator a sound basis for proposals and measures in the field of consumer health and food safety.

There is at present a general agreement that risk assessment is best addressed in four stages, i.e. hazard identification, hazard characterisation, exposure assessment and risk characterisation. These four stages are key common elements between all regulatory processes under analysis even if this classification is not always fully visible in the individual risk assessment guidance documents. Differences have been identified in the way risk assessments are

[40] Scientific Committee on Consumer Safety ("SCCS")
[41] Detailed information available at http://echa.europa.eu/regulations/reach/authorisation/applications-for-authorisation/authorisation-process
[42] Commission communication COM (97)183, 30 April 1997

conducted by the different Scientific Committees and Panels. The observed differences may, to a certain extent, be explained by a series of factors such as the specific characteristics of the technological sector, the availability of information and data, or by historical, administrative, legislative or regulatory requirements which, in a number of cases, impose constraints on how the risk from a particular factor should be assessed. These factors impacts on the use of specific methodologies which may range in sophistication from basic algorithms to use of mathematical modelling and detailed prescribed procedures.

This approach leads to the situation that the same product/substance/item will have to be registered independently via several regulatory frameworks if the business operator wishes to market it for several purposes. For example the benzoic acid substance is registered in several fields on the basis of individual sectorial authorisation/registration processes relying on the use claimed by the business operator. If the business operator claims to use the product/substance as a PPP, then it has to prepare an application for PPP, if it wants to market the same substance/product as a biocides, it will have to submit a separate application to the biocides registration authorities.

Whilst in most cases it is rather simple to identify the regulatory framework to be followed, there are situations where the framework to be applied for placing products on the market is not that obvious. These situations have been described for the cosmetic Regulation where "borderline situations" have been described between cosmetics and toys, cosmetics and biocides, cosmetics and pharmaceutical products, and cosmetics and medical devices. In these cases specific guidance documents have been developed to help applicants in defining which regulatory route should be followed.

These borderline situations are considered by the majority of the regulatory frameworks under analysis (see Table 7). In most cases, provisions on "dual use" are intended to address the case of products/substances which have a dual function, such as for instance biocidal products, which are used as both plant protection products and biocidal products.

**Table 7 Regulatory provisions related to dual use and borderline products**

| Regulatory framework | Provision |
|---|---|
| ***European legislations*** | |
| REACH registration | Not applicable: REACH excludes from its scope, substances already covered by the PPP and BPR regulations for respectively PPP and BPR uses only. |
| REACH authorisation | |
| PPP | Dual use provisions |
| BPR | Dual use provisions |
| CoP | Border line provisions |
| FoA | Dual use provisions |
| FeA | Dual use provisions |

*Source: compiled by Arcadia International*

For each case, detailed guidance on the interpretation of the provisions exist to allow applicants to clarify their approach to registration.

As mentioned above, most of the regulatory frameworks under analysis have an approach based on the "*use of the product/substance*". Union authorisations

granted under sectorial EU regulatory frameworks will, in principle, be valid in all Member States subject to the same terms and conditions. For regulatory frameworks where the commercial product is registered at MS level (BPR and PPP[43]), there is no common understanding related to the "usage" of products. The way to define the uses typology is not harmonised at EU level leading to possible issues when addressing the placing to the market of commercial products via mutual recognition or the zonal authorisation for PPPs. Harmonisation work is ongoing in the PPP field (the European and Mediterranean Plant Protection Organization-EPPO has initiated some work leading to the development of comparative tables of use) and a recent technical guideline has been developed for BPR products[44].

### 2.4.2 Types of authorisation granted

Risk managers grant two different types of authorisation:

- **Generic authorisation** applies when the sectorial legislation foresees the granting of a generic authorisation meaning that all operators can use/produce/market the regulated product/ingredient/item/substance independently of who submitted the (first) application ;
- **Holder authorisation** is granted in cases the legislation provides for an individual authorisation granted to a specific authorisation holder. This means that the applicant submitting the application is the single one that can produce/market the regulated product under the authorisation for which it applied.

**Table 8 Type of authorisation issued by legislative sector**

| Legislation | Generic authorisation | Holder authorisation |
|---|---|---|
| ***European legislations*** | | |
| REACH | | X |
| PPP | | X |
| BPR | | X |
| CoP | X | |
| FoA | X | |
| FeA (partly, < 20%) | | X |
| FeA (majority), >80%) | X | |
| ***Other legislations (source: EFSA)*** | | |
| GMO | | X |
| TSE tests | | X |
| Smoke Flavourings | | X |
| Recycling Plastic Processes | | X |
| Novel Foods | | X |
| Flavourings | X | |
| Extraction Solvents | X | |
| Food Contact Materials | X | |
| Animal by products | X | |
| Antimicrobial treatments | X | |

[43] Via zonal authorisation

[44] Note for Guidance on the Definition of Similar Conditions of Use across the Union CA-Feb13-Doc.5.1.e - Final

| | | |
|---|---|---|
| Health Claims | X | |
| Enzymes | X | |
| Nutrient sources | X | |
| Food Allergies (exemption from labelling) | X | |

*Source: Compiled by Arcadia and Commission working document*[45]

For the EU sector of feed additives the legislation foresees generic authorisations for most of the categories[46], but individual authorisations called "*brand specific authorisation – BSA*" are delivered for 3 categories of feed additives (zootechnics, coccidiostats and histomonostats, representing roughly 14.5%[47] of the applications/authorisations). It seems that this segmentation is the result of a compromise between the regulator and the industry. The regulator wanted to have generic authorisation only, when business operators (additives producers) favoured a holder authorisation approach.

The latest EFSA annual reports mention that about 58% of the sectors applying to EFSA for the scientific evaluation of regulated products deliver a generic authorisation leading to the conclusion that there is about a 50/50 ratio between regulatory frameworks delivering generic authorisations and holder authorisations. Safety of products deriving from generic and holder authorisation is ensured by using similar schemes adapted to the nature of the product to the exception that for generic authorisation, any company can placed products on the market when for holder authorisation, only companies that have access to data can place products to market.

### 2.4.3 What has to be authorised?

The different sectorial regulatory frameworks under analysis define several terms as the basis of the registration process. While the definitions of these terms are rather homogeneous across regulatory frameworks, each of these frameworks is based on a specific approach.

The main terms defining item(s) to be authorised are the followings:

- Substance or active substance;
- Material;
- Source material;
- Product;
- Commercial product;
- Preparation;
- Mixture;
- Compound, premixture;
- Article (specific to cosmetic products).

[45] Commission staff working document: Impact Assessment on the Revision of Regulation 178/2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority (EFSA) and laying down procedures in matters of food safety on the establishment of fees for EFSA - SWD(2013) 45 final

[46] Substances belonging to the following categories of additives "technological additives", "sensory additives" and "nutritional additives".

[47] Historical SANCO data.

**Table 9 Scope definition of the various sectorial legislations under analysis**

| Regulatory framework | Registration item |
|---|---|
| REACH registration<br>REACH authorisation | **"substance"** means a chemical element and its compounds in the natural state or obtained by any manufacturing process, including any additive necessary to preserve its stability and any impurity deriving from the process used, but excluding any solvent which may be separated without affecting the stability of the substance or changing its composition.<br>**"preparation"** means a mixture or solution composed of two or more substances.<br>"**article"** means an object which during production is being a special shape, surface or design which determines its function to a greater degree than does its chemical composition. |
| PPP | "**substance"** means chemical elements and their compounds, as they occur naturally or by manufacture, including any impurity inevitably resulting from the manufacturing process.<br>"**preparations**" means mixtures or solutions composed of two or more substances intended for use as a plant protection product or as an adjuvant. |
| BPR | **"biocidal product"** means 1) any substance or mixture, in the form in which it is supplied to the user, consisting of, containing or generating one or more active substances, with the intention of destroying, deterring, rendering harmless, preventing the action of, or otherwise exerting a controlling effect on, any harmful organism by any means other than mere physical or mechanical action Border line provisions or 2) any substance or mixture, generated from substances or mixtures which do not themselves fall under the first indent, to be used with the intention of destroying, deterring, rendering harmless, preventing the action of, or otherwise exerting a controlling effect on, any harmful organism by any means other than mere physical or mechanical action.<br>A treated article that has a primary biocidal function shall be considered a biocidal product.<br>**"active substance"** means a substance or a micro-organism that has an action on or against harmful organisms.<br>BPR Regulation defines 17 Product types (see annex of Regulation). |
| CoP | "**cosmetic product"** means any substance or mixture.<br>"**substance**" means a chemical element and its compounds in the natural state or obtained by any manufacturing process, including any additive necessary to preserve its stability and any impurity deriving from the process used but excluding any solvent which may be separated without affecting the stability of the substance or changing its composition;<br>"**mixture**" means a mixture or solution composed of two or more substances; |

| Regulatory framework | Registration item |
|---|---|
| FoA | "**Food additives**" means any substance not normally considered as a food in itself and not normally used as a characteristic, ingredient of food, whether or not it has a nutritive value.<br>**"Substances"** is not further defined in the basic legislation |
| FeA | "**feed additives**" mean substances, micro-organisms or preparations, other than feed material and premixtures, which are intentionally added to feed or water in order to perform, in particular, one or more of the functions mentioned in Article 5(3);<br>"**premixtures"** means mixtures of feed additives or mixtures of one or more feed additives with feed materials or water used as carriers, not intended for direct feeding to animals |

*Source: compiled by Arcadia International*

All legislations provisions are based on the registration of fully characterised products/substances/materials. These legislations have initially been established for the registration of chemical items for which the molecular characterisation was established (synthesized substances). During the last two decades, several alternative types of products with different origins and not fully characterised have emerged, such as plant extracts substances referred to as botanicals in the PPP Regulation.

The draft guidance documents on PPP botanicals clearly summarise the situation as follows:

> *"Synthesized chemicals are based on chemical reactions whereas oils and extracts are manufactured by physically processing material of biological origin. The significant difference between botanical active substances and synthetic chemicals is the composition or specification. Synthetic chemicals can be produced in standardised processes resulting in repeatable purity ranges. The composition of a botanical active substance, however depends on the material of biological origin, the manufacturing process(es) and may depend on further processing. Therefore, botanical active substances have a larger variation in the qualitative and quantitative composition than synthetic chemicals.*
>
> *The production of substances of (living) biological origin depends on the climatic conditions, e.g. time of sunshine, rain, soil etc. and differs each year. Therefore, the nature and concentrations of substances vary naturally and affect the quantitative and qualitative composition of the extract/oil produced from the biological material.*
>
> *In addition, the way of processing the botanical active substance has an impact on the composition of extracted material which varies depending on the technique applied, e.g. cold-pressing, water-steam-distillation, extraction with (organic) solvents or a combination of several steps but always resulting in a complex mixture of several components. As a result of this, a botanical active substance of the same biological origin could have different compositions. Therefore, certain physical parameters could be regarded as important for clarifying the identity of a botanical active substance."*

#### 2.4.3.1 Who are the applicants?

In the large majority of cases that have been studied, applicants are individual private business operators only. However in the case of food additives applicants can also be private bodies such as trade or other type of associations as well as Competent authorities (CA) from Member States. Individuals can also apply.

For food additives and for REACH, the applicant can take the legal form of a consortia composed of several private or a mixture of public and private actors in the case of food additives. The applicant is then the consortium. All members of the consortium are allowed to market the product for which the consortium was built in case of successful registration.

**Table 10 Type of applicants per sectorial legislation**

| Legislation | Who may apply for an authorisation as defined in the sectorial Regulation |
|---|---|
| ***European legislations*** | |
| REACH | Any legal person established in the Community |
| PPP | 1. The producer of an active substance<br>2. An association of producers |
| BPR | 1. The producer of an active substance<br>2. An association of producers |
| CoP | Any legal person established in the Community |
| FoA | 1. MS<br>2. Interested parties<br>a) Collectively<br>b) Individually<br>3 COM may ask EFSA on its own initiative |
| FeA | Any person established in the Community acting as the responsible for placing the product on the market |
| ***Other legislations (source: EFSA)*** | |
| GMO | Any person established in the Community |
| MRLs for PPP and Biocides | 1. The party who requested from a MS the authorisation for the use of PPP<br>2. All parties demonstrating a legitimate interest in health<br>3. Manufacturers, growers, importers and producers<br>4. MS |
| TSE | 1. Any natural or legal person, public or private body established within the EU<br>2. public or private body established within the EU |
| Smoke Flavourings | Not specified |
| Recycling Plastic Processes | Any person established in the Community |
| Novel Foods | "*The person responsible for placing the product on the EU market*" |
| Flavourings | 1. MS<br>2. Interested parties<br>a) Individually<br>b) Collectively<br>3. COM may ask EFSA on its own initiative |
| Extraction Solvents | Not specified |
| Food contact Materials | Anyone |

| Legislation | Who may apply for an authorisation as defined in the sectorial Regulation |
|---|---|
| Animal by products | 1. COM<br>2. MS (following an application)<br>3. Interested party which may represent several interested parties |
| Antimicrobial treatments | Not specified |
| Health Claims | Food Operators |
| Enzymes | 1. MS<br>2. Interested parties<br>a) Individually<br>b) Collectively<br>3. COM may ask EFSA on its own initiative |
| Nutrient sources | Not specified |
| Food Allergies (exemption from labelling) | Not specified |

*Source: compiled by Arcadia International*

### 2.4.4 The regulatory process and timing

This process is in most cases specified within the relevant legislation. The workflow for authorisations linked to the different sectors are heterogeneous and involve different sharing of work and responsibilities among EU and national staff, EU risk assessors (EFSA or ECHA), Scientific Committee/Panels, Member States and the European Union Reference Laboratories (EURL).

In most cases, the legislation provides for a detailed authorisation procedure including the procedural steps related to the risk assessment and risk management. The following common step procedure applies in the large majority of cases:

- *Step 1:* **Reception of the application dossier** by the European Commission, the risk assessor (EFSA or ECHA), or one MS. In certain cases, applications have to be submitted to the risk assessor directly (e.g. under REACH, FeA); in other cases the application is sent to the European Commission that forwards it to the corresponding authority in charge of risk assessment (e.g. FoA). In a limited number of sectors (plant protection products), the procedure is de-centralised and involves a preliminary scientific assessment by a designated Member State risk assessment agency.
- *Step 2:* **Completeness check/compliance check/validation of the dossier** is generally performed within a given period (about 30 working days) from the date of receipt of the application. This step involves a review of the dossier to check whether or not it includes all necessary information and documentation as prescribed by legislation.

  In case a dossier is considered not complete, the authority may contact and inform the applicant. The authority in charge of the completeness check may request the applicant to submit the missing or incomplete parts of the application dossier in order to fulfill the conditions of validity or may reject the dossier in the current form. The deadline for submitting the missing information is usually about 30 working days. However, this deadline can be extended upon request by the applicant.

A dossier is considered complete, and therefore the application considered valid, when it fulfills the requirements laid down in implementing regulations and further detailed in guidance documents.

Once a dossier is considered complete, a statement of validity is sent to the applicant. The date of validity is the starting point for the scientific assessment of the dossier. In the majority of cases, the risk assessor make all information supplied by the applicant available to the risk manager and other bodies whenever required (MS, EURL for analytical methods, etc…) via electronic means (secured and confidential intranets).

Under REACH the completeness check is performed by electronic means. An IT system (IUCLID) has been developed to automatically perform the completeness check. This completeness check does not go into details to verify whether or not the dossier contains all required information. Therefore a compliance check is performed on a limited number of registration dossiers (objective of 5% of the total number of registration dossiers). This compliance check has the objective of checking into details whether or not all required information is included in the dossier. It is obviously more than an administrative control, as a first look on the quality of the data is performed to verify whether or not enough information is provided to perform the evaluation of the dossier. It is however not yet a scientific/risk assessment. This compliance check is performed by staff experts.

- *Step 3:* **Scientific evaluation of the dossier by the competent scientific committee or panel** that the product/substance/ingredient meets the scientific requirements to allow its authorisation/registration/placing on the market. This scientific evaluation can take various forms and is generally performed at MS level or at EU level. However, depending on the sector, the scientific evaluation process foresees different sharing of work and responsibilities between RA's staff, RA's Panels, Member States and the EURL. Particular cases are, for instance, plant protection and biocides products where a Rapporteur MS carries out a preliminary risk assessment on active substances and in a second stage EFSA carries out a peer review. Timing for performing the scientific evaluation is always specified by legislations and ranges from 6 to 9 months.

  During this process, the risk assessor may request the applicant to submit supplementary information. In that case, the deadline may be extended at the request of the applicant. The risk assessor decides on the acceptability of the extension requested based on justification given by the applicant and the nature of data requested. In other specific cases (e.g. PPP, MRLs, GMOs), the regulation does not stipulate to set deadlines for submitting missing data. In these cases, the request for additional information will *"stop the clock"* regarding the time limit assigned to the risk assessor. After the missing information has been submitted by the applicant the risk assessor has to incorporate it in a new revision of the evaluation report. The clock will be started again when the evaluation report is revised and completed with the additional information. This procedure can take place several times for the same dossier.

- *Step 4:* **Adoption of a scientific opinion by the competent body.** After its adoption by the Committee in charge of the risk assessment, the opinion/conclusion is checked for editorial review and confidentiality following the request for confidentiality by the applicant. The

opinion/conclusion is commonly published within a given period from the date of adoption.

- *Step 5:* **Submission of this opinion/decision to the Risk Manager** that takes the final decision of granting or not granting the authorisation to the applicant. Within a given period mentioned in the legislation (about 3 months) of receipt of the opinion decision of the risk assessment authority, the risk manager (the Commission) shall prepare a draft proposal/regulation to grant or deny authorisation. When the draft is not in accordance with the opinion of the risk assessor, it has to provide an explanation of the reasons for differences. In exceptionally complex cases, the deadline may be extended. In the majority of cases, the Commission is assisted by representatives in the Standing Committees where all MS competent authorities are represented and where the decision of granting an authorisation or not is taken.
- *Step 6:* **Publication of the granting of authorisation in EU** (and/or national) official journal (refusals are not published on the OJ but in the standing committee's minutes which are available on the dedicated Commission websites and distributed to NCAs that are in charge of forwarding the decision to dedicated bodies (e.g. control bodies).

**This procedure applies in all cases when a pre-market approval is required. Steps 3 to 5 do not apply in case of procedure based on notifications** (e.g. REACH registration).

Under REACH the completeness check process comprises two distinct sub-processes:

- Technical completeness check: This process is aimed at checking the technical completeness of the dossier. The main purpose is to make sure that all required information has been provided. After being accepted for processing, each received dossier is screened for technical completeness using a specially created algorithm specific for each type of dossier, depending on the legal requirements. The system checks whether all required fields are filled and all testing proposals, derogation statements, waving statements etc. are included. In the case of a negative result, ECHA will verify the outcome of the completeness check to make sure that the decision is fully correct.
- Financial completeness check: ECHA monitors the payment of the fee as specified in the invoice and consider the dossier to be complete only once the fees have been paid by the applicant.

Once the registration is complete, the REACH IT system at ECHA automatically assigns a registration number to the registrant for the substance concerned and a registration date that will be the same as the submission date "retroactively". Without delay ECHA communicates the registration number and date to the concerned registrant(s). From that moment onwards the registrant(s) shall use the registration number for the subsequent correspondence regarding registration procedures. Marketing authorisation of the product under REACH is granted.

The registrant(s) may have to update his(their) registration as a consequence of an ECHA or a Commission decision under the evaluation procedure.

There are two main types of evaluation procedures, a substance evaluation and a dossier evaluation. The latter is further subdivided into an examination of any testing proposal and a compliance check of the registration dossier.

Compliance checks evaluate the substance identity description and the safety information in the dossier including the chemical safety report or specific parts of the dossier, for example the information related to the protection of human health.

In the targeted compliance checks, ECHA evaluates only a specific part of the registration dossier (e.g. either specific endpoints in IUCLID or in the chemical safety report (CSR)) based on a specified concern. This allows ECHA to target endpoints which are identified as relevant for the safe use of substances. Rather than evaluating the full dossier content at once, a part of the compliance checks will address targeted endpoints related to, for example, the persistent, bioaccumulative and toxic (PBT) or carcinogenic, mutagenic or toxic to reproduction (CMR) status of a substance.

ECHA may identify shortcomings that are not necessarily related to a lack of information. For example, the risk management measures proposed by the registrant may be inadequate or the proposed classification and labelling may not reflect the reported study results. In these cases, ECHA sends a quality observation letter and invite the registrant to update the dossier. A quality observation letter may also be sent to clarify certain aspects of the dossier. ECHA informs Member States about these letters and on the response of the registrants. If the registrant does not clarify the issue, the Member States may initiate some processes, for example a proposal for harmonised classification and labelling.

Following the compliance check, ECHA may conclude that additional testing or other information is required. In these cases, it prepares a draft decision to be sent to the registrant for comments. Based on the comments, the draft decision may be modified accordingly. The draft decision is sent to the Member States which can propose amendments to it. If any amendments are proposed, the issue is referred to the Member State Committee. All draft decisions made by the ECHA must be unanimously supported by the Member States and will only then become legally binding. The agency may combine issuing a draft decision by sending a quality observation letter. As a result of the targeted compliance check, registrants may receive multiple compliance check decisions to request additional information on the same dossier if it is found non-compliant for more than one information requirement.

### 2.4.5 Data protection

All the regulatory frameworks analysed as part of this study provide data protection provisions. Data protection duration varies across regulatory frameworks according to whether the data is in support of active substances or commercial products, whether the active substances are considered to be "*existing*" or "*new*" and the reason for submission.

Based on specific sectorial provisions duration of data protection varies between 5 to 15 years.

Data protection is not a *de facto acquis*. Whilst under the REACH Regulation, data protection is provided quite automatically whenever a number of conditions are met, the situation is quite different in other regulatory frameworks.

For example in the PPP Regulation (EC) No 1107/2009 the applicant should annotate the listing of individual tests and study reports to indicate whether or not data protection is claimed (Article 59). Due to the fact that data protection claims are related to product authorisations a claim for data protection cannot be done at EU-level at the time of approval of the active substance. However, according to Article 7(4) "*when submitting the application the applicant shall at the same time join……a list of any claims for data protection pursuant to Article 59*."

