Executive Summary:
The main objective of ProLarix was to facilitate the translation of an innovation developed under the FP7 project ForestSpeCs from an intriguing concept to a business model for European SMEs in forestry and the agricultural sector.

Constituents of larch (Larix) by-products were demonstrated in FP7 project ForestSpeCs to have high potential to be developed into a fungicide with (i) high efficacy against a key disease of agriculture, (ii) a favourable environmental profile with respect to environmental impact and use of renewable resources, as well as (iii) a high potential to generate added value in the forest industry and European production of ‘smart’ crop protection technologies.
ProLarix’ objectives included (i) the pilot production and identification of uses of a larch extract (Larixyne®), (ii) validation of efficacy and demonstration of its value as a PPP in European grapevine production systems, (iii) demonstration of large scale production of high quality product, (iv) filling in data gaps and provision of an initial data set to be used for future registration and (v) a road map for the development of a full dossier and capture of the market.

As part of WP2, the analytical methodology and protocols were developed to analyze Larix extracts and to quantify Larixyne® in raw material, technical extracts and formulated products, providing the set of analytical tools relevant for identification of sources, quality control and characterisation of technical material. Potential high-yield sources for extraction of Larixyne® constituents were identified by collecting over 50 samples of Larix across Europe. Three species of Larix were sampled; L. decidua, L. gmelinii and L. kaempferi. The survey indicated that raw material for Larixyne® extraction is available in large quantities and suitable for extraction at commercial scale. Scalable extraction protocols were developed to produce high quality technical grade extract from a range of sources of raw material. The evaluation process demonstrated that a resource-efficient, scalable and environmentally safe extraction protocol is feasible. Based on optimized low volume extraction protocols, upscaling of extraction was explored and further optimized in a pilot extraction plant. The pilot allowed for the production and formulation of 1 kg of Larixyne® in 2014 and more than 6 kg in 2015. The development of formulations of Larixyne® for field use resulted in two optimized formulations. Both formulations excelled with respect to shelf life (no loss of activity after 24 months storage), and handling.

WP3 focused on the evaluation of pilot extracts and formulations of Larixyne® on grapevine in field conditions as well as on the implementation of Larixyne® in European plant protection strategies adapted to a range of pedo-climatic conditions and varieties. Larixyne® treatments provided consistent and significant activity against downy mildew under a wide range of pedo-climatic conditions whether applied alone or implemented in a spray programme with reduced amounts of other fungicides.

WP 4 aimed at the identification of additional market opportunities for Larixyne® in plant protection. Larixyne® was evaluated in a series of plant-pathogen combinations elucidating five additional potential markets for its commercialization.

WP 5 aimed at (i) the compilation of a first stage registration dossier, (ii) the development of a roadmap for registration and market introduction and (iii) the adoption of an appropriate IP protection strategy including patenting and brand name protection.

The data package compilation conducted in ProLarix revealed no critical issues and was essential to obtain a clear view regarding the overall feasibility of commercialization of Larixyne®. As one of the core outputs of ProLarix, a roadmap for registration and market introduction of Larixyne® was developed. From the regulatory point of view, registration of Larixyne® seems feasible, especially since the available data do not suggest a problematic toxicological profile. Profitable production of Larixyne® will be feasible in the future, provided that a range of processes can be made more cost-efficient. This includes logistics as well as manufacturing processes. Necessary investments including registration costs, additional R&D as well as setting up logistics and manufacturing lines were estimated 5-10 m Euro. In a best case scenario, Larixyne® will enter the European market in 2022. The road map demonstrated that the market introduction of Larixyne® is indeed feasible from the technical and economic point of view, and an appropriate risk management strategy can be developed. To protect background and foreground IP related to Larixyne®, a protection scheme was developed and implemented.
Pests and diseases are a constant threat to agricultural production and climate change will probably escalate their occurrence, prevalence and severity. The availability of chemical agents to combat plant pathogens is limited, since pesticides have proven to be often hazardous for both the environment and human health and their use should be reduced or avoided whenever possible. For example, copper is widely used to control devastating plant diseases including downy mildew of grapevine (Plasmopara viticola), late blight of potato and tomato (Phytophthora infestans), apple scab (Venturia inaequalis) and a large range of other crops and plant pathogens. However, copper needs to be replaced urgently due to its unfavorable ecotoxicological profile. Thus the need for the discovery and development of new sustainable alternatives is significantly increased. Control of pathogens by means of plant-derived plant protection products (PPPs) can be an effective, sustainable and environmentally-friendly method for crop protection as part of pest management practices in integrated pest management (IPM) and organic farming systems. To utilise abundant sources of wood waste as raw material for value-added products such as fungicides has high business potential and this approach is consistent with the overall objectives of the EC’s 7th Framework Programme for sustainable use of renewable bio-resources.