### 2.4.6 Confidentiality

Confidentiality is the non-disclosure of information which must be actively invoked and substantiated by the concerned party. It is the responsibility of the applicant to identify at the stage of application the section of the registration dossier it wants to keep confidential. Both EFSA and ECHA recommend applicants to keep this confidential part as short as possible. The legal framework for EFSA and ECHA often provides for transparency rules in combination with confidentiality rules. The balance between transparency and confidentiality rules is determined by the approach that the maximum amount of information linked to agencies' activities is to be disclosed or made accessible to the public and that only the essential minimum shall be kept confidential. Any decision against disclosure needs to be based on a rule of law that grants confidentiality to specific information. Only those parts which are justified as confidential may be retained. It should be stressed that several regulations give the European Commission the exclusive competence to accept/reject confidentiality claims of third parties. In these cases agencies are bound by the outcome of such decisions by the European Commission.

Possible justifications for confidentiality include[48]:

- Commercial interests of a natural or legal person, including intellectual property;
- Serious harm to the decision-making processes;
- Protection of privacy and the integrity of the individual.

The confidentiality level is maintained throughout agencies´ operations by ensuring that all individuals involved in these operations have committed themselves to confidentiality undertakings. Therefore, members of the Scientific Committee and Panels, their working groups and all agencies staff sign an individual declaration concerning confidentiality.

### 2.4.7 Data requirements

The analysis of the data requirements sections of the guidance documents of the various regulatory frameworks considered during the study shows a rather high level of consistency. Even if data requirements are sectorial regulation specific, all these guidance documents are structured on the same general format and the following test areas can be identified in nearly all regulatory frameworks based on safety assessment before authorisation (not the one based on a notification approach):

- Identity and biological properties;

[48] See details in report "Transparency in risk assessment carried out by EFSA: Guidance Document on procedural aspects" [May 2006][Updated June 2006] available at http://bookshop.europa.eu/en/transparency-in-risk-assessment-carried-out-by-efsa-pbTM3112250/

- Function, mode of action, and handling;
- Physico-chemical properties;
- Manufacturing, quality control, and analytical methods;
- Residues;
- Efficacy;
- Toxicology, pathogenicity, and infectivity;
- Ecotoxicology; and
- Environmental fate

Furthermore, when risks are identified and mitigation measures need to be proposed, most of regulatory frameworks require considering the "conditions of use" in the evaluation. "Condition of use" includes several criteria e.g. dosages, timing, targets, optimal conditions, restriction, etc…

Specific major data requirements are substantiated below.

#### *2.4.7.1 Characterisation, composition, specifications, stability & homogeneity*

Each of the regulatory frameworks under analysis has developed guidance documents to allow the registration of non-fully characterised products. All these guidance documents present a quite similar approach:

- *Step 1:* Applicants present substances on the basis of their chemical characterisation and provide their reference number (e.g. CAS number). In the case of products, the detailed and complete formulation is presented and the active substance(s) identified. Multiple information has to be provided (see Excel database available with this report). OECD guidance documents have been set up and are available to present the required information[49].
- *Step 2:* In case the chemical characterisation cannot be provided, the applicant is required to describe its substance/product on the basis of one or several markers.

> *For example the characterisation of the cloves oil PPP active substance is established on the basis of the presence of a minima 60% of Eugenol (its main components). The other components are not defined.*
>
> *The fenugrec seed powder formely coded FEN560 has been listed as an active substance in the PPP Regulation 1107/2009. Its identity is defined as follows:*
>
> *Chemical name (IUPAC): None. The active substance is prepared from the seed powder of fenugreek (Trigonella foenum graecum L.), a leguminous plant. This product is a complex mixture of chemical substances.*
>
> *Minimum purity of the active substance as manufactured: 100 % fenugreek seed powder without any additive and no extraction; the seed being of human food grade quality.*
>
> *Three representative markers: trigonelline; 4-hydroxyleucine ; total proteins* [50]

Chapter 4 of ECHA's Guidance for identification and naming of substances under REACH provides a number of useful recommendations for substances of unknown or variable composition, complex reaction products or biological materials (UVCBs). Characterisation can be based

[49] OECD guidelines for the testing of chemicals – Section 1: Physical-chemical properties. Available at: http://www.oecd-ilibrary.org/environment/oecd-guidelines-for-the-testing-of-chemicals-section-1-physical-chemical-properties_20745753

[50] Source: Conclusions on pesticide peer review available on EFSA website

on the use of analytical methods (mainly chromatography and spectroscopy techniques) that are useful for generating useful data. For UVCBs substances the following key points are made:

- For cases where spectral data provide information on the composition of the UVCB substance, such information should be supplied;
- Chromatographic and spectral images that show a characteristic peak distribution pattern (i.e. fingerprints) can be used;
- Valid constituent separation techniques might be used where appropriate;
- The chemical composition and identity of the constituents should still be given if available. Information on chemical composition can be given on the basis of well-known reference samples and standards;
- "*It is the responsibility of the registrant to present appropriate spectral data*".

*In the case of the fenugrec seed powder, the following analytical techniques have been used:*

*For the trigonelline marker: HPLC method with UV detection (265 nm). The principle of the method is a reverse phase chromatography (water (pH 3)/Methanol; 50/50; v/v) with a LiCrirosorb SI 60-5 column (250 x 4.6 mm, 5 µm). A standard of trigonelline (batch number CGCR1-03) was used as external standard.*

*For the total proteins marker: The analytical method was based on the Bradford protein assay. The reference item was albumine. The Bradford protein assay is a dye-binding assay based on the differential colour change of a dye in response to a concentration of a given protein.*

*For the 4-hydroxyleucine marker: An analytical method using HPLC with visible detector (463 nm) was developed to quantify 4-hydroxyisoleucine in fenugreek seed powder. The principle of the method is a reverse phase chromatography (ammonium acetate 0.02 M in water/acetonitrile; 70/30; v/v) with a LC-18 column (250 x 4.6 mm, 5 µm). A standard of 4 – hydroxyisoleucine was used as external standard.*

- *Step 3:* The identification and use of a marker is not possible when the raw material being used varies considerably in its composition. In these cases, applicants are required to provide the complete list of raw materials and the percentage of each one used during manufacturing.

  This lack of complete characterisation particularly happens for plants extracts as plant quality varies from crop to crop. Agronomic practices used in cultivating the source botanical material may influence the quality of the botanical active substance: sufficient information on method of cultivation should be provided and participate to the definition of the technical grade. As the botanical raw material may be from more than one source, all these sources should be adequately described including geographical origin(s) of material used, region(s), country(ies), area/site(s) of cultivation.

  The manufacturing process shall also be described and form part of the botanical active substance specifications. The following information is considered necessary for assessing the safety of plant extracts, including detailing quality assurance principles that are followed such as Hazard and Critical Control Points (HACCP):

- Information on the method(s) of manufacture (e.g. the process by which the raw material is converted into a technical grade, such as physical processes, extraction or other procedure(s).
- Information on substances entering the manufacturing process, e.g. identity of any extraction solvent, stabilisers e.g. antioxidants, special precautions (light, humidity and temperature).
- Details of any purification processes.
- Standardisation criteria (e.g. see European Pharmacopoeia).

With the exception of the CoP Regulation (see Annex II of Regulation (EC) No 1223/2009), all other analysed regulatory frameworks do not list prohibited substances/products/items.

Stability and homogeneity of the registered items have also to be demonstrated as follows:

**Table 11 Data requirements addressing stability and homogeneity of substances/products during registration processes**

| Legislation | Stability and homogeneity requirements |
|---|---|
| ***European legislations*** | |
| REACH | In the context of substance identification only |
| PPP | No specific guidance documents for synthesised products<br>Not specified in draft guidance documents for PPP botanicals |
| BPR | No specific guidance documents for synthesised products |
| CoP | **Homogeneity** of the test solutions with respect to the content of the test substance, under experimental conditions, should be provided.<br>The **stability** of the test substance under the experimental conditions of various studies should be reported. In addition, the stability of the test substance under storage conditions as well as in typical cosmetic formulations should also be provided. |
| FoA | Following information should be provided:<br>The **chemical/physico-chemical stability** of the food additive in its food additive preparation and under the conditions of storage and effect of storage temperature, environment [light, oxygen, moisture, relative humidity (water activity)] or any other factor that might influence the stability of the food additive preparation.<br>• The chemical/physico-chemical stability of the additive during storage of the processed food: e.g. effect of the nature of the food to which the substance is added, processing temperature, pH, water activity or any other factor.<br>• The nature and reactivity of any degradation products and nature of interaction/reaction of degradation products with food components.<br>• Technologically intended reactions with food constituents and the resulting products in food. |
| FeA | The **stability** of each formulation of the additive, on exposure to different environmental conditions (light, temperature, pH, moisture, oxygen and packing material) shall be studied. Expected shelf-life of the additive as marketed should be based on at least two model situations covering the likely range of use conditions (e.g., 25 °C, 60% relative air humidity (HR) and 40 °C, 75% HR) as required by (EC) No 429/2008. **Homogeneity** in feeds : The capacity for |

| Legislation | Stability and homogeneity requirements |
|---|---|
| | homogeneous distribution of the feed additive (other than flavouring compounds) in premixtures, feedingstuffs or water must be demonstrated as required by (EC) No 429/2008 |

*Source: compiled by Arcadia International*

#### *2.4.7.2 Human and environmental safety requirements*

As a preliminary remark it should be indicated that several limitations inherent in this type of analysis should be kept in mind when reviewing this section. This summary aims at providing a useful overview of data requirements but it cannot capture the complexity of all toxicological and ecotoxicological testing and the use of judgment that accompanies implementation of the data requirements. For both scientific and practical reasons, most regulatory frameworks exercise some flexibility in their acceptance of data and in their waiving of certain requirements in certain cases. This flexibility can be very large and in certain cases data waiving is largely used by applicants to reduce the costs of the application dossier.

This summary can hardly reflect the complexity and uncertainty of the situation. Therefore this presentation has been limited to some key characteristics of the data requirement schemes and we invite the reader to look at additional information in the Excel Database and in the sectorial guidance documents developed by regulators. The majority of the guidance documents have been integrated in the above mentioned Excel DB available with this report.

#### *2.4.7.3 Guidance in support to applicants*

Most of the regulators in charge of the analysed regulatory frameworks have developed guidances for applicants in support of the preparation of the application/registration dossier. These guidances tend to be quite prescriptive and include detailed information. It should be noticed that two different type of guidance document co-exist: guidances from the Commission which are legally binding and the ones by the executive agencies which do not have any legal dimension.

These guidance documents generally include references to the testing guidance documents, mainly OECD, to be respected. In general terms, it can be concluded that the various regulatory frameworks use the same OECD testing methods whenever available. For example acute toxicity has to be measured on a set of similar tests based on OECD guidances across regulatory frameworks. When providing technical reports/studies, other than the ones based on OECD guidance documents, the tests and analyses shall be conducted in accordance with the principles of Good laboratory Practice (GLP) laid down in Directive 2004/10/EC. However, studies referred to from available scientific literature do not need to abide by the GLP requirements.

The draft guidance document for the registration of plant extracts in the context of the PPP Regulation[51] specifies that the history of safe use of a plant extract/botanical in plant protection or for other purposes shall be adequately taken into account. This includes the use of information from "*peer reviewed*"

[51] SANCO/11470/2012– rev. 5 3 08 May 2013 Draft guidance document on botanical active substances used in Plant Protection Products.

open literature and from other reliable public sources. Data requirements to be fulfilled are discussed in a pre-submission meeting with evaluators of a competent authority.

The CoP guidance documents are the only ones that provide guidance to applicant for alternative to animal testing. The majority of the other guidance documents do not refer to the objective of reducing animal testing.

Guidance documents on the registration of non-synthesised products (PPP Botanicals, PPP basic substances) invite applicants to present safety judgements based on scientific literature in addition to test results. For these types of products, applicants are also encouraged to request a pre-submission consultation with the competent authority, particularly if they are not familiar with the regulatory system. The main objective of pre-submission meetings is to discuss the information requirements. Although the data requirements are laid down in legislative documents, applicants may need some guidance on how to interpret these data requirements and whether studies, published literature and/or a reasoned approach can be accepted. It is up to the applicant to submit the relevant information. EFSA (e.g. feed additives) and ECHA have established dedicated helpdesks which, among other tasks, provide advice and support to the processing of dossier submissions.

#### *2.4.7.4 Tier testing*

The following table shows whether regulators have chosen to use tier testing in their data requirements on a formal or case-by-case basis (where tier testing refers to the use of a stepped testing sequence, in which tests in higher tiers are required only if specified hazard levels were exceeded at earlier stages.)

As seen in the following table, tier approaches are used in some limited cases only.

**Table 12 Safety assessment based on tiered approaches**

| Legislation | Toxicology | Ecotoxicology |
|---|---|---|
| ***European legislations*** | | |
| REACH | No | No |
| PPP | No | No |
| PPP botanicals | Decision tree but not based on a tier approach | |
| BPR | Partly (see below) | No |
| CoP | No | Not applicable |
| FoA | The guidance describes a tiered approach which balances data requirements against the risk, taking into consideration animal welfare by adopting animal testing strategies in line with the 3-Rs (replacement, refinement, reduction)[52]. **This tiered approach for toxicological studies consists of 3 tiers**, for | Not applicable |

[52] See http://www.efsa.europa.eu/fr/efsajournal/pub/2760.htm

| Legislation | Toxicology | Ecotoxicology |
|---|---|---|
| | which the testing requirements, key issues and triggers are described. A minimal dataset applicable to all compounds has been developed under Tier 1, while Tier 2 testing, generating more extensive data, will be required for compounds which are absorbed by human and/or demonstrate (geno)toxicity in Tier 1 tests. Tier 3 should be performed on a case-by-case basis taking into consideration all the available data, to elucidate specific endpoints needing further investigation of findings in Tier 2 tests. | |
| FeA | No | **Yes** (2 tiers). First tier lists mandatory test to be performed based a decision tree approach. Threshold values for endpoints (PEC and PNEC) have been established to decide whether or not Tier 2 has to be performed. |

*Source: compiled by Arcadia International*

As an example of the possible tier approach, the tier approach for PBR could be required for e.g. mixtures. The possible tier options could be:

- Tier 0:
  - Mixture assessment necessary? (Product use, composition, suspected synergism?);
  - Possible additive effect of concern?
- Tier 1
  - Multiple Action Factor (MAF) (in case of low data availability, default value=10);
  - Predictable Environmental Concentration /predictable no-effect concentration (PEC/PNEC) summation (use of the most sensitive species for each compound);
  - Testing with the product/leakage
- Tier 2:
  - Concentration addition (single substance data based on the same test, same species and the same endpoint, same assessment factor; no need for full concentration-response curves at the first stage, possible to use the basis of only NOEC and EC50 values);
- Tier 3:
  - Grouping according mode of action(s) may prove difficult and potentially controversial;

- E.g. Independent Action (need for defining low-dose effects of the single compounds means high demand, costly, resource demanding).

This description has to be seen as one example in many. The Tier approach is adapted to individual requirements. The multiple guidances documents developed for each regulatory frameworks presents the different possible approaches.

#### *2.4.7.5 Data waiving and bridging*

The data requirements as listed in the various guidance documents shall be regarded as a minimum set by applicants. However there are situations where data requirements can be waived. In principle waiving practices are accepted in the large majority of cases and probably in all regulatory frameworks. The research team has not identified any restriction or prohibition in using these waivers.

Generally, waivers are considered when a data endpoint is not relevant to the chemical, such as not requiring an acute oral toxicity study when the chemical exists as a vapour or gas.

Valid reasons for not submitting a complete core data set fall into the following categories:

- The study is not technically possible to perform. In some cases the intrinsic physico-chemical properties of the substances or product are such that not all the core data sets can be performed (e.g. volatile or unstable substances) ;
- Other existing data can be used instead of required data (bridging – see below) Information on a substance/product may be derived in certain circumstances from other sources. For example, it may be possible to read across from existing data when different salts are being used with the same basic substance ;
- The study is not scientifically necessary. In some cases it is not justified to perform a study due to the intrinsic properties of the substance/product. For example if the water solubility of the product is less than 1 mg/l, surface water study does not need to be performed. In cases of no exposure, data may not be required.

All waivers and non-submission of data for a given requirement have to be fully justified and sufficient explanation and evidences shall be documented in the registration dossier. Arguments should be supported by reference to appropriate data and a full list of the references cited should be provided to risk assessors. Any literature cited to support a reasoned case should be summarised in sufficient detail to determine the validity of the arguments presented. If an applicant refers to any literature owned by another company which are not in the public domain, they will be required to demonstrate that they are entitled to make use of the data, for example, by submission of a letter of access.

Information on technical limitations detailed in test guidance documents should always be respected. For any data waiving, the onus is on the applicant to make the case for not generating new data. Applicants should base their case on scientific arguments or other information which demonstrates that the generation of new data is unnecessary. Applicants may wish to comment briefly

on the commercial implications, but such concerns should not form the main basis of the case and can be tackled through a confidentiality claim. Safety remains the core concerns of waiving procedures.

None of the guidance documents that have been analysed list a limit to the usage of waivers. If properly documented, any data requirement can be waived if the requirement is not clearly mandatory.

Bridging refers to the use of an existing data set to characterise the hazard for another chemical for which there is little or no existing data. Generally, bridging can be supported when data already exist and then data do not need to be generated in each case. This option is not clearly mentioned in any of the analysed guidance documents. Some references are made on the use of other results when technical equivalence between a substance/product and a proposed substance/product is established and approved by risk assessors. Specific guidance documents exist in most of the regulatory frameworks for establishing equivalence when addressing fully-characterised (synthesised) substances/products[53].

#### *2.4.7.6 Efficacy/utility: proof of the claim*

As described under Section 2.1, regulatory frameworks are being structured by and segmented per usage (sectorial regulations) with the exception of the REACH Regulation which considers the chemical nature of a compound as the pillar of the approach without considering efficacy.

Hence all sectorial regulations require that applicants demonstrate the efficacy and/or utility of the product/substance they want to commercialise.

Efficacy can be defined as the balance between positive effects - e.g. pest control for PPP, improved weight growth for FeA - and negative effects - e.g. direct crop damage, toxicity to targets, low tolerance level. As a net result, efficacy should be proven through an overall improvement in crop or animal production sufficient to justify the use of the substance/product.

As a general trend, the EU regulator requests that applicants provide an increasing amount of information to prove the efficacy/utility of the product. For example there was no detailed consideration of the efficacy of new active substances under Council Directive 91/414/EEC related to PPP. Assessments were conducted almost entirely at Member State level within the Annex III "*product*" package (commercial product). Regulation (EC) No 1107/2009 now includes requirements related to the efficacy of an active substance[54] as an active substance may only be approved if it shows to be "sufficiently effective".

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[53] Examples: Guidance document on the assessment of the equivalence of technical materials of substances regulated under Regulation (EC) No 1107/2009. See http://ec.europa.eu/food/plant/protection/evaluation/guidance/wrkdoc23_en.pdf
Guidance document under REACH for biocides: http://echa.europa.eu/documents/10162/15623299/guidance_applications_technical_equivalence_en.pdf

[54] Regulation (EC) No 1107/2009 Annex II point 3.2 states that '*an active substance alone or associated with a safener or synergist shall only be approved where it has been established for one or more representative uses that the plant protection product, consequent on application consistent with good plant protection practice and having regard to realistic conditions of use, is sufficiently effective regard to realistic conditions of use. This requirement shall be evaluated in accordance with the*

### 2.4.7.7 Analytical method

The provision of an analytical method is a key requirement in all analysed regulatory framework. A complete report on the development of the analytical method(s) should be documented in the registration dossier, as well as a description of the final method intended for use. The method should be practical for control purposes and applicable to the business sector for which the substance/product is intended. Details pertaining to the precision, accuracy, variability (reproducibility), and specificity of the method should be supplied.

Wherever possible, the method should be subjected to collaborative study, with data and information supplied on variations within and between laboratories. This is the objective of the European Union Reference Laboratories.

Among the regulatory frameworks under analysis, only the Feed Additives Regulation refers to an EURL. The EURL has to validate the method proposed by the applicant and becomes the official analytical method used by public and private operators. A reference sample has to be provided to the JRC-IRMM centre (Joint Research Centre – Institute for reference Materials and Measurements).

The question related to characterisation and analytical methods for non-fully defined substances is being discussed at international level. For example, the OECD organised a seminar in 2012 addressing analytical methods for botanicals to be used as PPP.

The report of this seminar[55] explains that "*plant extracts usually consist of a mixture of a wide range of chemical compounds. Natural extracts are very complex mixtures and can have huge variability. Therefore to characterise them, there is a need for: i) metabolomics approaches combined to bioassay leading to identification of biomarker or fingerprint, and ii) a bio-guided purification or semi-purification leading to the bioactive compounds identification.*

*The question was asked whether the bioactive compound could be identified from such techniques. It was indicated that it was possible to establish a biomarker, but it might not necessarily be the bioactive compound. It was suggested that the required analytical technique only gives a method for quality assurance. It was pointed out that regulators ideally need to have techniques that completely characterise the active substance so that its potential negative effects can be identified, not only in terms of efficacy but also regarding the effects on non-targeted crops or living organisms. It was indicated that biomarkers have been used for some compounds. It was also suggested that there was a need for a harmonised approach. Therefore, regulators and industry need to discuss what is needed and what is feasible*."

*uniform principles for evaluation and authorisation of plant protection products referred to in Article 29(6).*'

[55] Available at: http://www.oecd.org/env/ehs/pesticides-biocides/env-jm-mono-2012-36-core%20report.pdf

#### 2.4.7.8 Post authorisation requirements (monitoring, obligations related to quality control)

Requirements for post authorisation monitoring or surveillance actions are rather limited. However, the following requirements can be found:

**Table 13 Post-authorisation obligations**

| Legislation | Post authorisation obligations |
|---|---|
| REACH | **Authorities:** Once new scientific findings suggest so, consider re-assessing classification of substance and dossier update if applicable |
| PPP | **Authorisation holder:** In some cases the competent authorities of the MS of introduction may set in the authorisation certificate a condition for authorisation holders to conduct stewardship programs to monitor for instance the impact from the use of the product on groundwater. Such programmes are usually specified in the authorisation certificate issued by the competent authority and the results of such stewardship programmes should be communicated to the competent authority. Whenever there is an obligation in the authorisation of the reference product, such an obligation is applicable to the holders of parallel trade permits<br>**Authorities:** Monitoring actions on the impact of use of pesticides to be established (obligations from Framework Directive 2009/128/EC). |
| BPR | See as for PPP when it relates to authorisation holders.<br>In accordance with Article 18 of the BPR the Commission shall analyse how this Regulation contributes to a sustainable use of biocidal products and may propose to introduce monitoring monitoring actions by national authorities |
| CoP | **Authorities:** MS shall ensure that the competent authorities "*cooperate in areas where such cooperation is necessary to the smooth application of the Directive*". The area identified to bolster Member States administrative cooperation is market surveillance. Member States are responsible for the surveillance of their market. To that end, they should cooperate and exchange information, including information on serious undesirable effects attributable to the use of cosmetics.<br>The market surveillance authorities of all Member States established the Platform of European Market Surveillance Authorities for Cosmetics, PEMSAC. The aim of this network is, in particular, to facilitate cooperation by: coordinating activities, exchanging information, developing and implementing joint projects, exchanging expertise and best practices in the field of cosmetics market surveillance. The members of PEMSAC are the representatives of market surveillance authorities of all Member States. They meet twice a year in plenary and in two technical groups dealing with market surveillance and analytical methods. |
| FoA | **Authorities:** Data on the normal use level are available from the food industry or from post marketing surveillance by food enforcement authorities in Member States. In principle, a normal use level is the average level of the food additive determined in a number of samples being representative for the food consumption a given European Member State. It is likely that within the European Member States different levels of food additives are typically found for the same food category. If so, the maximum reported use levels within the European Member States, or if available sufficiently representative data on the reported use level, should be used for exposure estimation. In most |

| Legislation | Post authorisation obligations |
|---|---|
| | cases, normal use levels are expected to be lower than the maximum permitted use level in a food category. The Panel will not be able to conclude on the safety of a food additive if only *quantum satis* use is proposed since exposure estimates cannot be calculated in this case |
| FeA | In the case of substances that are recognised antibiotics and its use shown to select resistant bacterial strains, field studies to monitor for bacterial resistance to the additive have to be undertaken as part of postmarket monitoring. For coccidiostats and histomonostats, field monitoring of *Eimeria* spp. and *Histomonas meleagridis* resistance have to be undertaken. Marketing of products consisting of, containing or produced from GMOs also must include a proposal for post-market monitoring. |

*Source: compiled by Arcadia International*

### 2.4.8 Cost of registration

This section presents the results of the cost analysis aiming at evaluating the cost for registration of different existing EU and national regulatory frameworks.

The following cost items are considered:

- Fees for applicants ;
- Cost for applicants ;
- Cost for authorities, including risk assessment and risk management at both EU and MS level as applicable.

The estimation of these costs per regulatory framework has proven to be difficult to achieve as many factors interfere with the *per se* "*registration cost*", such as:

- Complexity of the legal frameworks, cumulating the costs from various pieces of legislations;
- Heterogeneity of the authorisation procedures with various sharing of work between risk assessors, risk managers, reference laboratories, experts panels, and Member States;
- Number & content of dossiers for scientific risk assessment review received by the Commission is largely variable from one sector to another;
- Member States and EURL already charge fees in the framework of the same authorisation process in certain sectors;
- Different types of authorisation granted (generic and holder authorisations).

For example, according to EFSA's Activity Based Budget (ABB), the share of the budget attributed to handling applications for the scientific assessment of regulated products in 2012 represents 30.2% of EFSA's total budget. In 2012 over a total budget of € 78.76 Million, € 23.78 Million was allocated to the scientific assessment of regulated products. The other tasks (e.g. writing of the guidance documents) are indirect support activities that could not be completely distinguished from the registration process.

#### 2.4.8.1 Fees

Within the analysed regulatory frameworks, only those where ECHA and the EURL operate apply a system of fees. Other regulatory frameworks have opted for financing through public funds in order to strengthen the independence of the assessment.

The table shows the fees requested to applicants for regulatory frameworks under analysis.

**Table 14 Registration fees**

| Legislation | Post authorisation obligations |
|---|---|
| REACH Registration | **Application:** € 1,285 to € 33,201 / substance, depending on tonnage band and size of applicant's company. Reduction applies to SMEs and micro enterprises.<br>Many other fees apply[56]<br>However, application fees represent more than 90% of the total ECHA fees income[57] |
| REACH Authorisation | **Application:** Base fee € 53,300, may be higher depending on number of uses and applicants. Reduction applies to SMEs and micro enterprises<br>Many other fees apply[58] |
| PPP | Fees at MS level (see below) |
| BPR | **Application:**<br>• a.s. : € 20,000 - 120,000<br>• product : € 80,000 |
| CoP | n.a. |
| FoA | n.a. |
| FeA | n.a. |

*Source: compiled by Arcadia International*

Furthermore for feed additives, the legal framework establishes fees for the validation of the analytical method via the community reference laboratory. Fees are paid in the framework of an application for authorisation for which EFSA performs a risk assessment but remunerates EURL's activity in relation to analytical aspects: validation of the analytical method to be used for the control of the substance submitted for authorisation (task falling outside EFSA's remit). The legislation specifies the exact amount of fees that the relevant EURL can charge according to the type of tasks performed. For feed additives, the maximum amount that can be charged by the EURL is € 6,000 with descending tariffs for simpler applications and applications for extension of use. There are also fees established at national level in the case of decentralised procedures where the competent authority of a Member State carries out a preliminary risk assessment that is peer-reviewed by EFSA. This is the case for plant protection products (active substances and MRLs).

The amount of fees charged by MS also varies significantly from one to another. In the case of active substances for PPP for instance, the range of fees charged

[56, 55] See: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:2008R0340:LATEST:EN:PDF

[57] Source : interview with ECHA representatives

by the reporting MS varies from € 23,100 to € 450,000. In the case of MRL of PPP, the range of fees varies from € 200 to € 15,000. Concerning novel food, some MS do not charge any fee. Where a fee is in place, it ranges from € 830 to € 25,000. The Novel Food Regulation foresees the possibility of a simplified procedure. In this case, the amount of fees requested ranges from € 900 to € 2,000.

#### *2.4.8.2 Costs of registration for applicants outside fees paid to authorities*

On the basis of interviews with several business operators and competent authorities, the following range of costs for preparing, submitting a registration dossier can be reported. These costs do not involve the fees paid to authorities

**Table 15 Registration costs for applicants**

| Legislation | Registration costs for applicants outside fees |
|---|---|
| REACH Registration (for a natural plant based extract) | Total cost for the consortium: € 120-150 K<br>Costs per consortium member: € 28 – 35 K |
| REACH Authorisation | Substance specific: > € 700 K |
| PPP | Characterisation & analytical method: € 50 (botanicals) to € 500 K<br>Tox: € 200 K to € 3-5 million<br>Ecotox: € 200 K to € 3-5 million (in case of residues trials)<br>Efficacy: € 200 K to € 1 million (including phytotoxicity trials)<br>Dossier set-up & mgt: € 200-400 K |
| BPR | Characterisation & analytical method: € 100 to € 500 K<br>Tox: € 200 K to € 3-5 million<br>Ecotox: € 200 K to € 1-2 million<br>Efficacy: € 200-500 K<br>Dossier set-up & mgt: € 150-500 K |
| CoP | Characterisation & analytical method: € 100 – 300 K<br>Tox: € 200 K to € 2-3 million<br>Ecotox: Not applicable<br>Efficacy: € 100 to 500 K<br>Dossier set-up & mgt: 20% of the total cost for producing data |
| FoA | Characterisation & analytical method: € 150-300 K<br>Tox: € 200 K to € 2-3 million<br>Ecotox: Not applicable<br>Efficacy: € 100 to € 500 K<br>Dossier set-up & mgt: € 100 to € 250 K |
| FeA | Characterisation & analytical method: € 150-300 K<br>Tox: € 300 K to € 2 million<br>Ecotox: € 150 K if Tier 1 only, € 800 K for Tier 1 and 2<br>Efficacy: € 100 K to € 1 million<br>Dossier set-up & mgt: € 100 to € 250 K |

*Source: compiled by Arcadia International*

As mentioned above, these figures are overall estimations that do not consider possible reduction due to the application of data waiving by applicants for low-risk products (e.g. seaweeds and plant extracts in the case of PPP, cosmetics).

In order to better estimate costs for applicants, we have considered the case of registration of the "*fenugrec powder*" (FEN 560) in the context of the PPP

Regulation. Our estimation leads to total costs for the applicant of between EUR 350,000 and EUR 800,000 (see Annex III).

A plant based product has been registered under REACH for a total cost of € 30 per consortium member (total cost of about € 150 K with 5 consortium members).

#### 2.4.8.3 Costs for authorities

Very few data exist when it relates to the costs borne by the risk assessors (e.g. EFSA or ECHA or MS risk assessment agencies). DG SANCO made some preparatory work concerning the possible introduction of fees with regard to the processing of authorisation applications submitted by industry to EFSA and recently published an Impact Assessment report[59]. While highlighting that a significant effort was made to gather reliable and valid data through in-house data collection and surveys, limited data sets have been compiled.

In this analysis, it is mentioned that RA costs range from about € 100-200 K to > € 2-3 million (from reception of the application to the publication of the decision/opinion). Given the number and the heterogeneity of sectors covered by EFSA, it is logic that the evaluation of the cost of applications for EFSA has to be done sector by sector. It was necessary to break down all the activities required to assess the applications in order to identify the time required for each activity and quantify each related costs. It is important to mention that overhead costs and cost for general services, such as the development of guidances document, have been added to estimations presented in the following table.

In the following table, we have added data collected for REACH and for national registration systems.

**Table 16 Costs for risk assessors for processing application dossiers in various regulatory fields**

| Substance/ Product | Average cost of a dossier | Average cost for drafting guidelines | Average cost of a dossier | Average cost for drafting guidelines | Average cost of a dossier | Average cost for drafting guidelines |
|---|---|---|---|---|---|---|
| | *In €* | | | | | |
| | NEW | | REVIEW | | RENEWAL | |
| REACH | Operating expenditure for REACH (2013): € 24 Million | | | | | |
| PPP | 75,000 | 31,000 | 75,500 | 31,000 | / | / |
| BPR | ECHA 2014 budget for biocides: € 25 million, 100 staff for 80 opinions to be published in 2014, estimation of 300 opinions to be published in 2020 [60] | | | | | |
| FoA | 77,500 | 1,600 | 120,000 | 1,600 | | |
| FeA | 55,600 | 2,300 | 55,600 | 2,300 | 33,400 | 1,400 |
| ***Other legislations (source: EFSA)*** | | | | | | |

[59] Commission staff working document regarding the Impact Assessment on the Revision of Regulation 178/2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority (EFSA) and laying down procedures in matters of food safety on the establishment of fees for EFSA. (available on the IA webpage of the IA Board of the Secretariat General).

[60] Source: DG ENV

| Substance/ Product | Average cost of a dossier | Average cost for drafting guidelines | Average cost of a dossier | Average cost for drafting guidelines | Average cost of a dossier | Average cost for drafting guidelines |
|---|---|---|---|---|---|---|
| | *In €* | | | | | |
| | NEW | | REVIEW | | RENEWAL | |
| GMO for cultivation | 135,000 | 76,600 | 135,000 | 76,600 | / | / |
| MRLs for PPP and Biocides | 6,800 | / | 6,800 | / | | |
| Smoke Flavourings | | | 37,800 | / | 37,000 | / |
| Novel Foods | 83,100 | 5,900 | | | | |
| Flavourings | | | 37,800 | 4,000 | | |
| Food contact Materials | 37,800 | 4,000 | 37,800 | | | |
| Animal by products | 130,500 | 4,000 | | | | |
| Antimicrobial treatments | 113,400 | 10,000 | | | | |
| Health Claims | 59,300 | 13,700 | 59,300 | 13,700 | | |
| Enzymes | | | / | | | |
| Food Allergies (exemption from labelling) | 49,400 | / | | | | |

*Source: compiled by Arcadia International and Commission staff working document Impact Assessment on the Revision of Regulation (EC) No 178/2002.*

# 3 Approach to a legal framework for plant biostimulants and agronomic fertiliser additives

This section of the report lists the data requirements for the future legislation related to the placing of PB&AFA to the market and presents the regulatory process to be applied.

As a starting point and in order to set-up the scene for the proposed PB&AFA legislation the definitions of PB and AFA are presented and the main conclusions of the previous tasks are summarised.

## 3.1 Setting the scene: definitions of plant biostimulants and agronomic fertiliser additives, and their regulatory environment.

This introduction to the approach to a EU regulatory framework for PB&AFA proposes and justifies amended definitions of plant biostimulants and agronomic fertiliser additives in the perspective of the future regulation (section 3.1.1), and presents the main conclusions of Section 2 (business & regulatory context) in order to set up the scene and to place the proposal as regard the global business and regulatory environment (section 3.1.2).

### 3.1.1 Definitions of plant biostimulants and of agronomic fertiliser additives in the future regulation

The definitions of plant biostimulants and of agronomic fertiliser additives laid down in the terms of reference of this study have been commented in Section 2.1. Revised definitions are now proposed and justified.

For the purpose of the future Fertiliser Regulation, the following definitions are proposed:

- A **plant biostimulant** is *any substance or microorganism, in the form in which it is supplied to the user, applied to plants, seeds or the root environment with the intention to stimulate natural processes of plants to benefit their nutrient use efficiency and/or their tolerance to abiotic stress, regardless of its nutrients content, or any combination of such substances and/or microorganisms intended for this use*.
- An **agronomic fertiliser additive** is *any substance or microorganism, in the form in which it is supplied to the user, added to a fertiliser, soil improver, growing medium with the intention to improve the agronomic efficacy of the final product and/or to modify the environmental fate of the nutrients released by the fertiliser, the soil improver or the growing medium, or any combination of such substances and/or microorganisms intended for this use*.

In the above definitions, **substance** means *a chemical element and its compounds, as it occurs naturally or by manufacture, including any impurity inevitably resulting from the manufacturing process*.

The following categories of substances can be distinguished:

- **Synthesised substances**, which are based on chemical reactions that can be produced in standardised processes resulting in repeatable purity ranges;

- **Natural or botanical substances:** substances which occur in nature; meaning naturally occurring substances as such, unprocessed or processed only by manual, mechanical or gravitational means, by dissolution in water, by flotation, by extraction with water, by steam distillation or by heating solely to remove water, or which is extracted from air by any means.[61]

In the above definitions, **micro-organism** means any microbiological entity whose composition is defined in qualitative terms by the strain[62] and in quantitative terms by the number of viable cells or spores expressed as colony-forming units per gram of product.

**Table 17 Justification of the amendments to the definitions**

| Definition of the ToR | Proposals of this report | Justification |
|---|---|---|
| *"Plant biostimulant means a material which contains substances and/or microorganisms whose …"* | *"Plant biostimulant means any substance or micro-organism, in the form in which is supplied to the user, (…) or a combination of such substances and/or micro-organisms intended for this use."* | The word "material" is vague and is avoided in the amended definition, which now refers to substance, micro-organism and their combinations, in the form in which they are supplied to the user. This latter wording also makes clear that the regulated item is the product as supplied to the user. |
| *"…applied to plant or the rhizosphere, …"* | *"…applied to plants, seeds or the root environment, …"* | "Seeds" are generally not understood as "plants", but biostimulants might be applied as seed-coating material; the word "seeds" was added accordingly. Rhizosphere is too restrictive, as the rhizosphere is limited to the narrow soil area which is under the influence of the root activity. In order to cover possible application of biostimulants to e.g. growing media, "root environment" is preferred to rhizosphere. |
| *"… benefit nutrient uptake, nutrient efficiency …* | *"… benefiting nutrient use efficiency…"* | "Nutrient use efficiency" is a well-established concept in the ecophysiology of plant nutrition, which covers the uptake, transport and use (assimilation) of the nutrients. It covers all plant physiological activities related with the |

[61] The REACH regulation (EC) No 1907/2006, refers to complex substances in the following terms : « *UVCB substances (substances of unknown or variable composition, complex reaction products or biological materials) may be registered as a single substance under this Regulation, despite their variable composition, provided that the hazardous properties do not differ significantly and warrant the same classification* ».

[62] "Strain" takes here the definition of the OECD Working Document on the evaluation of microbials for pest control (OECD Environment, Health and Safety Publications – Series on Pesticides No. 43, ENV/JM/MONO(2008)36) : " *a strain is a population of organisms that descends from a single cell or a pure culture isolate. Typically, it is the result of a succession of cultures ultimately deriving from an initial single colony."*

| Definition of the ToR | Proposals of this report | Justification |
|---|---|---|
| | | efficiency of nutrition, on which many biostimulants will act, and seems much appropriate in this context. |
| *"…and/crop quality…"* | *"..." (deleted)* | "crop quality" is vague. Many plant growth regulators acting on plant development and metabolism will impact "crop quality" (desirable output traits), and these compounds, both natural and synthetic, are currently regulated as PPP in EU. |

### 3.1.2 Business and regulatory environments

From the description of the business context, it can be highlighted that:

- The plant biostimulant and the agronomic fertiliser additives businesses are two separate and different ones for the majority of criteria (see Table 3);
- Both product types take place in the context of global agricultural policy which is to "*produce more and produce better*". These two types of products also act on the protection of the environment as they help reducing the needs of chemical products;
- The number of registration dossiers to be expected is difficult to estimate at this stage. EBIC has estimated that for its members only about 600-700 PB registration dossiers will have to be prepared. The number of registration dossiers for AFA will be limited (less than 50) as most AFA substances are already included in Annex I of Regulation (EC) No 2003/2003.

The description of the MS & international regulatory schemes (focus on PB) leads to the following conclusions:

- None of the studied regulatory frameworks defines the term "*plant biostimulants*" but substances/products can be placed on the market in all countries covered under the study;
- Plant biostimulants are regulated either under the fertiliser acts or the plant protection products acts. In some cases by both schemes (e.g. Canada);
- The regulatory process are highly variable ranging from free access to the market to a complete registration process that includes a risk assessment process and including a variety of notification procedures with or without data requirements (see Figure 2);
- The different regulatory schemes ask for a detailed characterisation and identification of the substances but allow the application of non-fully defined/characterised substances. In the majority of the schemes under study the furniture of analytical methods is not a mandatory requirement;
- Toxicological and ecotoxicological data are required only in few schemes (based on a complete registration process). However, none of the legal texts analysed lists the tests and study results to be provided. The regulatory schemes remain general in indicating that safety to human health and the environment has to be demonstrated and risk

management measures presented. It is of the applicant responsibility to present the data it considers necessary to this end;

- Efficacy has to be demonstrated in all countries. Data requirements are preferably based on field trial data but efficacy can also be demonstrated by results from lab testing or other assays. Belgium has established a system which obliges applicants to demonstrate field efficacy preferably at the moment of the submission or later on when the provisional authorisation has been delivered as supplementing data to confirm the authorisation;
- The most demanding schemes in terms of data seems to have a long (> 1 year) and non-predictable data examination timing (from application to registration).

The analysis of comparable existing EU regulatory schemes shows that:

- Two types of EU regulation co-exist: REACH and the other regulatory frameworks based on a pre-market approval (the food safety frameworks);
- These other regulatory frameworks have been developed in the 1960s. They are all based on the assessment of chemical substances. The majority of them have developed specific schemes and requirements for non-chemical products. However it can be observed that in a majority of cases, these adaptations are not perceived as fully satisfactory by a majority of stakeholders;
- None of these two types of approaches can be considered as fully suitable for PB&AFA and a novel approach should be the preferred approach:
    - Designing a regulatory approach on the basis of REACH would lead to the impression that PB are dangerous chemical products when the majority of them are not of synthetised chemical nature;
    - Applying a pre-market approval system with an in-depth risk assessment procedure would lead to excessive costs for applicants (> € 500,000).
- Several substances that are used as PB&AFA are already registered under other regulatory frameworks. These substances can be ranged in three categories:
    - Substances already registered under REACH for fertiliser and other usages;
    - Substances already registered notified at MS levels;
    - Substances authorised at EU level in another EU legislation (e.g. seaweed extracts in cosmetics, FeA)

  Provisions have to be defined in the EU PB&AFA registration scheme to secure avoidance of double registration. In any case, the PB&AFA regulatory scheme shall allow applicants to use existing data (data sharing and data bridging) in order to avoid repeating studies (especially animal testing);
- All studied regulatory frameworks are risk based approaches that fully consider the business environment of each sector.

Last but not least, the following key elements addressing use of PB&AFA have to be considered:

- Farmers are asking for alternative products to chemical substances and are willing to use PB&AFA together with the existing chemical products;
- Historical data on the efficacy of PB and AFA indicates that it tends to vary considerably in time and space, raising some scepticism among users and scientists. However several PB substances such as raw dried seaweeds have been used by farmers as soil improvers and fertilisers for decades.

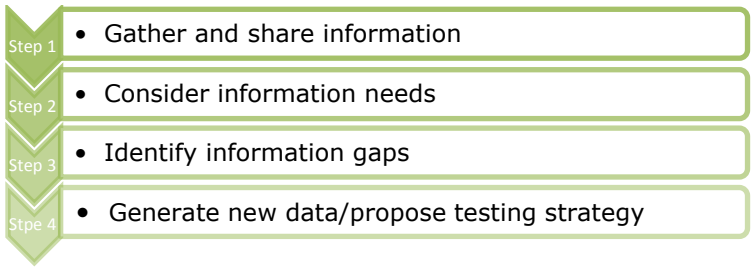
### 3.1.3 Who are the applicants?

For the purpose of the future regulation "*an applicant*" should mean any entity (e.g. business operators, consortia composed of industry companies, industry associations, users and users association, consultancy companies, individuals, etc…), regardless of whether it is situated within or outside the EU, which is interested in submitting an application.

The list of type of entities that could be applicants has been considered as large as possible to consider the case of submission of applicants for substances and group of substances (e.g. agronomic fertiliser additives already listed in Annex I of Regulation (EC) No 2003/2003). It follows the definition of applicant according to food additives regulations.