The FP7 research project ForestSpeCs (completed in October 2012), succeeded in identifying that highly active fungicidal constituents (Larixyne®) are present in Larix sp. (patent filed). There is a high potential economic and societal interest in producing Larix extracts as a ‘green’ plant protection product, but further steps are required before commercialization can be undertaken.

The development of Larixyne® fitted into the business and innovation needs of consortium partner TM, a SME specialized in the production of plant-derived PPPs. Furthermore, using Larixyne® as a show case for the registration of botanicals under the new ‘guidance document on botanicals used in plant protection products’ opened the avenue to the market for other innovative PPPs and also will attract investors to the sector. The European forest and furniture industry will find an opportunity to utilise abundant sources of wood waste as raw material for value-added products. This will set an important example since, so far, the possibilities of using bark as a raw material for bioactive compounds have gained only moderate attention in comparison with using bark as a marginal and small-scale energy source.

The approval process for an active substance and subsequent authorization of a plant protection product has become increasingly complex over the last years. This counts in particular for botanicals. DG SANTE developed a new revised ‘EU Guidance Document on Botanical Active Substances used in Plant Protection Products’ (SANCO/11470/2012– rev. 8, 20 March 2014). There is an urgent need to gain experience with the revised registration process in order to facilitate the rapid commercialization of a range of novel botanicals that are currently developed by innovative companies and FP7 supported RTD activities.

The overall objective of the FP7 project ProLarix was to facilitate the market introduction of an innovative plant protection product (Larixyne®) made from by-products of the European forest industry. The specific objectives were to

- Optimize extraction and up scale the production of standardized technical grade Larix extract,
- Validate the efficacy and to integrate Larix extracts in state-of-the-art grapevine production systems and to explore further markets
- Develop a roadmap for registration and market introduction at EU and member state level.

Project Results:

WP2 aimed at the optimization of extraction and up-scaled production of standardized technical grade Larix extract (‘Larixyne®’). As part of WP2, analytical methodology and protocols were developed to
analyze Larix extracts and to quantify Larixyne® components and co-constituents in raw material, technical extracts and formulated products. The active constituents of Larix species are two diterpenoids, LD-001 and LD-002. A third component has a structure similar to LD-002 but has a lower activity, so it is considered a compound of interest as a primary impurity. Qualitative and quantitative GC-FID and HPLC methods to identify and quantify LD-001, LD-002 and the third component have been identified, providing the set of analytical tools relevant for identification of sources, quality control and characterisation of technical material in manufacturing and registration dossiers. These methods satisfy the requirements for identification and quantification of the compounds of interest in plant extracts.

Potential high-yield sources for extraction of Larixyne® constituents were identified by collecting over 50 samples of Larix across Europe. Three species of Larix were sampled, L. decidua L. gmelinii and L. kaempferi. Sampling covered seven different countries ranging from Finland to Italy, and included altitudes ranging from sea-level to high Alps. The collected samples consisted of bark, wood, twigs of different size, trees of different age, and single trees vs. aggregate samples (e.g. at sawmills).

The concentration of Larixyne® constituents was found to vary between bark samples. No correlation between latitude, altitude or height respectively and Larixyne® content was found. The survey indicates that raw material for Larixyne® extraction is available in large quantities, suitable for extraction at commercial scale.