## 3.2 General principles

**Data waiving:** The process of providing the data and information requirements for a given end-point can be summarised in four consecutive steps:



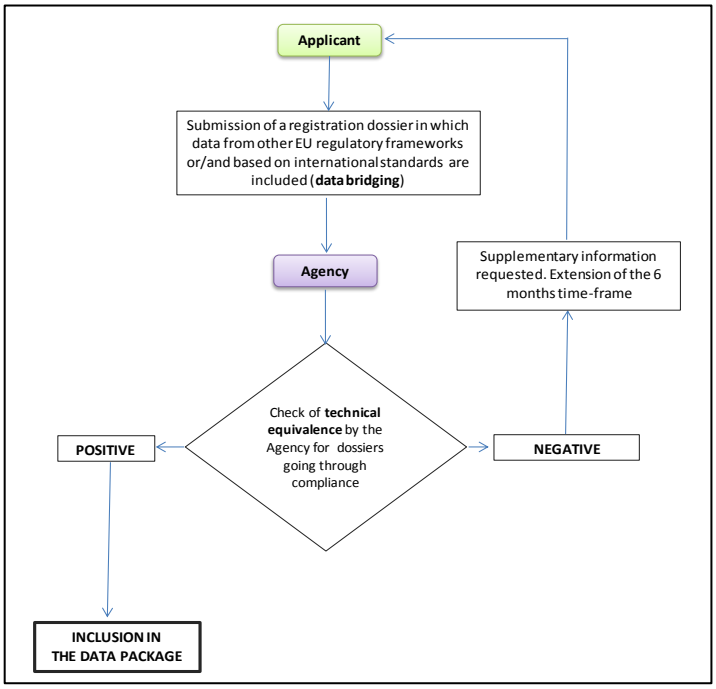

According to the REACH guidance document on data waiving[63], "*waiving of the information requirements for a given end-point means that the submission of the standard information for this particular end-point is not considered necessary in a specific case or in case when testing is technically impossible, either due to the substance's properties or to technical limitations of the test methods or when substance tailored exposure driven testing may be applied*".

In any case of waiving, applicants have to explain the reason(s) why it is not submitting the expected results.

[63] ECHA – Practical Guide 4: How to report data waiving. Available at: http://echa.europa.eu/documents/10162/13655/pg_report_data_waiving_en.pdf

**Bridging of information & related studies** from similar materials should be encouraged by the future PB&AFA regulation but the relevance should be justified by the applicant.

**Figure 3 Approach to data bridging**




Argumentation and **data justification based on history of use** shall be fully considered by the regulatory authority. This includes the use of information from the open literature and from other reliable public sources. Several EU legislations consider the possible valuation/"re-use" of history of safe use data during the risk assessment (e.g. PPP botanicals, FeA, REACH) which can be summarised as follows[64]:

- History of safe use in human nutrition (food or food additives e.g. spices or flavours, lecithin, rape seed oil) at similar concentrations may provide justifications to replace some or all oral toxicity and residue studies ;
- History of safe use in animal feeding at similar concentrations may provide justifications to replace some or all oral toxicity and residue studies.
- History of safe use in cosmetics may provide justifications to replace some or all dermal irritation/sensitisation and oral toxicity studies.
- History of safe use in pharmacopoeia (called traditional use in this context) may provide justifications to replace toxicity studies in particular chronic ones;
- History of safe use as a biocide may provide justifications to replace studies as above;

[64] Extracts from the draft guidance document on botanical active substances used in plant protection products – SANCO/11470/2012-Rev. 5 08 May 2013

- Existing exposure assessments may provide justifications to replace some or all ecotoxicology and environmental fate studies, but these need to be verified case-by-case.

Regarding micro-organisms, the concept of Qualified Presumptions of Safety (QPS) has evolved in the EU for the safe introduction of micro-organisms in the food and feed chains. QPS is an operating tool within European regulatory bodies for safety assessment and priority setting by focussing on those organisms which represent the greatest risks or uncertainties. Data on the history of safe use and on taxonomic similarity are used for granting the QPS status to microorganisms used in the food chain, making the evaluation more proportionate to the risk. QPS as a concept aims at providing a generic assessment system *that* could be applied to all requests received by EFSA for the safety assessments of microorganisms deliberately introduced into the food chain[65]. This QPS approach is similar to the GRAS (Generally Recognised As Safe) concept develop in the USA. Discussion on how to implement similar QPS strategies for the safety assessment of Botanical substances in the food chain is on-going in EFSA scientific committees.

## 3.3 Data requirements

This section of the report presents the data requirements to be proposed by applicants in their registration dossier. It is structured by considering the following needs:

- Identification and characterisation;
- Function and mode of action;
- Physical and chemical properties;
- Contaminants;
- Manufacturing, quality control and analytical methods;
- Efficacy/utility;
- Toxicology, ecotoxicology and environmental fate.

### 3.3.1 Identification and characterisation

Applicants are required to provide a detailed description of the composition of the PB&AFA product(s) they want to register. The PB&AFA has to be fully identified and characterised. This description is of high importance for the safety analysis approach.

This description in this section shall be based on the final product(s) for which registration is sought. In-house identifiers should be avoided unless already documented in open literature. In this case a statement is required to confirm that the identifier(s) refers to the product(s) for which the claim is made.

[65]Further information on QPS in the two next references :
- QPS – Qualified Presumption of Safety of Micro-organisms in Food and Feed. EFSA Scientific Colloquium Summary report, 2005, European Food Safety Authority;
- Opinion of the Scientific Committee on a request from EFSA on the introduction of a Qualified Presumption of Safety (QPS) approach for assessment of selected microorganisms referred to EFSA. The EFSA Journal (2007) 587, 1-16

**In the case of preparations**[66], they must be described in the forms in which they are supplied to the user, as clearly as possible; all ingredients shall be described. A clear distinction between the substance(s) conferring the PB or AFA activity and the other ingredients shall be made, giving the proportion by weight in the final product. Within the substances conferring the PB or AFA activity, the active components (where relevant) shall be listed, giving the proportion by weight in the final product.

If the active part of the preparation is a mixture of active substances (*i.e.* conferring distinct PB and/or AFA functionalities), each of which is clearly definable (qualitatively and quantitatively), the active substance(s) must be described separately and the proportions in the mixture given.

A qualitative description of the active substance shall be given. This shall include purity and origin of the substance or agent, plus any other relevant characteristics (e.g. physical state of each form of the product).

Chemically well-defined substances should be described by generic name, chemical name according to the International Union of Pure and Applied Chemistry (IUPAC) nomenclature, other generic international names and abbreviations and/or Chemical Abstract Service (CAS) Number. The structural and molecular formula and molecular weight must be included. Where relevant, data on isomeric forms and accompanying structurally related compounds should be included.

Requirements for formulated products are similar to the ones that can be found in other EU regulatory frameworks (e.g. FeA, FoA, PPP, REACH, etc.).

**For PB&AFA products non-chemically well-defined** the constituents contributing to the claimed effects should be identified whenever possible. By their very nature, these types of products can raise analytical challenges and their characterisation demands a somewhat different approach.

Applicants are invited to perform identification tests that should be specific to the preparation and optimally should be discriminatory with respect to other products and substances that are likely to be marketed. The major components should whenever possible be identified, quantified and their range or variability provided.

The approach for non-chemically well-defined products described for feed additives can be considered in the context of the PB&AFA future regulation.

Guidance documents for feed additives indicate that:

"*For natural products – botanically defined, the characterisation should include the scientific name of the plant of origin, its botanical classification (family, genus, species, if appropriate subspecies and variety) and the common names and synonyms in official European languages. Synonyms in other language(s) should be given only if relevant to the place of origin. The parts of the plant used (leaves, flowers, seeds, fruits, tubers, etc.) should be indicated. The place of cultivation of the plant, the identification criteria and other relevant aspects of the plants should be indicated. Specifications of the applicant for any plant material supplied by a third party should also be provided. For complex mixtures*

[66] A preparation is a product, as supplied to the user, containing PB and/or AFA substance(s) and/or microorganism(s) , and the technological additives and/or solvents used in the final product.

*of many compounds obtained by an extraction process, it is recommended to follow the relevant terminology such as essential oil, absolute, tincture, extract and related terms widely used for botanically defined products to describe the extraction process. The major components shall be identified and quantified and their range or variability provided. The phytochemical marker(s) characteristic* of the plant of origin must be included."

For natural products of non-plant origin, an equivalent approach of the above may be used.

As proposed for UVCBs substances under REACH, for the production of phytomarker(s)/biomarker(s) characteristics, the main analytical techniques are:

1) Chromatography
    a. Gas chromatographic techniques (GC-MS)
    b. Liquid chromatographic techniques(HPLC)
2) Spectroscopy
    a. H and C NMR spectroscopy
    b. FR-IT and Raman spectroscopy
    c. UV-visible spectroscopy
3) Other techniques
    a. Refractive index measurement
    b. Polarimetry
    c. Specific gravity measurement
    d. Titration
    e. Solubility in alcohol
    f. Evaporation residue

This list shall be considered as illustrative and other analytical techniques shall be proposed on a case-by-case basis by registrants.

In the case of natural products of botanical sources, the draft guidance document on botanical active substances used in plant protection products (SANCO/14470/2012-Rev 5) stresses the need for the applicant to further describe the raw material as follows:

*"For identification (taxonomy) of the botanical source and botanical preparation it is recommended to follow as much as possible the nomenclature of the European Pharmacopoeia. Additional nomenclature sources are as follows: World Checklist of Selected Plant Families (Royal Botanic Gardens, Kew); books by Peter Hanelt (e.g. Mansfeld's encyclopedia of agricultural and horticultural crops (except ornamentals), Hanelt et al., 2001) also available on the Internet as Mansfeld's World Database of Agricultural and Horticultural Crops; and the database by United States Department of Agriculture.*

*If a scientific name is not found in any of the above-named references, its existence may be checked in The International Plant Names Index (http://www.ipni.org).Since there have been many instances where species have been reclassified or renamed, the same species may be known by different scientific names which should be quoted Common (vernacular) names may also be provided, but it should be noted that a common name used in one region to refer to a particular plant may be used elsewhere to refer to another quite unrelated species. Hence common names may not uniquely identify a species and are not as reliable as the scientific names. The following scheme summarizes the requirements for description of the identity of the botanical:*

- *Scientific name: full systematic species name including botanical family, genus, species, and where relevant variety, subspecies, author's name, and chemotype;*
- *Synonyms: botanical name(s) that may be used interchangeably with the preferred scientific name;*
- *Common names: vernacular name(s);*
- *Biogeography: region(s), country(ies), natural habitat(s);*
- *Part of plant used: e.g. root, leaf, seed, fruit;*
- *Growth stage(es) of plant used.*

*Identification (taxonomy) of the botanical source and botanical preparation may in some cases be complicated. Taxonomic confirmation of species may need to be made by an independent botanical expert."*

The same draft guidance highlights the importance of providing detailed information on the source of botanical material as follows:

*"It is common knowledge that plant quality varies from crop to crop therefore sample to sample conformity of technical grade is required.*

*Also agronomic practices used in cultivating the source botanical material may influence the quality of the botanical active substance: sufficient information on method of cultivation should be provided such that it can be used as part of the definition of the technical grade.*

*The botanical raw material may be from more than one source. The sources should all be adequately described including geographical origin(s) of material used, region(s), country(ies), area/site(s) of cultivation.*

*Cultivation:*

- *Wild harvest or cultivated, if cultivated, seed and cultivation material should be specified;*
- *Ecology/habitat or cultivation practices;*
- *Usual agronomic conditions;*
- *Where relevant, plant protection measures.*

*Harvest:*

- *Time of year of harvest;*
- *Growth stage at harvest;*
- *Method of harvest and time to storage (e.g. including any drying in the field).*

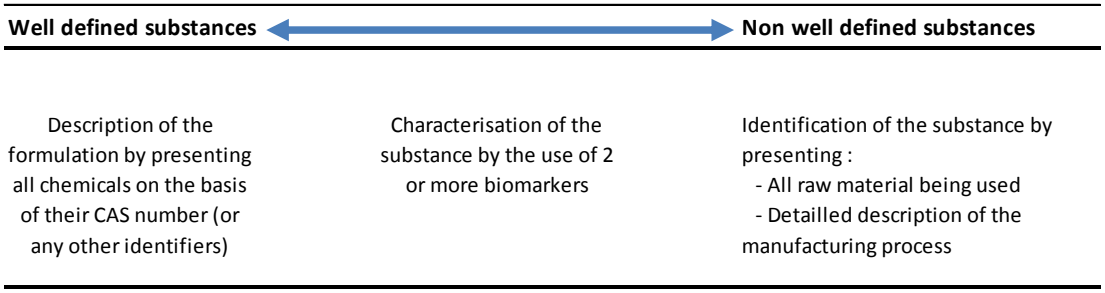
*Post-harvest storage:*

- *Storage conditions prior to any primary processing (e.g. time, humidity, drying, temperature) of the material from harvest to processing. Details should be provided indicating how storage conditions will avoid growth of micro-organisms e.g. the humidity has not exceeded a maximal tolerance limit for moisture in stored plant material.*
-

*Primary processing:*

- *For plant material from more than one (cultivation) source: where relevant, sources of material will need to be described for their cultivation, harvest and storage (as above);*
- *Preparation of material prior to any extraction (e.g. removal of seed pods, crushing, milling, etc.);*
- *Conditions (e.g. time, humidity, temperature) of storage of the botanical material prior to manufacturing process.*

**Figure 4 Approach to data bridging**




**For micro-organisms used as PB** as indicated in the guidance on additives, "*the microbial origin (bacteria, yeasts, filamentous fungi and micro-algae) of the additive* (NB: *mutatis mutandis* PB&ABA) *produced by fermentation/cultivation should be described and any history of modification of the production organism should be indicated. It should be clearly stated whether the microorganism is genetically modified or not within the meaning of the legislation (Directive 2001/18/EC). The name and taxonomic classification of each microorganism should be provided, according to the latest published information in the International Codes of Nomenclature. Microbial strains should be deposited in an internationally recognised culture collection (preferably in the European Union) and maintained by the culture collection for the authorised life of the additive. A certificate of deposition from the collection, which should specify the accession number under which the strain is held, must be provided*."

### 3.3.2 Function, mode of action

Any evidences to demonstrate the function and mode of action of the PB&AFA product should be presented in details.

These evidences can be based on scientific publications as well as on "*grey*" literature and/or history of use. They present the function(s) and mode(s) of action of the active substance(s) and their individual components (when identified), as defined in the characterisation section of the registration dossier.

Registrants are also invited to include additional evidences from related substances/active components whenever relevant.

Applicants are required to provide a short review of all these publications and the full text of each publication shall also be included in the registration dossier. As many substances, especially of the plant biostimulants category, show multiple

modes of action on the physiology of plants, the scientific review should provide information on the effects related with the intended use of the product (the "*claim*") but also on any other documented effects that would be unrelated with the claim but could be relevant from an agronomic, environmental, and safety point of view.

This information shall be used by the Agency to verify that the PB&AFA substance falls under the scope of the appropriate law (e.g. to verify that the substance is not a PPP).

### 3.3.3 Physico-chemical properties

The physical and chemical properties of PB&AFA products have to be reported by the applicant in individual registration dossiers.

The chemistry and specifications of a substance (or mixture of substances), in terms of chemical structure(s) and physico-chemical properties, is critical information required for safety assessment. Applicants are invited to provide information on the purity of a single substance that needs to be defined by specifications, and adequate chemical characterisation of simple mixtures needs to be performed, whenever possible. It may not always be possible to fully characterise more complex mixtures or substances of natural origin, but as much information as possible is required to understand the extent to which variability in composition is controlled during manufacture. Information on the manufacturing process is used during the safety assessment to identify impurities, reaction intermediates, and reagents that could have an influence in the evaluation.

Depending on the nature of the product to be registered the requirements are rather different. The requirements which are listed below are inspired by REACH Annexes VII for the 1-19 t/year bands for fully synthesised chemicals and by the French guidance on the approval of fertilising materials ("guide pour homologation des matières fertilisantes et support de cultures"[67]).

**Table 18 Physico-chemical data requirements for synthetised chemical products**

| Properties | Conditions |
|---|---|
| State of the substance at 20 °C at atmospheric pressure (1 atm) | Signed declaration by the manufacturer/company placing the product on the market |
| Melting/freezing point | The study does not need to be conducted below a lower limit of minus 20°C. |
| Boiling point | The study does not need to be conducted:<br>- for gases, or<br>- for solids which either melt above 300°C or decompose before boiling. In such cases the boiling point under reduced pressure may be estimated or measured, or |

[67] Detailed information available at http://www.anses.fr/fr/content/documents-dinformation-pour-les-dossiers-sur-les-mati%C3%A8res-fertilisantes-et-supports-de

| Properties | Conditions |
|---|---|
| | - for substances which decompose before boiling (e.g. auto-oxidation, rearrangement, degradation, decomposition, etc.). |
| Relative density | The study does not need to be conducted if:<br>- the substance is only stable in solution in a particular solvent and the solution density is similar to that of the solvent. In such cases, an indication of whether the solution density is higher or lower than the solvent density is sufficient, or<br>- the substance is a gas. In this case, an estimation based on calculation shall be made from its molecular weight and the Ideal Gas Laws. |
| Vapour pressure | The study does not need to be conducted if the melting point is above 300°C. If the melting point is between 200°C and 300°C, a limit value based on measurement or a recognised calculation method is sufficient. |
| Surface tension | The study needs only to be conducted if:<br>- based on structure, surface activity is expected or can be predicted, or<br>- surface activity is a desired property of the material. If the water solubility is below 1 mg/l at 20°C the test does not need to be conducted. |
| Water solubility | The study does not need to be conducted if:<br>- the substance is hydrolytically unstable at pH 4, 7 and 9 (half-life less than 12 hours), or<br>- the substance is readily oxidisable in water. If the substance appears 'insoluble' in water, a limit test up to the detection limit of the analytical method shall be performed. |
| *Partition coefficient n-octanol/water* | The study does not need to be conducted if the substance is inorganic. If the test cannot be performed (e.g. the substance decomposes, has a high surface activity, reacts violently during the performance of the test or does not dissolve in water or in octanol, or it is not possible to obtain a sufficiently pure substance). A calculated value for log P as well as details of the calculation method shall be provided. |
| Flash-point | The study does not need to be conducted if: |

| Properties | Conditions |
|---|---|
| | - the substance is inorganic, or<br>- the substance only contains volatile organic components with flash-points above 100°C for aqueous solutions, or<br>- the estimated flash-point is above 200°C, or<br>- the flash-point can be accurately predicted by interpolation from existing characterised materials. |
| *Flammability* | The study does not need to be conducted:<br>- if the substance is a solid which possesses explosive or pyrophoric properties. These properties should always be considered before considering flammability, or<br>- for gases, if the concentration of the flammable gas in a mixture with inert gases is so low that, when mixed with air, the concentration is all time below the lower limit, or<br>- for substances which spontaneously ignite when in contact with air. |
| *Explosive properties* | The study does not need to be conducted if:<br>- there are no chemical groups associated with explosive properties present in the molecule, or<br>- the substance contains chemical groups associated with explosive properties which include oxygen and the calculated oxygen balance is less than -200, or<br>- the organic substance or a homogenous mixture of organic substances contains chemical groups associated with explosive properties, but the exothermic decomposition energy is less than 500 J/g and the onset of exothermic decomposition is below 500 °C, or<br>- for mixtures of inorganic oxidising substances (UN Division 5.1) with organic materials, the concentration of the inorganic oxidising substance is:<br>o less than 15%, by mass, if assigned to UN Packaging Group I (high hazard) or II (medium hazard), |

| Properties | Conditions |
|---|---|
| | ○ less than 30%, by mass, if assigned to UN Packaging Group III (low hazard).<br><br>Note: Neither a test for propagation of detonation nor a test for sensitivity to detonative shock is required if the exothermic decomposition energy of organic materials is less than 800 J/g. |
| *Self-ignition temperature* | The study does not need to be conducted:<br><br>- if the substance is explosive or ignites spontaneously with air at room temperature, or<br><br>- for liquids non flammable in air, e.g. no flash point up to 200°C, or<br><br>- for gases having no flammable range, or<br><br>- for solids, if the substance has a melting point ≤ 160°C, or if preliminary results exclude self-heating of the substance up to 400°C. |
| *Oxidising properties* | The study does not need to be conducted if:<br><br>- the substance is explosive, or<br><br>- the substance is highly flammable, or<br><br>- the substance is incapable of reacting exothermically with combustible materials, for example on the basis of the chemical structure (e.g. organic substances not containing oxygen or halogen atoms and these elements are not chemically bonded to nitrogen or oxygen, or inorganic substances not containing oxygen or halogen atoms).<br><br>The full test does not need to be conducted for solids if the preliminary test clearly indicates that the test substance has oxidising properties. Note that as there is no test method to determine the oxidising properties of gaseous mixtures, the evaluation of these properties must be realised by an estimation method based on the comparison of the oxidising potential of gases in a mixture with that of the oxidising potential of oxygen in air. |
| Granulometry | The study does not need to be conducted if the substance is marketed or used in a non solid or granular form. |

**For other products**, on the basis of the requirements found, in particular, in the French; Italian and Hungarian existing legislation the following physico-chemical properties should be provided:

**Table 19 Physico-chemical data requirements for non synthetised chemical products**

| Properties | Conditions/examples |
|---|---|
| Dry matter | In % |
| pH | |
| N, P2O5, K2O total | Major nutrients |
| CaO, MgO, SO3, Na2O, Cl total | Secondary nutrients |
| B, Co, Cu, Fe, Mn, Mo, Zn total | Micro nutrients |
| As, Cd, Cr, Hg, Ni, Pb, Se total | Trace elements/heavy metals |
| Chemical form of any other fertilising material present in the substance | No3, NH4, Cyanamid for nitrogen, hydroxide, carbonate for CaO |
| Any other element, ingredient or characteristic of which the applicant wishes to claim efficacy | |
| All substances used during the manufacturing process (e.g. solvents for plant extraction, etc…) | |
| Organic matter, organic N, C/N ratio, microbiological analysis | For any product containing organic matters from animal or crop origin |
| For liquid products, it shall be indicated whether the product is a suspension or a solution | |
| Species strain contained in the product[68] (including its concentration, its viability, its WHO classification[69])[7071] (for micro-organisms) | |

[68] No information should be required on "relatives" of the strain because there is significant variability among strains within a species, in part due to the difficulties that microbiologist have applying a taxonomic system designed for higher life forms to micro-organisms. See the separate EBIC-commissioned paper on micro-organisms for more details.

[69] WHO Risk Group 1 (no or low individual and community risk): a microorganism that is unlikely to cause human disease or animal disease

WHO Risk Group 2 (moderate individual risk, low community risk): a pathogen or a microorganism? that can cause human or animal disease but is unlikely to be a serious hazard to laboratory workers, the community, livestock or the environment. Laboratory exposures may cause serious infection, but effective treatment and preventative measures are available and the risk of spread of infection is limited.

WHO Risk Group 3 (high individual risk, low community risk). A pathogen that usually causes serious human or animal disease but does not ordinarily spread from one infected individual to another. Effective treatment and preventive measures are available.

WHO Risk Group 4 (high individual and community risk). A pathogen that usually causes serious human or animal disease and that can be readily transmitted from one individual to another, directly or indirectly. Effective treatment and preventive measures are not usually available. !

This approach may not be applicable in all cases; therefore applicants are requested to add information whenever requested. Data waiving can also be used to justify the absence of some data.

### 3.3.4 Contaminants

Depending on the nature of the PB&AFA, different information has to be provided. For substances of mineral nature, trace elements/heavy metals criteria have to be considered when organic contaminants only apply on organic substances. Several test results on several batches have to be reported. As an example, Programme 108 requires 3 tests results on 3 different batches as a minimum requirement.

**Trace-elements/heavy metals**

The presence of heavy metals/trace elements shall be declared by the applicant. PB&AFA are generally applied at much lower rates than NPK fertilisers, so higher limits could be considered for these products than for other categories of fertilising materials according to the conclusions of the stakeholders consultation conducted by the Commission in 2012. At the same time, PB&AFA are applied to either soils or through foliar application, which have very different consequences.

EBIC recommends using the following maximum limit values:

- Cd: 3 mg/kg;
- Cr: 2 mg/kg;
- Hg: 2 mg/kg;
- Ni: 120 mg/kg;
- Pb: 140 mg/kg;
- As: 60 mg/kg;
- Cu, Zn, Se: No limits, but mandatory labelling only when non-negligible levels of the nutrients are present[72].

These higher limits are already in force in some Member States (notably France) and these limits are seen as sufficient under best available scientific knowledge.

**Organic contaminants:**

The following questions can determine whether testing is necessary to control for biological contaminants:

- Can the nature of the raw materials and/or of the final product exclude the possibility of biological contamination?
- Can the origin of the raw materials exclude biological contamination?

[70] See also articles 2, 3 and 18 of Directive 2000/54/EC.
[71] The American Biological Safety Association (ABSA) provides a useful database of how bacteria, viruses, fungi and parasites have been classified in a number of key jurisdictions around the world: http://www.absa.org/riskgroups/index.html.
[72] To be decided by registrants

- Do any steps of the production process or risk management measures prevent or eliminate contamination?

One of the WG established in the context of the revision of the Fertiliser Regulation (WG3) has outlined a two-step process to identify the presence of organic contaminants, using markers in the first instance to reduce the costs of testing.

1. *Organic contaminants:* PB&AFA manufacturers should be subject to these measures unless they can demonstrate either that the source of raw materials eliminations any risk of organic contaminants or that any such contaminants are effectively removed by the production process. This approach shall apply to:
   - PCB and PCDD/F;
   - Fluoranthen;
   - Benzo(b)fluoranthen;
   - Benzo(a)pyren.

Tresholds for these contaminants are defined in the French guidances documents on the basis of maximum annual flow (in gram per ha) but only for products based on waste raw materials. They read as follows:

- PCB: 0.3 max /form or 1.2 for all forms
- Fluoranthen: 6.0
- Benzo(b)fluoranthen: 4.0
- Benzo(a)pyren: 2.0.

2. *Pathogens/microbials:* (criteria suggested by WG3)[73].
   - *E. Coli*
   - *Salmonella:* recontamination of product after manufacturing
   - Helminth eggs Ascaris: marker to validate any alternative efficient chemical processes to reduce biological risks

A microbial analysis is required for any product likely to contain micro-organisms or allowing for their growth. Where the applicant chooses not to submit this analysis, it must be justified, for example, specifying that the pH renders microbial (re)contamination impossible, that production processes would destroy micro-organisms or that the product contains no ingredients of animal origin since the indicators in question are derived from Regulation (EU) No 1069/2009 on animal by-products.

*3. Plant pathogens/diseases/invasive species*

With regard to the concerns for maintaining plant health inside the European Union as laid out in Directive 2000/29/EC[74], manufacturers must demonstrate that any products containing plant-based raw materials have been verified to be

[73] Proposals for threshold available at http://www.anses.fr/sites/default/files/documents/DPR-Ft-MFSC-2013-08_0.pdf. Page 38.

[74] Council Directive 2000/29/EC of 8 May 2000 on protective measures against the introduction into the Community of organisms harmful to plants or plant products and against their spread within the Community (OJ L 169, 10.7.2000,

not containing any of the plant pathogens or diseases listed in the annexes to that directive or shall demonstrate that the manufacturing process of the raw material and/or final plant biostimulant eliminates any risk of contamination.

Given the naturally occurring long-range mobility of micro-organisms, the soil micro fauna at diverse locations around the globe are very similar, with the greatest variations seeming to be the result of the effect of human interventions, such as long-term use of fertilisers. As a result, EBIC questions whether the concept of invasive species is valid for microbial life forms.[75].

This question related to contaminants being heavy metals for mineral products, organic for organic products or pathogens is being addressed in the majority of the EU and national regulatory frameworks for products comparable to PB&AFA. For example, the French "Guide pour homologation des matières fertilisantes et support de cultures"[76]» which addresses data requirements for registration of PB&AFA presents the list of criteria to be analysed. This guide demonstrates the complexity of the issue as requirements have been defined for several categories of products. The same approach is included in the Hungarian legislation.

Further expert work is required for PB&AFA as it was done in the case of heavy metals for mineral fertilisers.

### 3.3.5 Manufacturing, quality control, and analytical methods

**Manufacturing process**

The detailed manufacturing process shall be provided by the registrant. It will form part of the PB&AFA product specifications.

The following information is considered necessary:

- Information on the method(s) of manufacture. For botanical products, the process by which the raw material is converted into a technical grade, such as physical processes, extraction and other procedures shall be provided;
- Information on ALL substances entering the manufacturing process (Applicants shall identify all these substances and provide all relevant MSDS);
- Details of any purification process;
- Details of any cultivation process (e.g. micro-organisms);
- Standardisation criteria;
- Detailed quality assurance principles such as Hazard and Critical Control Points (HACCP)[77].

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See "*Ensuring the safe use of micro-organisms in agricultural biostimulants: the false problem of invasive species*" by Dr. Rolf Arnt Olsen Professor Emeritus in Terrestrial Microbial Ecology FRAS Technology, Ås, Norway . Available at : http://www.biostimulants.eu/wp-content/uploads/2012/10/Microbial_Safety_ROlsen_Final1.pdf for more information on this issue.

[76] Detailed information available at http://www.anses.fr/fr/content/documents-dinformation-pour-les-dossiers-sur-les-mati%C3%A8res-fertilisantes-et-supports-de

[77] Introduction to HACCP availbale at http://www.fao.org/docrep/005/y1579e/y1579e03.htm

The draft guidance document on botanical active substances used in plant protection products (SANCO/14470/2012-Rev 5) recommends the following approach for the description of any extraction process:

*"The yield of all physical processes or extractions is primarily driven by the content of those components which can be extracted.*

*In the case of physical extraction (e.g. cold pressing, crushing, milling) the nature (mechanical, thermal or both combined) and exact process in particular, the temperature can greatly influence the final composition of the technical grade substance. Mechanical cold extraction is less likely to alter the original components than extraction with application of heat. Increasing heat may also considerably increase the proportion of less volatile components.*

*In the case of extraction, the ability of the solvent to extract substances (polarity and capacity of dissolving the different components) is relevant. Where possible, solvent(s) for extraction should be selected that maximise the botanical substances required and minimise harmful components or combinations of components although it may not be possible to guarantee the final profile.*

*The extraction solvent used for the extraction and even the total ratio of water to a water miscible organic solvent used for extraction, will affect the contents of components in the extract, any change may lead to different composition. Therefore, the method and solvents used should be clearly defined.*

*Any repeated extraction of the natural source may lead to a significant increase in components which were not fully extracted in the previous extraction step. Therefore, the number of extractions, as well as the mass relation of natural source to extraction solvent in each step, has to be clearly defined.*

*Further, processing e.g. concentrating or purifying of the primary extract to increase the efficacy may in some cases lead to higher or more specific efficacy. In case the component(s) responsible for the efficacy is/are identical to the harmful component(s) the harm will not increase in relation to the benefit (efficacy), the margin of safety remains the same. More usual is that, harmful components can reasonably be expected to be reduced in the extract. Therefore, the processing of the primary extract has a large influence on the toxicological and eco-toxicological profile and has to be done in a rather standardised way even if the component of the chemical composition cannot be clearly identified and followed up by chemical analysis. Any additional processing must be clearly defined.*

*The extraction method is an integral part of the specification of a botanical active substance.*

*It must be provided in sufficient detail to define the active substance. It is recognised that there is commercial sensitivity relating to this aspect so information about it should be provided in the confidential sections of the dossiers.*

*If a plant extract from another extraction method is approved and considered equivalent, the 'extraction method' can be added to the review report (respecting the confidential parts, if relevant)."*

This approach shall be considered as a model for PB&AFA which are based on plant or botanical extracts raw materials as it seems to be the most detailed guidance that has been developed so far in this area. Additional work is still ongoing at DG SANCO and it is recommended to closely follow this exercise.

**Analytical methods**

Analytical data (laboratory data) are required for the determination of the ingredients, impurities, degradation products and residues in the commercial products in support to the quality control scheme.

At least one validated analytical method[78] should be provided for quality control of the product in commercial batches. Validation of an analytical method ensures that the results of an analysis are reliable, consistent and perhaps more importantly that there is a degree of confidence in the results. Method validation provides the necessary proof that a method is "fit for purpose" and works on the appropriate parameters.

Analytical methods can rely on biomarkers in cases where the PB&AFA is non fully defined. The UVCB guidance document on "*analytical characterisation of UVCBs for REACH*"[79] provides good recommendations on how to develop an analytical strategy for products of non-fully characterised nature.

In case none of these two approaches fits, for example for PB&AFA characterised only by the description of the used raw material and of the manufacturing process, the applicant shall provide a quality assurance scheme that should guarantee that the quality and properties of the raw material are stable and that the same manufacturing process is always applied.

The stability and homogeneity of the PB&AFA products shall be evaluated and described. The information requirement for establishing the stability and homogeneity during storage conditions is based on the identification of hazards which might arise from degradation of products.

Appropriate information should be provided on:

- The chemical/physical-chemical stability of the product in its commercial preparation and under the conditions of storage and effect of storage temperature, environment [light, oxygen, moisture, relative humidity (water activity)] or any other factor that might influence the stability of the preparation.
- The nature and reactivity of any degradation products and nature of interaction/reaction of degradation products with food components.

### 3.3.6 Efficacy/utility

As mentioned under Section 2, proving the efficacy of a substance/product is increasingly becoming mandatory in the large majority of EU regulatory frameworks and in all analysed national and international regulations. Even for PPP active substances that are registered at EU level, efficacy data on one crop as a minimum are required.

Additionally on the basis of discussions with farmers representatives, historical data on the efficacy of PB and AFA indicate that agronomic efficacy may

[78] The validation process of the analytical method (if not validated yet by national or international bodies) shall be defined

[79] Available at http://www.thereachcentre.com/uploaded/whitepapers/Analytical_Characterisation_of_UVCBs_for_REACH.pdf

considerably vary in time and space, thus raising some scepticism among users and scientists. Therefore it seems justified that the future regulatory framework for PB&AFA develop data requirements that guarantee the agronomic efficacy of PB&AFA.

In the other hand, some stakeholders consider that the efficacy should not be regulated but left for the market to decide, and that it is ultimately up to farmers to test whether a product fits the intended purposes.

Finally, it shall be highlighted that many agro-climatic conditions may influence the agronomic efficacy of a PB&A. Requirements for agronomic claims justification shall consider such sources of variation.

On the basis on this situation, two specific options are proposed for the establishment of data requirements related to efficacy.

**Option A: Applicants provide data showing that a positive biological activity and/or some field efficacy are observed ahead of registration AND mandatory post-registration field studies have to be carried-out to confirm efficacy.**

Applicants shall report on studies aiming at demonstrating the efficacy/utility of the PB&AFA products under optimal conditions of use[80]. Both the intended effects referred to as "*claims*" and any unintended effects (e.g. absence of phytotoxicity) will be presented in details.

The design, methodology and protocols of the studies will be described with a level of details allowing external reviewers to evaluate the quality of the data and the conclusions drawn from it by the applicants.

The FAO guidelines on efficacy evaluation for the registration of PPP[81] should provide advice to applicants on how to set-up field trials. It is the responsibility of the applicant to provide all relevant information for a sound evaluation of the conclusions. As an example, in the case of biostimulants claiming an improved capacity for the plant to resist abiotic stress factors, this might include records of the environmental stressful conditions during the crop growing seasons. The studies should consider common crop growing and agronomic practices in the European Union.

If performed outside the EU, the studies must permit conclusions to be extrapolated on the efficacy of the products when used in the EU. In any case, the number of growing seasons and the locations of the field trials shall be indicated and justified.

Studies should be designed to demonstrate the efficacy of the PB&AFA under conditions of use that shall include:

- Crops or group(s) of crops on which the efficacy of the product is claimed;
- Dosage (any observed phytotoxicity range should also be indicated);

[80] To be described by applicants in registration dossiers.
[81] (available at: http://www.fao.org/fileadmin/templates/agphome/documents/Pests_Pesticides/Code/Efficacy.pdf)

- Optimal conditions of use: timing, preferred crop stage, agro-climatic limitations of efficacy.

These studies should not be limited to laboratory and greenhouse studies. Applicants shall provide field data due to the expected discrepancies between data from controlled (e.g. under laboratory conditions) and field conditions.

Study results should be completed by any other evidences (e.g. scientific publications) whenever it substantiates the efficacy of the product in optimal conditions.

In each registration dossier, a summary describing the efficacy/utility of the product shall be presented together with the study results.

For obligations related to post-authorisation field studies, please refer to section 3.4.3.6.

**Option B: Applicants shall provide a minimum data set showing efficacy of the PB&AFA in field conditions for crops and/or group of crops it is requesting registration. Under this option no mandatory post-registration field studies results are required.**

Under this option applicants are required to provide field studies results coming from multi locations and multi-year data. In total it is required to submit results from at least 4 locations over a minimum period of 2 crop cycles.

As for Option A, the design, methodology and protocols of the studies will be described with a level of details allowing external reviewers to evaluate the quality of the data and the conclusions drawn by the applicants from the data.

These field trials shall include a minimum of 4 replications and the registration item shall be compared, whenever feasible, to a product already in use on the targeted crop or group of crops

It is the responsibility of the applicant to present evidences related to the efficacy of its product. The volume of data to be presented by the applicants depends on the claim and the conditions of use. Given the variety of possible effects, crops/crop groups and growing conditions, applicants need flexibility to define volumes of required data that are adapted to the specific situation. Furthermore, it should be recognised that with regard to products that improve the availability of nutrients (notably micro-organisms), soil types and conditions are often more relevant than crop types.

As an alternative, EBIC has proposed a guidance document for determining the number of trials needed[82].

The applicant shall analyse and comment on the statistical significance and biological/agronomical relevance of all differences observed between treatments. Sources of variability will be described.

Both options are already in place at national levels: Option A in BE, Option B in ES, FR, IT, HU which are the largest markets for PB. The Option B approach which has been in place for several years has not fully demonstrated its efficacy.

[82] See Annex IV

**Table 20 Advantages and disadvantages of the two options for the data requirements related to PB&AFA efficacy**

| Option | Advantages | Disadvantages |
|---|---|---|
| **A** | • Balanced workload before and after authorisation<br>• Secure flow of information down to farmer via an information chain<br>• Preferred options for farmers and several industry players<br>• Reduce risks of lack of efficiency<br>• Add credibility to the sector<br>• Spread the registration costs over a longer period | • Risk of registering a product without knowing how it will behave under various soil-climatic conditions and various use conditions.<br>• How to protect the data (and for how long?) when they are provided after registration? |
| **B** | • May provide better knowledge of product efficacy for the registration process. | • Difficulties for proving reliable efficacy before authorisation<br>• Require the provision of multi-year and multi-location field trials that will make the registration process longer |

The proposal for the future registration scheme for PB&AFA shall include provisions to grant authorisation for group(s) of crops. Registrant shall have the possibility to request authorisation to place PB&AFA on the market at EU level based on a group of crops rather than on a particular crop. When an applicant will seek registration for one or several group(s) of crops, it will have to demonstrate efficacy for the corresponding group(s) of crops. The demonstration of the efficacy shall then be based on a minimum of two different crops per group. Registrant will have to choose two crop species representative of the crop group in order to demonstrate efficacy of its product. The volume of field trials data to be reported under Option B remains similar to what has been described above.

The possible grouping of crops reads as follows (based on a proposal made by French fertiliser industry to its national authority):

- **Annual crops**
  - Vegetables:
    - Vegetable crops whose roots, tubers and bulbs are harvested
    - Vegetable crops whose leaves, stalks and fruits are harvested
  - Cereals
  - Fodder grasses and fiber crops
  - Leguminous, oleaginous and protein crops
  - Root crops
  - Floral crops and green plants

- Lawns

- **Perennial crops**
  - Fruit and vine crops
  - Stone fruits
  - Nuts
  - Pome fruits
  - Small fruits

- **Ornamental trees and shrubs**

Aromatic plants are grouped with either vegetables or floral plants according to their agronomic interest. Tropical crops are either grouped with vegetables or fruit crops according to agronomic interest.

### 3.3.7 Toxicology, ecotoxicology and environmental fate

This section provides a baseline on data requirements for applications supporting the authorisation of new PB&AFA or modifications to an already authorised substance.

It seeks to describe the toxicological and eco-toxicological test results which shall be used (in conjunction with other data requirements e.g. data on characterisation) to identify potential hazards. As mentioned above, applicants are invited to provide detailed information on the characterisation of their substance. This approach leads to a better identification of the potential hazards and related risks.

PB&AFA can be of variable nature ranging from an extract of a natural source (e.g. seaweeds, plant extracts) which has not been chemically processed to a synthethised chemical product. Therefore it is important that product safety is approached by considering this variability of nature of PB&AFA. This consideration leads to the proposal of a modular approach based on 3 tiers which balances data requirements against risk (risk-based approach).

The various application methods of PB&AFA (e.g. application to soil, spraying on leaves, coating to fertilisers, seeds, etc…) also have to be considered. The way of application directly affect exposure routes of possibly harmed organisms, which renders difficult a general approach that would take into account each existing PB&AFA. The most important exposure routes are considered below (worst case scenario) when selecting adequate toxicity tests.

Additionally, applicants shall base their dossier on sound science and state of the art principles of safety assessment. Additionally, in order to avoid unnecessary testing and experimentation or double registration registrants should be able to cross-reference the risk assessments of the PB&AFA being registered, subject to the following limitations:

- Data from evaluations carried out for the substance(s)/mixtures in any EU member state or OECD country in the context of approval of fertilisers, plant biostimulants, food additives, cosmetics, food, feed, pharmaceuticals, pesticides, biocides or other chemicals can be referenced to the extent that the specific data is relevant for agricultural

use and reflects the proposed "good agricultural practice" (conditions for use). Technical equivalence shall be established.

- Risk assessments carried out for a Hazard Analysis and Critical Control Point (HACCP) should be eligible to meet the criteria of the safety assessment under the future PB&AFA registry.

Any reference to any existing data made by the applicant in its dossier shall be fully documented and reports shall be added to the PB&AFA registration dossier.

A minimal dataset applicable to all PB&AFA has been developed under Tier 1 for which the testing requirements, key issues and triggers are described, whenever possible. Tier 1 consists of simple in-vitro toxicity tests.

Tier 2 and 3 include higher levels where toxicity was identified under Tier 1 testing. Tier 2 testing will be required on a case-by-case basis for products for which the toxicity and ecotoxicity end-points should be further specified according to the expert judgement of the notifying companies in first instance, to be confirmed during the compliance check by the Agency. A detailed technical guidance regarding the application of this principle shall be elaborated by the Commission to help the preparation of the dossier

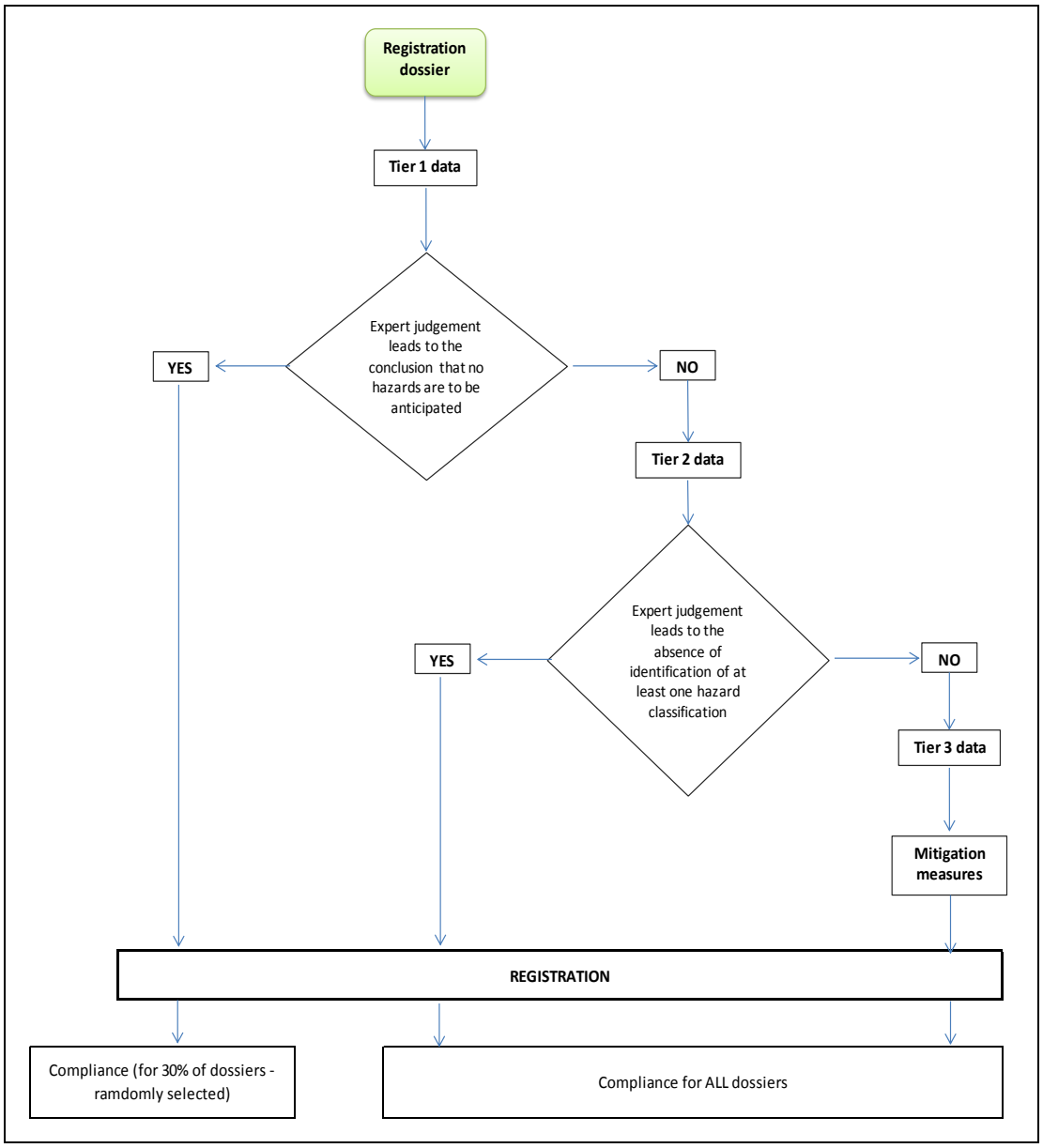
When some level of toxicity or eco-toxicity is demonstrated under Tier 2, Tier 3 testing shall be performed in order to generate more extensive data.