Extraction technology at commercial scale aims at the production of technical grade extract containing a high concentration of active ingredients, a high purity, efficient use of unproblematic solvents, low energy consumption, constant quality across a range of variable raw material, and excellent storage stability. Scalable extraction protocols were developed to produce high quality technical grade extract from a range of sources of raw material. The evaluation included a wide range of solvents and sequences thereof, as well as optimized temperature regimes. The evaluation process demonstrated that a resource-efficient, scalable and environmentally safe extraction protocol is feasible.

The formulation of botanicals is essential to achieve solubility in spray solutions, optimum spread on leaf surfaces, protection against degradation by UV as well as to provide rain fastness. Furthermore, the formulation is often crucial to prevent degradation of active components during storage. The development of formulations of Larixyne® included phys-chem trials as well as controlled conditions trials on grapevine plants and artificial inoculation with Plasmopara viticola. In this process, more than 100 formulations were evaluated for phys-chem properties and the best 38 pilot formulations were also evaluated for efficacy against downy mildew, rain fastness and lack of phytotoxic effects in controlled conditions bioassays. For the season 2014, LAR-016 and LAR-023 were selected as best suited formulations to be used in field trials. After a second series of optimization trials, LAR-016 and LAR-042 were selected for further evaluation of efficacy and LAR-016 was selected for the evaluation of the toxicological profile (human and ecotox). Both formulations excelled with respect to shelf life (no loss of activity after 24 months storage), and handling. Further activities will aim at improving rain fastness.

Based on optimized low volume extraction protocols, upscaling of extraction was explored and further optimized for efficacy in a pilot extraction plant. The pilot allowed for the production and formulation of 1 kg of Larixyne® in 2014 and more than 6 kg in 2015. The optimization of the extraction method could not be finished within the project. There are trade-offs between the currently identified methods, e.g. uses of more cost-effective solvents also often lead to lower extraction efficiency while higher extraction efficacy also often leads to more impurities. However, there are many options to further simplify/improve the process, giving higher yields, fewer waste products and lower costs.

WP3 focused on the evaluation of pilot extracts and formulations of Larixyne® on grapevine in field
The aim of the experiments under task 3.1 were to test the efficacy of Larixyne® pilot formulations against downy mildew, caused by Plasmopara viticola, under field conditions. The experiments were carried out 2014 and 2015 in the screening vineyard situated at FiBL in Frick, Switzerland on the cultivars ‘Müller-Thurgau’ and ‘Chasselas’. The experiment was arranged in a randomized block design according to EPPO guidelines.

Throughout the whole season, grapevine plants were treated according to weather conditions and infection risk, calculated by the forecast model ‘vitimeteo’. A copper reference treatment, a low copper reference treatment (only in 2014) and a standard fungicide strategy were compared to Larixyne® pilot formulations and to an untreated control. In both years, Larixyne® was tested in two formulations (2014: LAR-016 and LAR-023; 2015: LAR-016 and LAR-042). Products were sprayed with compressor based spray equipment. Several assessments of disease incidence and disease severity were carried out during the season on leaves and on grapes. In 2014, disease incidence and disease severity of downy mildew reached 100% and 50% respectively on leaves of the untreated control at the end of the season in August. In 2015, disease incidence and severity remained relatively low, with 52% and 9% respectively, due to hot and dry weather conditions in July and August. The standard fungicide program as recommended for Swiss organic grapevine production protected leaves and fruit very efficiently from downy and powdery mildew (>92% efficacy with 16 treatments).

Larixyne® formulations showed significant efficacy against downy mildew on leaves and grapes at the end of the field season in August 2014. The efficacy was further improved by optimized formulations in 2015. Differences between Larixyne® formulations were not significant in 2015, albeit LAR-042 demonstrated the potential for further improvements of the formulation.

In 2014 and 2015, there was unusually high disease pressure by powdery mildew caused by Oidium tuckeri. The standard fungicide program, recommended for Swiss organic grapevine production, protected leaves and fruit very efficiently from powdery mildew (>90% efficacy). In both seasons, Larixyne® pilot formulations showed good efficacy against powdery mildew on grapes.