Tier 3 only applies to PB&AFA that are classified in at least one hazard class as per the CLP Regulation.

Tier 2 and Tier 3 testing should be performed on a case-by-case basis by taking into consideration 1) the nature of the PB&AFA and 2) all available data, to elucidate specific endpoints needing further investigation of findings in Tier 1 tests. Applicants are advised to design the actual testing taking into account physico-chemical data of the compound, toxicity data on structurally related compounds and any other relevant information.

Inherent to the rationale of a tiered approach is the concept that results of studies at higher tiers will in principle supersede results at lower tiers.

**Figure 5 The human and environmental safety tier approach**




*Source: Compiled by Arcadia International*

Methodologies to be used to produce the requested information per end point for the majority of Tier 1 and Tier 2 requirements can be found in the Guidance on the application of the CLP criteria – Version 4.0 – November 2013[83].

For each requirement, the following consecutive steps shall be respected whenever possible:

1) A literature review presenting a summary of scientific publications related;
2) *In vitro* testing;
3) *In vivo* testing.

[83] Available at: www.echa.europa.eu/documents/10162/13562/clp_en.pdf

For many organic substances, the testing and interpretation of data present no problems when applying both the relevant Test Methods Regulation (EC) No 440/2008 and/or OECD Test Guidelines. There are a number of typical interpretational problems, however, that can be characterised by the properties of the substance being studied. These are commonly called 'difficult substances'. Testing considerations for these substances can be found in the OECD specific guidance on aquatic toxicity testing of difficult substances and mixtures[84].

#### *3.3.7.1 Tier 1 requirements*

*Data requirements:*

As regards Tier 1, the following toxicological information shall be provided in each individual dossier. Data waiving justifications are not permitted under Tier 1 to the exception of the acute inhalation toxicity. All these tests have to be done under Good Laboratory Practices by a lab having received this recognition by the appropriate authority.

As regard to human toxicity, the following requirements apply:

- **Topical toxicity**
  - **Skin irritation** means the production of reversible damage to the skin following the application of a test substance for up to 4 hours **or skin corrosion** means the production of irreversible damage to the skin; namely, visible necrosis through the epidermis and into the dermis, following the application of a test substance for up to 4 hours.

    The *in vivo* test in rabbits according to OECD TG 404 is the standard in vivo test for the hazard assessment under many EU Regulations. The EU standardised B4 method can also be used.

    In recent years, the OECD has accepted new guidelines for *in vitro* skin corrosion tests as alternatives for the standard *in vivo* rabbit skin test (OECD TG 404). Accepted *in vitro* tests for skin corrosivity are found in the EU Test Methods Regulation (EC) No 440/2008 and in OECD Test Guidelines (OECD TG):
    - The transcutaneous electrical resistance (TER; using rat skin) test (OECD TG 430)
    - Human skin model (HSM) tests (OECD TG 431)
    - The *in vitro* membrane barrier test method (OECD TG 435)

    Three *in vitro* skin irritation test methods based on reconstructed human epidermis (RHE) technology have been recently accepted by the OECD in the OECD TG 439.

  - **Serious eye damage/eye irritation:** Serious eye damage means the production of tissue damage in the eye, or serious physical decay of vision, following application of a test substance to the anterior surface of the eye, which is not fully reversible within 21 days of application. Eye irritation means the production of changes in the eye following the application of test substance to

[84] Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures. OECD Environmental Health and Safety Publication. Series on Testing and Assessment. No 23. Paris 2000.

the anterior surface of the eye, which are fully reversible within 21 days of application.

The *in vivo* OECD Test Guideline 405 is the most common test being used for eye irritation. It offers a stepwise testing strategy is described for the determination of the eye irritation/corrosion properties of substances.

- **Respiratory or skin sensitisation:** Respiratory sensitiser means a substance that will lead to hypersensitivity of the airways following inhalation of the substance. Skin sensitiser means a substance that will lead to an allergic response following skin contact.

  Several testing methods exist. Council Regulation (EC) No 440/2208 proposes the B.6 (Guinea Pig Maximisation Test – GPMT testing) and B.42 (Local Lymph Node Assay mouse testing) methods. Corresponding OECD methods are TG 406, 429, 422A, and 422B.

  The Mouse Local Lymph Node Assay (LLNA) (EU B.42 or OECD TG 429) should be the first choice method for in vivo testing as The Local Lymph Node assay is considered a reduction and refinement method compared to the traditional guinea pigs tests since it provides advantages in terms of animal welfare. Other test methods should only be used in exceptional circumstances. Justification of use of other tests should be provided

An additional test related to phototoxicity (photo irritation) is generally performed to complete the topical toxicity package. It is defined as a toxic response that is elicited after the initial exposure of skin to certain chemicals and subsequent exposure to light, or that is induced by skin irradiation after systemic administration (oral, intravenous) of a chemical substance [1]. If a chemical absorbs UV or visible light, it needs to be determined if it is likely to cause adverse phototoxic effects when intended for human use.

In the context of PB&AFA, we consider that this test is not necessary as skin tests have already been planned and as exposure could be considered as low to very low.

- **Systemic toxicity**

  - **Acute systemic toxicity testing** involves an assessment of the general toxic effects of a single dose or multiple doses of a chemical or product, within 24 hours by a particular route (oral, dermal, inhalation), and that occur during a subsequent 21-day observation period. Acute toxicity data are common requirements under many regulatory frameworks to provide classification and labelling warning or the possible consequence of exposure to a chemical. Substances that require classification and labelling include industrial chemicals (REACH Annex VII and VIII), biocides, pesticides, cosmetic ingredients.

    The hazard class acute toxicity is differentiated into:

    - Acute oral toxicity;
    - Acute dermal toxicity;

- Acute inhalation toxicity.

There are no agreed *in vitro* methods. The following guidelines for *in vivo* methods are currently used: OECD 401 or OECD 420 or EU B.1 bis: Acute oral toxicity; OECD 402 or EU B.3: Acute dermal toxicity; OECD 403: Acute inhalation toxicity.

Standard environmental toxicity and fate required for Tier 1 is:

- **Aquatic toxicity:** Aquatic toxicity refers to the effects of a compound to organisms living in the water and is usually determined on organisms representing the three trophic levels, i.e. vertebrates (fish), invertebrates (crustaceans as *Daphnia* spp.) and plants (algae).
    - As a first step to evaluate aquatic toxicity we propose to limit Tier 1 testing to:
        - Short-term toxicity testing on invertebrates (preferred species *Daphnia*) (OECD TG 202 or ISO 6341)
        - Growth inhibition study aquatic plants (algae preferred) (OECD 201 or ISO 8692).

    These studies does not need to be conducted if there are factors indicating that aquatic toxicity is unlikely to occur, for instance if the substance is highly insoluble in water or the substance unlikely to cross biological membranes. The long-term aquatic toxicity study on *Daphnia* shall be considered only if the substance is poorly water soluble.

Specific additional requirements may be required by PB&AFA if their nature justifies it, such as in the case of micro-organisms. The exposure route to terrestrial organisms seems to be more relevant than aquatic organisms; examples for tests will then be: earthworms acute toxicity test (OECD TG 207), soil respiration[85]. Some substances might not even reach water bodies because they accumulate in the soil or are ”controlled” or do not survive the soil conditions before they reach groundwater or surface water bodies. Microorganisms’ viability may be targeted by soil respiration tests[86]. In these cases, it is proposed that applicants discuss directly with national safety agencies to see whether or not additional data should be provided.

For micro-organisms, registrants are invited to provide additional information such as:

- Soil microorganisms nitrogen transformation test (OECD TG 216), which aims at investigating the long-term effects of chemicals, after a single exposure, on nitrogen transformation activity of soil microorganisms.;
- Soil microorganisms carbon transformation test (OECD TG 217) which aims at investigating long term potential effects of a single exposure of agrochemicals/non agrochemicals on carbon transformation activity of soil microorganisms.

[85] There is for instance an OECD standard test (carbon transformation), see http://www.oecd-ilibrary.org/content/book/9789264070240-en. Important to note that this in an example for a test with which one sum parameter is measured. With other tests / other endpoints, other parameters can be detected which also provide useful results. To be adapted on a case by case basis.

[86] Soil respiration refers to the production of carbon dioxide when soil organisms respire. This includes respiration of plant roots, the rhizosphere, microbes and fauna.

These two tests are the most common basic tests being used when it relates to microorganisms testing under several EU regulatory frameworks.

*Tier 1 expert judgement:*

On the basis of all study results applicants shall present an expert judgement and a justification why Tier 2 testing shall/shall not apply to the PB&AFA product under consideration.

This expert judgement for assessing quantitative data will be presented in the form of a summary of the above mentioned test results first per test study and secondly across test studies.

Then applicants are required to assess the possible risks of the PB&AFA under registration by considering exposure of the PB&AFA in qualitative terms.

If predicted environmental concentration or environmentally relevant concentrations were found to be toxic in Tier 1, go to Tier 2. If not: stop assessment after Tier 1.

Applicants are invited to substantiate their conclusions on the basis the Acute Toxicity Estimate approach for classification as described in Annex I of CLP, Table 3.1.1 should be used whenever possible.

#### *3.3.7.2 Tier 2 requirements*

Tier 2 requirements shall complete Tier 1 by the addition of systemic toxicity tests such as chronic toxicity tests (repeated dose).

The assessment is based on the respective criteria and consideration of all available adequate and reliable information, primarily such relating to repeated-dose tests (chronic toxicity) but also taking into account the general physico-chemical nature of the substance. The most useful information is generally from animal studies, but information obtained using read-across from similar substances and from appropriate *in vitro* models can also be used, where appropriate.

- **Repeated dose toxicity (chronic toxicity)** comprises the adverse general toxicological effects occurring as a result of repeated daily dosing with, or exposure, to a substance for a specified period up to the expected lifespan of the test species. The repeated dose study is an integral part of the data package produced to perform quantitative risk assessment (QRA) of industrial chemicals, cosmetic ingredients, biocides, pesticides, and pharmaceuticals. The point of departure most commonly used for systemic toxicity safety assessment is the NOAEL (Non-Observed Adverse Effect Level) which is used in the calculation of the MoS (Margin of Safety) or MoE (Margin of Exposure).

  Several *in vivo* repeated dose toxicity tests are available:
  - 28-day oral toxicity study in rodents (EU B.7 or OECD TG 407);
  - 90-day oral toxicity study in rodents (EU B.26 or OECD TG 408);
  - 90-day oral toxicity in non-rodents (EU B.27 or OECD TG 409);
  - Dermal toxicity: 21/28-day study (rat, rabbit or guinea pig) (EU B.9 or OECD TG 410);

- Dermal toxicity: 90-day study (rat, rabbit or guinea pig) (EU B.28 or OECD TG 411);
- Inhalation Toxicity: 28-Day Study in Rodents (EU B.8 or OECD TG 412);
- Inhalation Toxicity: 90-day Study in Rodent (EU B.29 or OECD TG 413);
- Chronic Toxicity Studies in Rodents (EU B.30 or OECD TG 452).

It is of the responsibility of the applicant to select the most appropriate test(s) in line with the nature of the substance and the conclusions of the Tier 1 expert judgment.

Ecotoxicological studies shall lead to an expert judgment related to hazardous to the aquatic environment[87]. The aquatic environment is considered in terms of the aquatic organisms that live in the water, and the aquatic ecosystem of which they are part. The basis, therefore, of the identification of acute (short-term) and long-term hazards is the aquatic toxicity of the PB&AFA, although this shall be modified by taking account of further information on the degradation and bioaccumulation behaviour, if appropriate.

- **Repeated dose toxicity (chronic fish toxicity)** should also be performed (long term exposure that covers life-cycle of the fish and determine No Observed Effect Concentration – NOEC, ECx).

  This endpoint shall start with a fish acute toxicity test (EU C.1 or OECD TG 203) which allows conducting a limit test, where fish are exposed to a single concentration (100 mg/L). If no mortality is observed at this concentration it is concluded that the LC50 is greater than 100 mg/L and in consequence the substance not toxic to fish. Then the chronic fish toxicity tests are not required.

  When chronic fish toxicity has to be performed, the following test study(ies) should be carried out:

  - Fish early-life stage toxicity (OECD TG 210);
  - Fish short-term toxicity test on embryo and sac-fry stages (EU C. 15 or OECD TG 212);
  - Fish juvenile growth (EU C.14 or OECD TG 215).

  For each of these two set of endpoints, registrants shall select test study(ies) to be carried out on a case by case basis. Data waiving justifications are permitted.

  A second expert judgment (similar to the one described under Tier 1) shall be carried out at the end of the Tier 2 level and will complete the one done for Tier 1. If the conclusions of this analysis leads to the conclusion that the PB&AFA is subject to a minima one hazard classification (based on CLP Regulation), then Tier 3 applies.

[87] In principle the assessment of ecotoxicity the substance should address all organism taxa as defined in the majority of the EU regulatory frameworks. However ecotoxicity to aquatic organisms should be the preferred approach whenever relevant exposure is observed. In other cases, soil toxicity may be more relevant, in particular if the substance is not exposed to fresh water nor marine water nor sediments. To be defined by applicants

#### *3.3.7.3 Tier 3 requirements*

Tier 3 shall then be developed on a case-by-case basis. Applicants have the obligations to carry out additional tests on the basis of the identified hazard and to present a complete exposure assessment and mitigations measures.

Registrants in that situation are invited to contact their national RA Agency to discuss about their strategy for the completion of this Tier. This strategy could usefully be discussed with ECHA at the end of the compliance check that will apply de facto to all PB&AFA reaching Tier 3.

This Tier may include a large number of test studies and exposure analysis. Environmental fate criteria such as biodegradation, long term persistence in the soil and residues & metabolites in plants should also be considered whenever necessary.

For ecotoxicity assessment, applicants are invited to justify their approach on the basis of the following steps:

1) Consider most relevant exposure routes;
2) Readily biodegradable: ( yes or no);
3) Upon 1 and 2 decide which tests are relevant;
4) Test concentrations that cover the predicted environmental concentration PEC;
5) If only concentration several ranges above PEC are toxic in tests -> no further assessment needed -> no tier of higher level necessary.

The environmental risk shall be identified by a comparison of the predicted environmental concentration (PEC) and the predicted no-effect concentration (PNEC) for a group of test species covering various parts of the ecosystem in question. The risk is assessed for as well the soil compartment as for adjacent freshwater systems. Data needed for the generic risk assessment includes data on physicochemical properties and ecotoxicological effect data for a group of aquatic and soil species typical available from the REACH dossier.

### 3.3.7.4 *Summary of the toxicology, ecotoxicology and environmental fate data requirements*

**Table 21 Summary of the toxicology, ecotoxicology and environmental fate data requirements**

| | Test guidelines | | Expert judgement | Data waiving |
|---|---|---|---|---|
| | in vitro (M=mandatory) | In vivo (M=mandatory) | | |
| ***Tier 1*** | | | | |
| *1) Human toxicity - Topical toxicity* | | | | |
| 1.1) Skin irritation/corrosion | OECD TG 430, 431, 435, 439 | **OECD TG 404 (M)** | Required | Not permitted |
| 1.2) Eye damage/irritation | | **OECD TG 405 (M)** | Required | Not permitted |
| 1.3) Respiratory/skin sensitisation | | **EU B.42 or OECD TG 429 (M)** | Required | Not permitted |
| *2) Human toxicity - Systemic toxicity* | | | | |
| 2.1) Acute systemic toxicity testing | | | | |
| 2.1.1) Acute oral toxicity | No agreed method | **OECD 401 or OECD 420 or EU B.1 bis (M)** | Required | Not permitted |
| 2.1.2) Acute dermal toxicity | | **OECD 402 or EU B.3 (M)** | Required | Not permitted |
| 2.1.3) Acute inhalation toxicity | | **OECD 403 (M)** | Required | Not permitted |
| *3) Environmental toxicity* | | | | |
| 3.1) Aquatic toxicity | | | | |
| 3.1.1) Short-term toxicity testing on invertebrates (preferably Daphnia) | | **OECD TG 202 or ISO 6341** | Required | Permitted (justification to be provided) |
| 3.1.2) Growth inhibition study aquatic plants (algae preferred) | | **OECD 201 or ISO 8692** | Required | Permitted (justification to be provided) |
| 3.2) Soil toxicity (mainly for microorganisms) | | | | |
| 3.2.1) Nitrogen transformation test | | **OECD TG 216** | Required | Permitted (justification to be provided) |
| 3.2.2) Carbon transformation test | | **OECD TG 217** | Required | Permitted (justification to be provided) |
| 3.2.3) Earthworms acute toxicity test | | **OECD TG 207** | Required | Permitted (justification to be provided) |

| | Test guidelines | | Expert judgement | Data waiving |
|---|---|---|---|---|
| | in vitro (M=mandatory) | In vivo (M=mandatory) | | |
| ***Tier 2*** | | | | |
| *1) Human toxicity* | | | | |
| 1.1) Repeated dose toxicity (chronic toxicity) | | **One or several tests in the list below to be carried out** | Required | Permitted |
| 1.1.1) 28-day oral toxicity study in rodents | | **EU B.7 or OECD TG 407** | | |
| 1.1.2) 90-day oral toxicity study in rodents | | **EU B.26 or OECD TG 408** | | |
| 1.1.3) 90-day oral toxicity in non-rodents | | **EU B.27 or OECD TG 409** | | |
| 1.1.4) Dermal toxicity: 21/28-day study | | **EU B.9 or OECD TG 410** | | |
| 1.1.5) Dermal toxicity: 90-day study | | **EU B.28 or OECD TG 411** | | |
| 1.1.6) Inhalation Toxicity: 28-Day Study in Rodents | | **EU B.8 or OECD TG 412** | | |
| 1.1.7) Inhalation Toxicity: 90-day Study in Rodent | | **EU B.29 or OECD TG 413** | | |
| 1.1.8) Chronic Toxicity Studies in Rodents | | **EU B.30 or OECD TG 452** | | |
| 2) *Environmental toxicity* | | | | |
| 2.1) Repeated dose toxicity (chronic fish toxicity) | | | | |
| 2.1.1) Fish acute toxicity test | | **EU C.1 or OECD TG 203 (M)** | Required | Not Permitted |
| 2.1.2) Fish early-life stage toxicity | | **OECD TG 210** | Required | Permitted |
| 2.1.3) Fish short-term toxicity test on embryo | | **EU C. 15 or OECD TG 212** | Required | Permitted |
| 2.1.4) Fish juvenile growth | | **EU C.14 or OECD TG 215** | Required | Permitted |
| ***Tier 3*** | | | | |
| Data requirements based on experts judgements from Tier 1 and Tier 2 (hazard identification). The possible list of tests and the data waiving principles to be followed principles should follow the Plant Protection Products guidelines. | | | | |

## 3.4 Registration process and responsibilities

### 3.4.1 Authorisation procedure

#### *3.4.1.1 Pre-registration meeting & registration support*

Applicants are encouraged to request a pre-submission consultation with the helpdesk structure, particularly if they are not familiar with the regulatory system or don't have clear view on how to classify their product(s) and which data to be generated and included in the registration dossier. The main objective of pre-submission meetings is to discuss the information requirements.

Although the data requirements are laid down in legislative documents applicants may need some guidance on how to interpret these data requirements and whether studies, published literature and/or reasoned approach can be accepted. This approach is considered in several EU legislations and in particular in the draft guidance document on botanical active substances used in PPP and a pre-registration helpdesk, managed by EFSA, exists for feed additives.

This helpdesk structure should be available in each Member State to allow SME applicants to talk to local experts before submitting an EU dossier. One option is that this support is organised by the private sector (national fertiliser's associations). Another option would be the national helpdesks which have been set up in the context of the REACH Regulation with their associated costs.

#### *3.4.1.2 Application*

An application "*dossier*" shall consist of:

- An **accompanying letter**;
- An **administrative dossier** including a checklist: the applicant has to fill in and submit the checklist in order to verify that the dossier is complete. The checklist shall be drafted in accordance with the model that shall be developed by the Commission as part of the Guidance for applicants;
- A **technical dossier** that consists of all data required for risk assessment and the data required for risk management as well as all expert judgments required to conclude on the risk and on the efficacy assessment ;
- A **summary of the dossier**. The applicant shall propose an overall conclusion on the safety of the proposed uses of the product. The overall evaluation of potential risk to human health and to the environment shall be made in the context of known or likely human and environmental exposure. Efficacy of the product in optimal conditions of use shall be demonstrated.

Application dossiers shall be written in English.

#### *3.4.1.3 Data protection and data confidentiality*

Generating data to secure regulatory approval in sectors, such as the food safety and agricultural chemicals in which product safety and efficacy are of key importance, has become ever more extensive and expensive. There is a need to

provide an incentive to undertake such data generation efforts by protecting their investment against so-called "free riders". This protection applies via data protection and data confidentiality.

De facto, data protection cannot extend to the complete dossier as e.g. public literature may be included to evaluate the safety and/or efficacy of a product. Article 59 of the PPP Regulation indicates the conditions under which data protection applies. Under REACH Regulation, data protection is automatically granted.

The protection of data generated for regulatory purposes prevents from direct or indirect use of the data filed in support of a marketing authorisation by subsequent applicants seeking marketing authorisation for the same substance. The protection applies unless the subsequent applicant has obtained the consent of the first party that filed the data and obtained the original marketing authorisation. Data protection starts when authorisation is granted. Data protection does not have to be requested by applicants. It is granted automatically and applies to those parts of the dossiers specified in the Regulation.

Protection is granted for a limited time, so that subsequent applicants can use the information free of charge after an appropriate period. It is proposed that data protection applies for a period of 20 years. Although the protection of regulatory data has its origin in laws regulating confidential information and indeed is addressed in the same article of the Agreement on Trade-Related aspects of Intellectual Property Rights (TRIPS) that mandate the protection of confidential information, it is a separate right subject to discussions in the legal experts' community.

As under similar regulatory frameworks (e.g. cosmetics, REACH, etc.) a data sharing mechanism shall be provided for if other applicants apply for a similar or equivalent substances.

On the other hand, away from protecting the investment in studies through data protection, other submitted data may be deemed worth of protection by the applicant, notably for commercial reasons. Existing regulatory frameworks have expressly provided for the possibility to grant confidentiality to product compositions or manufacturer processes as they are the intellectual property of the company that has developed them. All information is not eligible for confidentiality. For example some information related to the hazard of the products has to be clearly mentioned on the Material Data Safety Sheet (MSDS) and on the product label to allow users to protect themselves against these hazards. This information cannot remain confidential and have to be made freely available to third parties.

As for the majority of EU regulatory frameworks under analysis, provisions have to be defined in the future EU PB&AFA legislation to enable maintenance of confidentiality of data which goes beyond the above-mentioned MSDS. Applicants should have the right to request a confidential treatment of certain sections of their application dossier. It is the responsibility of the applicant to indicate which sections and data they wish to be treated as confidential and give justification for each part for which a confidential treatment is required. General requests for confidentiality which are not substantiated shall not be accepted.

#### 3.4.1.4 Submission of application registration dossier

In order to reduce administrative burden, it is proposed that submission is performed by electronic interfaces. The IT tools that have been developed for REACH (REACH-IUCLID) should be further studied and a similar system should preferably be set up for plant biostimulants and agronomic fertiliser additives.

Applicants will be required to submit their data via this IT portal of the responsible EU Agency (ECHA or EFSA).

The submission of the registration file requires a number of practical steps with which the applicant should be familiar with before attempting it. Guidance documents shall be developed to support applicants during the process.

In case of joint submission of data, each applicant shall be required to submit its own registration dossier for each of his substances but certain data will be submitted together. For a given "*joint substance*" all commercial product names shall be provided.

The information submitted by the applicant in the IT system will have to be kept up-to-date and it will be of the applicant responsibility to update its information whenever required and communicated to relevant authorities whenever relevant (to be defined).

Where applicable, application fees will have to be paid at the same time the application is submitted.

When the dossier is complete, applicants will receive an electronic mail indicating that their application is accepted for processing.

#### 3.4.1.5 What happens after the application has been accepted for processing?

All dossiers electronically submitted to the responsible Agency and accepted for processing shall undergo a completeness check in order to ensure they can be handled properly and that the required regulatory process as described below can be successfully carried out.

**Completeness check**

A completeness check will be performed for each application. This check aims at verifying the completeness of the dossier and will ideally include the following actions:

1) Verification of whether all required fields are filled correctly and all testing proposals, derogation statements, waiving statements etc. are included;
2) Verification that the substance falls under the scope of the Regulation and that it can be considered as a PB or an AFA;
3) Verification that the substance categorisation proposed by the applicant is correct;
4) Verification that fee payment (if occurs) has been received by the Agency administration.

Not all these actions can be done by IT means. This remark leads to two options:

- Option 1: The objective is to have a completeness check fully performed electronically and therefore actions 2 and 3 will have to be moved to the compliance check procedure;
- Option 2: Completeness check is performed electronically for actions 1 and 4 and manually by Agency staff for actions 2 and 3.

**Table 22 Advantages and disadvantages of the two options for the completeness check process**

| Option | Advantages | Disadvantages |
|---|---|---|
| **1** | • Reduces workload and administrative burden<br>• Quicker procedure | • Actions 2 and 3 not performed on all substances as compliance check doesn't apply on all registration<br>• Possible wrong classification of substances<br>• Possible insertion of a non PB & AFA in the Register |
| **2** | • Secures substances classification<br>• Avoids that non PB&AFA substances are inserted in the Register | • Requires involvement of expert staff<br>• Longer procedure |

Where necessary, the Agency may request additional information from the applicant on matters regarding the validity of the application and inform the applicant of the period within which that information shall be provided. The Agency will set a reasonable deadline for providing the necessary missing information. This deadline will be dossier specific.

When the application does not fall within the scope of the Fertilisers Regulation as outlined in the definition or when it does not contain all the elements required the application shall be rejected. In that the Agency shall inform the applicant in writing indicating the reasons why the application is considered not valid.

The completeness check shall also be used to check the claim justification/proof of claim. Registrants shall provide enough evidences indicating that the proposed claim falls under the scope of the legislation (proof of claim). This has not to be confused with guaranteeing efficacy which is discussed later under this section.

Completeness check shall be based on a check list document (evaluation form) that will have to be developed. It is proposed to follow the approach as described in document 1663/VI/94 rev. 8 of 22 April 1998, *"Guidelines and criteria for the preparation and presentation of complete dossiers and summary dossiers for the inclusions of active substances in Annex I of Directive 99/414/EEC ( Articles 5.3 and 8.2)*". Additionally this check list document should include the following requirements (on the following list is an extract from the above mentioned guidelines):

| | |
|---|---|
| Date: | should be given as YY-MM-DD |
| Information test/study provided: | Four answers (yes, in part, no, not relevant) are possible. |

| | |
|---|---|
| Yes: | The data or information are available at the time when the dossier is being submitted. |
| In part: | A part of the data is available in a physically prepared form but supplementary studies are still missing as well as possible justifications. |
| No: | There is no data or information available. This answer is also correct, if in column two (justification provided) the place of the justification in the dossier (e.g. Doc. MII) is given. |
| Not relevant: | – Data and information which would not be necessary owing to the nature of the substance/product or its supported uses are not provided, or<br><br>- If it is not scientifically necessary or technically possible to supply information and/or data.<br><br>=> Data waivers justifications |
| Justification provided: | If Y (=yes) the chapter in the application dossier shall be mentioned (e.g. Doc. MII).<br><br>N stands for no. |
| Undertaking provided: | If Y (=yes) give date (YY-MM-DD).<br><br>N stands for no |

The Agency will undertake the completeness check of a registration dossier within one week under option 1 and one month under option 2 of the submission date.

### Notification of registration

After the completion of the completeness check, the Agency will notify the applicant of the outcomes of the completeness check. .

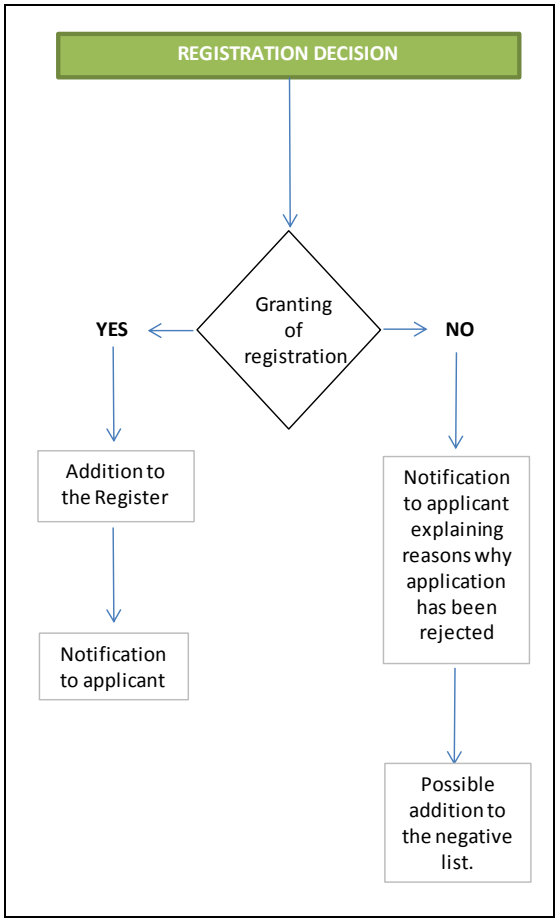
This information will either include:

- **The grant of the registration** and therefore the Agency will deliver a registration number which will then allow the placing on the market of the plant biostimulant or the agronomic fertiliser additive under the conditions specified by the registrant (i.e. conditions of use) and reported in a transparent way in the EU Registry. This Register will be updated by the Agency and the applicant will be informed of the registration of its substance(s) by electronic means (this letter will include the registration number to be indicated on the product label) but there will be no other kind of publications.

The registration will remain valid for a period of 10 years during which granted data protection and data confidentiality will apply. Registrations are renewable for 10-year periods (application for renewal sent to the Agency at least 1 year before expiration)

- **The refusal of the registration.** In any case the Agency shall motivate the reasons for which the granting of registration has been refused. The product may then be included in a negative list[88] by delegated acts.

**Figure 6 The registration process: from registration decision to notification**




The EU Register will take the form of a "catalogue" that will include several listings:

- A positive list for plant biostimulants;
- A positive list for agronomic fertiliser additives;
- A negative list for plant biostimulants to be up-dated after the adoption of the appropriate delegated act by the Commission;

[88] As a result of several consultations organised with Member States and stakeholders, the Commission has indicated that the future Fertilisers Regulation proposal would include as a safety net for fertilising materials and additives which cause concern for health, for the environment or which obviously do not deliver the expected functionalities, a negative list. The latter will be amended on a regular basis and could include total bans or restrictions for a specific or a group of fertilisers, soil improvers, growing media, plant biostimulants or agronomic fertilisers additives, on the basis of a proposal made by any Member State or the Commission itself and duly approved according to the new comitology rules.

- A negative list for agronomic fertiliser additives to be up-dated after the adoption of the appropriate delegated act by the Commission.

For each of the two positive lists, sub-lists (per category, functional group, type of product) may be developed if it helps the transparency of the information.

Each list will include the following information[89]:

- Product (in case of generic registration all commercial products linked to the generic authorisation shall be listed);
- Registration number;
- Category/functional group (if apply);
- Registration type (holder or generic);
- Registration holder(s);
- Date of Registration/expiry;
- Date of first registration;
- Conditions of use (crop, dosage, recommendations of optimal use).

The Agency shall be responsible for updating and maintaining the Register and the different lists. The Register being electronic, it is considered that any changes can be automatically communicated to a list of bodies and individuals that have indicated their interest for being informed of these modifications. This approach would allow sending modifications to national competent authorities and any other relevant official bodies.

#### *3.4.1.6 What happens after the registration has been granted?*

**Compliance check**

After registration decision and notification to applicants, the Agency may examine any dossier to verify if the information submitted by the applicant fully complies with the legal requirements. More precisely, compliance checks will aim at:

1) Evaluate in details the substance identity description and the safety information in the dossiers;
2) Assessing whether data waivers in Tier 2 and Tier 3 dossiers are well justified;
3) Assessing the quality of the data sets and evaluating the conclusions and expert judgements made by the applicant;
4) Actions 2 and 4 of option 2 of completeness check.

The compliance check will not apply to all dossiers. Applications will be selected for compliance check on the basis of the following principles:

- 30% of Tier 1 dossiers will be selected randomly;
- All dossiers where data required under Tier 2 and/or Tier 3 are presented; and

[89] See : French catalogue of Matières Fertilisantes et Support de culture avalable at: http://e-phy.agriculture.gouv.fr/

- A minimum of one dossier per applicant company will be selected for compliance checking.

In the targeted compliance checks, the Agency shall first evaluate the overall dossier and then shall focus on specific parts of the technical dossier based on specific safety and efficacy concerns.

The compliance check could lead to two main possible outcomes:

1) There is no administrative action if the dossier is considered as compliant with the information requirements.;
2) The compliance exercise may identify shortcomings that are not necessarily related to a lack of information. For example, the risk assessment data proposed by the applicant may be inadequate or the expert judgement may not reflect the reported study results. In these cases, the Agency will invite the registrant by written procedure to update and complete the dossier. When severe shortcomings are observed, the Agency may decide to delete the substance from the Register and therefore to withdraw the registration.

Following the compliance check, the Agency may conclude that additional testing or other information is required (e.g. modification of the mitigation measures). In these cases, the Agency prepares a draft decision to be sent to the applicant for comments. Based on the replied comments, the draft decision may be modified. The draft decision is sent to the Member States which can propose amendments. The final decision is drafted by the Agency after the examination of all received comments.

Whilst completeness check can be performed by administrative staff, the compliance check has to be performed by experts (toxicologists, eco-toxicologists, regulatory experts). Plant physiologists and agronomists are also required for checking compliance of the proposed claim (efficacy/utility). These experts should either be part of the Agency staff or/and could be part of dedicated experts panels or external consultants.

When a dossier is selected for compliance, the Agency shall provide its conclusions within a period of 6 months[90] of the date the Agency received a valid application. This period may be extended where the Agency requests additional information from applicants on matters related to compliance check. In exceptional circumstances the time limits for compliance may be extended if the nature of the matter in question so justifies.

### Review of the registration conditions by Member States

At any moment after the granting of the registration, data submitted by registrants could be examined by MS competent authorities on a voluntary basis in view of changing or confirming the conditions of the existing registration.

If a MS concludes on the basis of its own analysis that there is a need for reconsidering an existing registration, it is of the responsibility of the MS CA to submit a request to the Agency.

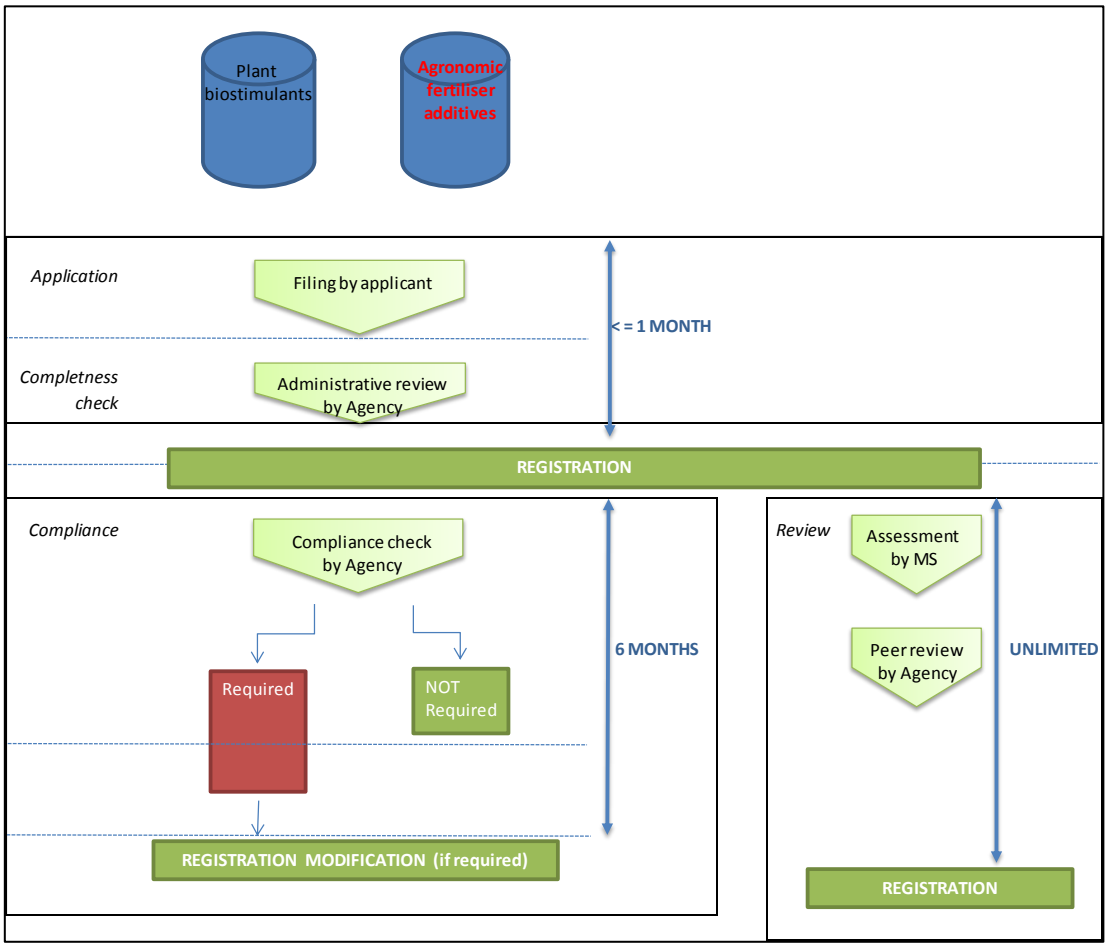
[90] Technical feasibility of respecting this timeline to be further analysed when discussions on the details of the approach take place.

This request for review shall include a detailed scientific based argumentation on the reason(s) why the MS considers that the registered product can lead to human and/or environmental safety issues.

This argumentation shall be based on data included in the dossier validated at the end of the completeness/compliance procedure. MS will not be authorised to ask for additional data to the applicants but can based its judgement on third relevant data.

The Agency will then organise a peer-review of the conclusions drawn by this MS. This peer-review will be circulated to all MS for comments and possibly for revision before a final decision (to withdraw, confirm or modify the authorisation consent) is taken.

**Figure 7 The overall registration process**



### Labelling obligations & MSDS

For each registered PB&AFA a MSDS shall be prepared by the registration holder. This MSDS shall be made available by publishing it online. It shall be developed according to the Global Harmonised System (GHS)[91].

PB&AFA shall be labelled with the following information:

- EC plant biostimulant or EC agronomic fertiliser additive followed by EU authorisation number;
- Substance name including its concentration in the commercial product. In case of microorganisms, the strain name and its concentration shall be mentioned on the label. In case of mixture of substances, each individual substance and its concentration in the final product shall be listed;
- Commercial name;
- Registry claim(s);
- Indication of conditions of use (dose rate, crops, group of crops, timing of applications, optimal conditions of use, others) as listed in the EU Register;
- Net mass or volume for fluid products at time manufacture measured and expressed as kg or L
- Expiration date;
- Batch number;
- Name and address of the distributor. When the product has been manufactured in another MS, the country of manufacturing shall be inserted (example: "*manufactured in Belgium*") ;
- Link to the website where the MSDS of the product can be consulted.

When a registered PB&AFA is mixed with an EC fertilising materials, labelling obligations of the EC FM and of the PB&AFA apply.

Products distributors are allowed to add additional information on the label but shall not claim additional benefit than the ones listed in the Register.

The items of information shall be clearly separated by means of a printed border from any other information provided, with the exception of the batch code which may be printed elsewhere on the package.

If the PB&AFA is packed, the information shall appear on the packages or on labels attached. The labels printed on the package must be placed in a conspicuous position and must be and must remain visible, indelible and clearly legible.

If the PB&AFA is delivered in bulk, the same information shall appear on the accompanying documents. In the case of PB&AFA delivered in bulk direct to the end-user by the manufacturer, the documents containing the labelling

[91] They have been made an integral part of the system of Regulation (EC) No 1907/2006 (REACH). The original requirements of REACH for SDSs have been further adapted to take into account the rules for safety data sheets of the Global Harmonised System (GHS) and the implementation of other elements of the GHS into EU legislation that were introduced by Regulation (EC) No 1272/2008 (CLP) via an update to Annex II of REACH

information shall accompany the goods and be accessible for inspection purposes, whether the goods are in loose form or in generic packaging.

The labelling and the accompanying documents must appear in at least the national language or languages of the Member State(s) in which the plant biostimulant is marketed.

### Post registration efficacy studies

These requirements apply to Option A only (see section 3.3.6).

The future fertiliser regulation shall refer to the possibility of requesting the marketing registration holder(s) to conduct post-registration efficacy studies, complementing data that have been made available at the time of initial registration. This applies to both holder and generic registrations.

Post-registration efficacy studies are not without precedent in the European Union's regulatory framework as it applies to the human medicinal products legislation and has been used for many years in the PPP regulatory framework. PPP were placed on the market on the basis of provisional authorisation of sale for a given period during which the registrant was asked to provide additional efficacy data. The Belgian authorities accept to deliver an authorisation for PB&AFA (called "derogation") on the basis of efficacy data performed in laboratories only. In these cases, registration holders are required to provide field trials data within a given period of time (defined on the case by case basis). Finally, the French bureau in charge of drafting new standards for fertilisers and other fertilising materials have made this proposal of establishing post-authorisation requirements for further proving field efficacy of PB.

It should be stressed from the outset that post-registration data should not lead to premature granting of marketing registrations. They cannot be used to compromise the initial level of evidence that is required to grant a standard registration (see chapter on data requirements).

The obligation to conduct post-registration trials addresses the impossibility to demonstrate efficacy in all agro-environmental EU conditions before registration. This approach also leads to the need for registration holders to perform agronomic trials together with independent advisory groups (e.g. Universities, technical institutes, etc.) for a couple of years.

These field trials shall preferably be performed under Good Experimental Practices even if no standardised protocols exist for PB&AFA.

A general summary[92] of these post-registration trials shall be submitted to the Agency by the registration holder(s) within a 3-year period after registration. This summary is meant to provide the Agency with additional key information of the efficacy of the PB&AFA under general and/or specific growing and climatic conditions, in order to either complement initial evidence or to verify whether the marketing registration should be maintained as granted, modified or even withdrawn on the basis of the new data resulting from the study. In case no data is submitted, the Agency shall decide to withdraw the registration.

A guidance document shall be provided on how information should be submitted. Data waiving can apply to this requirement.