In conclusion, Larixyne® reduced downy mildew significantly in two subsequent seasons. Yet, to use Larixyne® as a stand-alone fungicide, efficacies have to be further improved e.g. by improved formulation or higher concentrations. The implementation of Larixyne® in a spray programme with other fungicides could also provide an interesting strategy that was explored in 2015 in a field trial in two field trials in Italy and Greece.

To evaluate the potential for implementation of Larixyne® in current IPM and organic grapevine production systems, efficacy of Larixyne® (formulation LAR-016) was tested in 2015 (i) at three locations (Frick, Switzerland; S. Micheletto a/A, Trento, north-east Italy; Veria, Northern Greece) under different climatic conditions in experimental vineyards on disease susceptible cultivars (cv. Müller-Thurgau and Chasselas in Frick, cv. Pinot gris in S. Micheletto and cv. Chardonnay in Veria) and (ii) in a commercial vineyard in Frick (Switzerland) on ten different partially disease resistant grapevine (‘PiWi’) cultivars. All field trials were arranged in complete randomized block designs with three (PiWi trial) or four (all other trials) blocks.

In the field trial on susceptible cultivars in Switzerland, LAR-016 was used in a stand-alone strategy, with a total of 16 treatments. In Italy, treatments started with LAR-016 until bloom, then copper was used during the period with the highest disease pressure, before changing back to the LAR-016 treatment, resulting in a total of 15 treatments, 11 of which were LAR-016. In Greece, two treatments with LAR-016 were followed by one treatment with the copper reference and then eight LAR-016 treatments. In the PiWi field
trial, only five treatments with LAR-016 were conducted during the whole season, during periods with highest risk of infection. All field trials included either a copper reference (field trials on susceptible cultivars) or an organic standard fungicide treatment consisting of sulphur plus acidified clay minerals (Myco-Sin) (PiWi-trial).

In 2015, disease pressure by downy mildew was moderate in Switzerland, Italy and Greece due to very hot and dry weather conditions in July and August. In all three field trials on four different susceptible grapevine varieties, LAR-016 showed significant activity against downy mildew on leaves as well as on grapes. In the PiWi trial, efficacy of LAR-016 against downy mildew was insufficient, probably due to large intervals between sprays and limited rain fastness, while efficacy against powdery mildew was significant on leaves as well as grapes.

In conclusion, LAR-016 treatments provided consistent and significant activity against downy mildew under a wide range of pedo-climatic conditions. However, to use Larixyne® as a stand-alone fungicide, activity needs be further improved e.g. by improved formulation. In contrast, implementation of Larixyne® in a spray programme with reduced amounts of other fungicides is a promising strategy.

WP 4 aimed at the identification of additional market opportunities for Larixyne® in plant protection. In order to identify the range of action and the additional uses of Larixyne® as a biological fungicide in the field of plant protection, Larixyne® was evaluated in a series of plant-pathogen combinations. The efficacy of Larixyne® was explored in the economically important cropping commodities as well as selected high-value ‘minor uses’: Tomato – Phytophthora infestans (Oomycete); Cucumber – Pseudoperonospora cubensis (Oomycete); Parsley – Plasmopara petroselini (Oomycete); sweet basil - Peronospora belbahrii (Oomycete); Bean – Uromyces appendiculatus (Basidiomycete); Rosemary – Neoërysiphe galeopsidis (Ascomycete); Grapevine – Oidium Tuckeri (Ascomycete); Apple - Erwinia amylovora (bacteria); Tomato – Pseudomonas sp. (bacterium). In five out of nine of the evaluated test systems, Larixyne® significantly reduced disease, thus elucidating additional potential markets for its commercialization.

WP 5 aimed at (i) the compilation of a first stage registration dossier, (ii) the development of a roadmap for registration and market introduction and (iii) the adoption of an appropriate IP protection strategy including patenting and brand name protection.

Data requirements for the approval of Larixyne® as an active substance and for registration of a formulated product under Regulation (EC) 1107/2009 were evaluated using EU data requirements (Commission Regulations (EU) No 283/2013 and 284/2013 EU for active substances and formulated products) and the EU Guidance Document on Botanical Active Substances used in Plant Protection Products (SANCO/11470/2012– rev. 8, 20 March 2014).