[92] Detailed field trials results shall not be submitted but shall be made available on Agency request

#### Modification of registration

At any time after registration, the registration holder may request for a modification of its registration, by submitting a notification to the Agency in charge of the EU registry including all relevant data supporting the request for the changes.

After validation these modifications will be inserted in the Registry by the Agency. In case, the modification is deemed as unacceptable by the Agency, it shall motivate by writing its decision to the notifier. An appeal procedure shall be developed.

## 3.5 Costs of implementation

This section presents a preliminary approach to the implementation costs. Ideally this approach should consider the costs for the registrants in one hand and the cost for authorities in the other hand and then should segment between one-time cost at implementation and recurring costs.

This approach seems feasible for registrant costs and is presented below but for authority costs too many variable are unknown at this stage:

- The exact role of the Commission vs the responsible Agency is not yet sufficiently defined ;
- The responsible Agency is unknown. If EFSA is preferred no fees system will probably applied. If ECHA is the preferred choice then fees will have to levied;
- The number of registration dossiers will depend on the regulatory process to be anticipated. In 2011, DG ENTR asks EBIC to estimate the number of registration dossiers to be anticipated. EBIC estimated that its members would bring about 600-700 dossiers. However this estimation does not include the non-EBIC members;
- The exact registration process remains to be decided.

When consulting ECHA to discuss about the fees approach they would take if they would be the responsible Agency and then the costs of implementation, ECHA's responsible persons indicate that it is far too early to start estimating the required budget. Instead ECHA proposed to follow the approach applied for biocides which seems to have demonstrated efficiency. This approach relies on a detailed description of tasks for the Agency and on a pre-notification approach that would allow estimating the number of applications.

As our proposal leads to the possibility of having joint submissions, the details of the costs presented below apply to dossier and not to registrant to the exception of the post-registration costs that will certainly be company specific as part of the technical development strategy of each of them.

### 3.5.1 Costs per dossier

The costs per dossier[93] can be grouped under several cost items and reads as follows:

1) Fees: Fees shall apply at application time and other fees shall be paid for additional tasks performed by the Agency. DG ENTR proposed to set-up

[93] Arcadia International estimation based on discussion with industry representatives

the fees for application at € 1,758 per dossier and then to apply € 2,000 annual fees per dossier[94]. Some industry representatives met during the study considers that that level of fees is acceptable for application but too high for annual fees. According to them the additional fees should be based on true tasks carried out by the Agency and not a flat annual fee.

2) Production of the required data:

   a. Characterisation & identification of the PB&AFA (including analytical method, the proof of homogeneity and stability). These costs are highly dependent of the nature of the PB&AFA.

| Type of PB&AFA | Cost estimation *(in €)* | |
|---|---|---|
| | Low | High |
| Synthetised PB&AFA with fully defined formulation | 100,000 | 500,000 |
| PB&AFA defined by its raw materials and the manufacturing process | 10,000 | 20,000 |

All synthetised chemicals are subject to REACH registration and therefore these costs will apply anyway and no substantial extra costs will be required due to the use as PB or AFA (with the exception of an adaptation of the analytical method for instance)

   b. Safety data package (toxicology & ecotoxicology). Cost related to the production and analysis of the safety data largely depends on the volume of data that are included in registration dossier. Therefore these costs are estimated per Tier and may vary if some data are already available from REACH/CLP obligations and/or other sources (national registration, registration in other EU regulatory frameworks).

| Tox & Ecotox | Cost estimation *(in €)* | |
|---|---|---|
| | Low | High |
| Tier 1 only | 10,000 | 30,000 |
| Tier 1 + Tier 2 | 100,000 | 350,000 |
| Tier 1 + Tier 2 + Tier 3 | <500,000 | Up to 1-2 million |

   c. Efficacy data package

| Efficacy | Cost estimation *(in €)* | |
|---|---|---|
| | Low | High |
| Option A | | |
| - Pre application data | 10,000 | 30,000 |
| - Post-authorisation data | 20,000 | > 50,000 |
| Option B | 30,000 | 60,000 |

Option A – pre application data have the objectives to demonstrate the biological activity of the PB&AFA by any means and particularly literature review and laboratory testing. It is preferred to add field testing results but it is not a mandatory requirements as field trials will be performed after authorisation.

[94] Information provided during the course of the study by Commission

Under Option B, field trials are mandatory. On the basis of interviews with companies running field trials under GEP (e.g. Staphyt), it shall be noticed that individual trials are more expensive than trials for e.g. PPP as the protocol has to be drafted per type of product and as field efficacy is more difficult to establish. Our estimation is based on a unit cost of a minimum of € 5,000 for a replicated trial including 4-5 entries.

3) Registration dossier preparation and submission. This cost item includes the preparation of the registration dossier, the formulation of all expert judgements and the overall coordination with the Contract Research Organisations (VROs) in charge of carrying out the study tests. On average, regulatory consultants estimate the costs for these tasks at 20% of the total study costs.

4) Post application costs other than post-authorisation efficacy trials (follow-up and submission of additional data when required). These costs are highly depending of the outcome of the registration process. Industry is invited to provision these additional costs but no cost estimation can be given at this stage.

**Table 23 Summary of cost for registrant (Estimation per dossier - in €)**

| | Cost estimation *(in €)* | |
|---|---|---|
| | **Low** | **High** |
| ***Fees*** | | |
| Fees for application | 1,000 | |
| Annual fees per dossier | 2,000 | |
| ***Identification, characterisation, analytical methods & quality control*** | | |
| Well defined substances | 100,000 | 500,000 |
| NOT well defined substances | 10,000 | 20,000 |
| ***Tox, ecotox and environmental costs*** | | |
| Tier 1 only | 10,000 | 30,000 |
| Tier 1 + Tier 2 | 100,000 | 350,000 |
| Tier 1 + Tier 2 + Tier 3 | <500,000 | Up to 1-2 million |
| ***Efficacy*** | | |
| Option A | | |
| Pre application data | 10,000 | 30,000 |
| Post-authorisation data | 20,000 | > 50,000 |
| Option B | 30,000 | 60,000 |
| ***Preparation of registration dossier*** | | |
| | About 20% of above mentioned costs | |
| ***Preparation of registration dossier*** | | |
| | Cost specific to individual dossier. No estimation given | |

# Annex I: Cost of OECD test studies

| No. | Title | Price in Euros |
|---|---|---|
| *SECTION 1 - PHYSICAL-CHEMICAL PROPERTIES* | | |
| *Summary of Considerations in the Report from the OECD Expert Group on Physical Chemistry* | | |
| 105 | Water Solubility | 4250 |
| *SECTION 2 - EFFECTS ON BIOTIC SYSTEMS* | | |
| *Summary of Considerations in the Report from the OECD Expert Group on Ecotoxicology* | | |
| 201 | Freshwater Alga and Cyanobacteria, Growth Inhibition Test | 1695 -2120 |
| 202 | Daphnia sp. Acute Immobilisation Test | 1695-2120 |
| 203 | Fish, Acute Toxicity Test | 1695-2120 |
| 204 | Fish, Prolonged Toxicity Test: 14-Day Study<br>Supported analysis | 5985<br>5145 |
| 205 | Avian Dietary Toxicity Test | 4150-8250 |
| 207 | Earthworm, Acute Toxicity Tests | 1995 |
| 208 | Terrestrial Plants, Growth Test | 7650 |
| 211 | Daphnia magna Reproduction Test<br>Supported analysis | 16280<br>8190 |
| 212 | Fish, Short- term Toxicity Test on Embryo and Sac-fry Stages | 22230 |
| 213<br>214 | Honeybees, Acute Oral Toxicity Test<br>Honeybees, Acute Contact Toxicity Test | 2420-3300 |
| 216 | Soil Microorganisms: Nitrogen Transformation Test | 8890 |
| 217 | Soil Microorganisms:Carbon Transformation Test | 8890 |
| 219 | Sediment-Water Chironomid Toxicity Using Spiked Water | |
| 222 | Earthworm Reproduction Test (Eisenia fetida/Eisenia andrei) | 5565 |
| 223 | Avian Acute Oral Toxicity Test | 3530-5880 |
| 237 | Honey bee (Apis mellifera) larval toxicity test, single exposure | |
| *SECTION 3 - DEGRADATION AND ACCUMULATION* | | |
| *Summary of Considerations in the Report from the OECD Expert Group on Degradation/Accumulation* | | |
| 301 | Ready Biodegradability 301A : DOC Die-Away Test | 4450 |
| 301 | 301B : CO2 Evolution Test | 5960 |
| 301 | 301C : Modified MITI Test (I) | 5560 |
| 301 | 301D : Closed Bottle Test | 2600 or 3070 |
| 301 | 301E : Modified OECD Screening Test | 3445 |
| 301 | 301F : Manometric Respirometry Test | 2600 |
| 305 | Bioaccumulation in Fish: Aqueous and Dietary Exposure<br>Prelim study of 28 days<br>Main study | <br>20000<br>45000 to 65000 |
| *SECTION 4 - HEALTH EFFECTS* | | |
| *Summary of Considerations in the Report from the OECD Expert Groups on Short and Long Term Toxicology* | | |
| 401 | Acute Oral Toxicity | 1050 - 1600 |
| 402 | Acute Dermal Toxicity | 1050 - 1600 |
| 403 | Acute Inhalation Toxicity | 11450 - 15950 |
| 404 | Acute Dermal Irritation/Corrosion | 1000 |
| 405 | Acute Eye Irritation/Corrosion | 3000 |
| 406 | Skin Sensitisation | 5950 |
| 407 | Repeated Dose 28-Day<br>Oral Toxicity Study in Rodents | 39950 |
| 408 | Repeated Dose 90-Day<br>Oral Toxicity Study in Rodents | 87250 |
| 409 | Repeated Dose 90-Day<br>Oral Toxicity Study in Non-Rodents | 129950 |
| 410 | Repeated Dose Dermal Toxicity:90-Day | 62950 |
| 411 | Subchronic Dermal Toxicity: 90-day Study | 112995 |
| 424 | Neurotoxicity Study in Rodents | 70000 |
| 451 | Carcinogenicity Studies | 699950 |
| 452 | Chronic Toxicity Studies | 289950 |
| 453 | Combined Chronic Toxicity/Carcinogenicity Studies | 799950 |

## Annex II: Comparison between EFSA and ECHA

Extract from Commission staff working document Impact Assessment on the Revision of Regulation 178/2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority (EFSA) and laying down procedures in matters of food safety on the establishment of fees for EFSA. (Available on the IA webpage of the IA Board of the Commission Secretariat General).

*13. ANNEX VII DIFFERENCES BETWEEN ECHA AND EFSA SYSTEMS*

*As it happens for substances/products authorised within the EFSA system, chemical substances/products are used in many different end products. The EU chemicals industry has a key position in the value chain. A series of operators (biocides, plastics, pesticides for example) are also concerned by the two legislative frameworks governing chemical safety and food safety.*

*The chemical and food legislative framework on safety are however based on completely different premises.*

*The ECHA system relies on the principle that chemical substances might contain hazardous properties but, if managed properly, can be safely used. The distinction between hazard and risk is, therefore, key to the safe management of chemicals. Chemicals are mainly used by industry and only a limited range of products are sold to final consumers. The approach adopted within the ECHA system is that industry itself is best placed to ensure that the chemicals it manufactures and puts on the EU market do not adversely affect human health and environment. To this end, industry has to have sufficient knowledge of the properties and characteristics of chemical substances to be able to manage their potential risks properly.*

*The EU chemical sector is therefore based on the principle "no data, no access to the market" and a registration system was established to put in a concrete form this principle. The registration of chemical substances aims at providing data on all chemical substances produced and imported in the EU in a tonnage per year exceeding 1 tonne. The registration and other tools linked to it (i.e. classification and labelling, safety data sheets) ensure that sufficient knowledge on substances is given to the relevant actors of the chemical chain in order to adequately manage the risks.*

*Only substances of very high concern are submitted to restrictions and authorisation. Where there is an unacceptable risk to health or the environment, restrictions at the EU level concerning the manufacture, placing on the market or use or prohibition of any of these activities may also be imposed. Proposals for restrictions may be prepared by a Member State or by the Agency on behalf of the Commission in the form of a structured dossier that shall demonstrate that there is a risk to human health or the environment that needs to be addressed at EU level and to identify the most appropriate set of risk reduction measures. ECHA manages several tools and support the whole system.*

*The food legislative system on safety and the tools used in that field are based on different principles due to the specificity of risks linked to food. The risk of exposure always exists in that sector since food is consumed every day by final consumers. In addition, consumers cannot take any risk management measures on substances foodstuffs contain. For this reason all food legislations are based on the principle that only*

*safe food can be put on the market. This principle implies that all substances added to food or that can be present as residues in food are subject to an authorisation before being put on the market (pre-market approval). Such pre-market approvals exist since the beginning of the EU (the harmonisation of national systems is in place since the beginning of the XX century) and they now cover all safety issues linked to the addition of substances in food. Since substances ingested by animals can be found in food pre-market approvals cover also feed.*

*The use of a registration system instead of a pre-market approval would not guarantee an adequate protection to consumers. Even if the latter knew the characteristics of substances contained in food or sold as a food (e.g. sweeteners) they could not take any measure at their level to avoid the risk or limit it, except by not consuming it. Labelling and information are not sufficient to protect them.*

*As a consequence, it is not possible to align the chemical safety system and the food one because each one is tailored to the specificity of the risks in its own area.*

*Also, from a legal point of view, the putting in place of a registration system for EFSA would require the modification of the legislation regulating the 19 sectors falling under EFSA's mandate. In addition, historically the REACH system required the registration of all chemical substances because 99% of the substances on the market were unknown. This involved a rather high cost for industry (€2.1 billion for the first registration period[95]). A similar need for registration of substances used in the food sector does not exist because they have been subject to a pre-market approval since a long time and they are thus known.*

*As far as the fee system is concerned, the number of applications received by the two agencies is significantly different. ECHA received roughly 6 900 applications per year from 2008 to 2011, while EFSA from 2003 to 2010 received on average 189 (without reviews) applications per year. This has a great impact on the income the Agency can get from fees. However, in the food legislative framework, it is not possible to identify a larger series of operators as fee-payers than applicants for generic and individual authorisation. It would also not be justified to create a system requiring a large number of operators to register because the safety of substances/products added to food have already been assessed and authorised since a long time.*

*Moreover, tasks of ECHA mostly relate to the registration of chemicals substances. This is reflected in its system of fees that provide for the payment of a fee in the following cases:*

- *Submission of a registration;*
- *Request (in a registration submission) that certain information is kept confidential;*
- *Update of a registration submission that refers to a change in the tonnage range;*
- *Update of a registration submission that relates to a change in the identity of the legal personality of the registrant;*
- *Update of a registration submission that relates to a change in the access granted contained in the registration submission;*
- *Notification to the Agency of product and process orientated research and development activities, with a view to obtain an exemption from the obligation to register;*
- *Application for an authorisation under Article 62 of the REACH Regulation;*

[95] See, CSES, Interim Evaluation: Functioning of the European chemical market after the introduction of REACH, 30 March 2012, available at http://ec.europa.eu/enterprise/sectors/chemicals/files/reach/review2012/market-final-report_en.pdf.

- *Appeals to the Board of Appeals of the Agency against decisions of the Agency listed in Article 91(1) of the REACH Regulation.*

*On the contrary, the tasks of EFSA relate to the risk assessment process linked to the authorisation of substances/products added to food or that can be present as residues in food (residues of pesticides for example).*

*If a registration system was not to be put in place for EFSA, only ECHA authorisation tasks and the correlated fee could be considered as a relevant example for EFSA. However, the procedure for authorisation foreseen in the ECHA system is rather peculiar since it is aimed at ensuring that the risk is properly controlled and favouring substitutes.*

## Annex III: Estimated application cost of an active substance based on a plant extract in the context of the Plant Protection Product Regulation (EC) No 1107/2009

| | | Min. | Max. |
|---|---|---|---|
| Identity | | | |
| Analytical methods for characterisation | Development of 3 markers | 50,000.0 | 150,000.0 |
| Analytical methods for impurities | ELISA methods for mycotoxins | 10,000.0 | 20,000.0 |
| Analytical methods for residues | No data submitted | | |
| | | | |
| Physical & chemical properties | 9 studies provided | 50,000.0 | 150,000.0 |
| | | | |
| Monitoring/enforcement methods | No data submitted | | |
| | | | |
| Classification & proposed labelling | see consultancy & mgt costs | | |
| | | | |
| Impact on human and animal health | | | |
| Absorption, distribution in mammals | No data submitted | | |
| Acute toxicity | | | |
| Rat LD50 oral | | 1,050.0 | 1,600.0 |
| Rat LD50 dermal | Not required | | |
| Rat LC50 inhalation | Not required | | |
| Skin iritation, rabbit | OECD 404 | 1,000.0 | 1,000.0 |
| Eye irritation, rabbit | OECD 405 | 3,000.0 | 3,000.0 |
| Skin sensitization | LLNA - OECD 429 | 5,950.0 | 5,950.0 |
| Short term tox | | | |
| Relevant oral NOAEL | 90-day oral rat | 112,000.0 | 113,000.0 |
| Genotoxicity | AMES test OECD 471 | 50,000.0 | 50,000.0 |
| Long term tox | No data provided | | |
| Reproductive target | No data provided | | |
| Neurotoxicity | No data provided | | |
| Other tox studies | Literature data on genotoxicity of 4-hydroxyisoleucine, trigonelline, flavonoids: not mutagenic. | | |
| Medical data | No data provided | | |

| | | | |
|---|---|---|---|
| Residues | No data provided | | |
| Metabolism in livestock | No data provided | | |
| Consumer risk assessment | Not relevant | | |
| Processing factors | No data provided | | |
| Proposed MRL | Not relevant | | |

| | | | | |
|---|---|---|---|---|
| Fate & behaviour in the environment | | | | |
| | Route of degradation in soil | No data submitted | | |
| | Soil adsorption/desorption | No data submitted | | |
| | Mobility in soil | No data submitted | | |
| | PEC (soil) Value | see consultancy & mgt costs | | |
| | Route of degradation in water | No data submitted | | |
| | PEC (surface water) Value | see consultancy & mgt costs | | |
| | PEC (sediment) Value | No data submitted | | |
| | PEC (groundwater) Value | No data submitted | | |
| | | | | |
| Fate and behaviour in air | | No data submitted | | |
| | | | | |
| Ecotox | | | | |
| | Effects on terrestrial vertebrates | | | |
| | Acute tox to mammals | | (see above) | (see above) |
| | Sub-chronic tox to mammals | | (see above) | (see above) |
| | Acute tox to birds | | 3,600.0 | 6,000.0 |
| | Tox data for aquatic species | | | |
| | Oncorhynchus mykiss (acute) | | 1,695.0 | 2,120.0 |
| | Daphnia (acute) | | 1,695.0 | 2,120.0 |
| | Scenedesmus (acute) | | 1,695.0 | 2,120.0 |
| | BCF | Not required | | |
| | Oral tox on bees | | 2,420.0 | 3,300.0 |
| | Acute contact on bees | | | |
| | | | | |
| | Other arthropod species | No data submitted | | |
| | | | | |
| | Effects on earthworms | | | |
| | Acute tox | OECD 207 | 1,900.0 | 2,000.0 |
| | | | | |
| | Effect on micro-organisms | | | |
| | Nitrogen mineralisation | | 8,800.0 | 8,900.0 |
| | Carbon mineralisation | | 8,800.0 | 8,900.0 |
| | | | | |
| Efficacy | | | 30,000.0 | 50,000.0 |
| | | | | |
| | | ***Total (cost of studies)*** | ***343,605.00*** | ***580,010.00*** |
| | | | | |
| | ***Regulatory costs, drafting of the registration file, overhead costs (25% of costs of the studies)*** | | **85,901.25** | **145,002.50** |
| | | | | |
| | | ***Total*** | ***429,506.25*** | ***725,012.50*** |

## Annex IV: EBIC proposal: Guidance document for determining the number of trials needed

"*EBIC suggests the following guideline to help applicants determine the appropriate number of trials, depending on the nature of the claim and to prevent excessive requests for trials from reviewing authorities. Notwithstanding this guideline, applicants will need to adapt their trial regime to the specific claim being made, especially as several of the examples listed below may apply. Where applicable, appropriate scientific literature may be substituted for one or more of the trials suggested:*

| Claim that can credibly be made on this basis | Suggested number of trials |
|---|---|
| *Effect claimed for a specific crop*<br><br>*Example: Improves strawberry ripening* | *2 trials on the crop either over two years or in two different growing contexts*[96] *during the same year.*<br><br>*Example: Product is successfully demonstrated on strawberries in the field in a single location over two years or tested in the field and in a greenhouse the same year.* |
| *Effect can be claimed for the entire crop group*<br><br>*Example: Fosters fruit setting in pome fruits* | *2 trials on 2 different crops within a single group either over two years or in two growing contexts the same year.*<br><br>*Example: Product is successfully demonstrated on apples and pears in a single location over two years or in two different locations with different growing conditions in a single year.* |
| *Effect can be claimed without being required to limit it to any specific crop grouping*<br><br>*Example: Helps crops tolerate drought stress in open-air growing contexts* | *3 trials on 3 crops from 3 different groups.*<br><br>*Example: Product is successfully demonstrated on cereals, apples and peppers.* |
| *Effect can be claimed without having to restrict it to any specific* | *3 trials in 3 different growing contexts*<br><br>*Example: Product is successfully* |

[96] Robust descriptions of the growing contexts including variables such as climate, soil conditions/growing media, irrigation versus rain-fed, etc. should be provided by the applicant in the description of the research. No standardized list of growing contexts or soil types/growing media is necessary.

| Claim that can credibly be made on this basis | Suggested number of trials |
|---|---|
| *growing contexts*<br><br>*Example: Fosters tomato ripening under most growing conditions* | *demonstrated under greenhouse conditions, in irrigated semi-arid conditions and in a temperate agricultural zone.* |

*The nature of the claim is important because it may naturally limit the variations in trials needed to demonstrate an effect. For example, it would make no sense to submit a trial on cereals for a biostimulant that fosters fruit ripening or sugar content of fruit.*

*Broadening claims*

*If at any point, the applicant wants to broaden the registered product claims, it must notify the implementing agency and provide results from two trials to validate the new parameter(s). GEP/GLP certification is not required for this data as long as the quality can be considered substantially equivalent to what a certified facility would achieve."*