A regulatory strategy was developed using the SANCO guidance document 11470 “Guidance Document on Botanical Active Substances used in Plant Protection Products” from March 2014. This strategy is based on the definition of the technical grade extract as the active ingredient.

Data requirements for approval to use Larixyne® as plant protection product under Regulation (EU) 1107/2009 were compared with data generated during the project, resulting in a standardized ‘Check of Completeness’ (CoC) study. Based on the CoC, a data gap analysis was conducted and a strategy to address the gaps by means of literature studies and/or experimental studies was devised. Data from the project partners, information from published literature and data generated during the project were compared to data requirements for physical-chemical properties, analytical methods, toxicology, residues, environmental fate and behaviour, ecotoxicology, and efficacy. Information on extraction methods, extract composition and product formulation was also included and complemented by the description of analytical methods for generation of a chromatographic “fingerprint”. The specification of the active ingredient will be
finalized based on up scaled extraction of material using the pilot plant. Field trials and the first toxicological and ecotoxicological studies were conducted using the pilot formulation LAR-016 which may need further refinement. These studies can serve as “supportive data” for dossier preparation. Additional studies need to be conducted once the final extraction process and product formulation are established. As part of the preparation of the roadmap to registration, a range of selected toxicity related trials and ecotoxicological trials was conducted with the technical grade extract containing LD-001 and LD-002 and its pilot formulation LAR-016. No vertebrate studies were conducted with the product at this stage as the extraction method and specification were not yet defined. These studies need to be conducted once raw material and the extraction method are fixed and the specification is defined. Toxicology studies were conducted in vitro to determine whether Larixyne® has mutagenic (two independent experiments on Salmonella typhimurium assay on strains TA98, TA100, TA102, TA1535 and TA1537) or genotoxic activity (micronucleus test using human peripheral lymphocytes). Under the present test conditions, Larixyne® caused no mutagenic effect in the strains TA98, TA100, TA102, TA1535 and TA1537 neither in the plate incorporation test nor in the preincubation test each carried out without and with metabolic activation. Larixyne® tested up to cytotoxic concentrations in the absence and in the presence of metabolic activation revealed no indications of chromosomal damage in the in vitro micronucleus test. Exposure of humans (operators, workers, bystanders and residents) was calculated using EFSA guidance based on the application rates for Larixyne® which were used in the field trials. These exposure data will need to be compared with data on toxicity trials which need to be generated in vertebrate experiments.

Formal studies following EU guidelines were conducted to assess the effect of the formulated product on aquatic and terrestrial non-target arthropods. Additionally, initial experimental data on oral toxicity and contact toxicity of a Larixyne® formulation to honeybees were tested in a design comparable to “OECD GUIDELINES FOR THE TESTING OF CHEMICALS 213” and “OECD GUIDELINES FOR THE TESTING OF CHEMICALS 214” respectively, and compared to a blank formulation. No mortality and no changes in behaviour were observed during the entire test period, indicating that Larixyne® did not show acute toxic effects on bees at the rates that were tested.

Based on the existing data, demonstrating a safe use for a plant protection product containing Larixyne® as the active substance achieving registration of Larixyne® as a PPP seems realistic. Consequently, approval of Larixyne® as active ingredient for the use in Plant Protection under Regulation (EC) 1107/2009 is feasible. The initial assessment of feasibility of registration does not replace the necessity to provide further data related to i.e. the final detailed specification of the technical grade active ingredient and studies addressing the effects of the active ingredient and/or the formulated product on mammals and other non-target organisms that need to be conducted to assess their effects on humans and the environment. Proposals were made how to address requirements where data are missing and costs for necessary studies were determined. In conclusion, the data package compilation conducted in Prolarix revealed no critical issues and was essential to guide the next steps by assessing potential risks in the registration process and thus obtain a clear view regarding the overall feasibility of commercialization of Larixyne®.

As one of the core outputs of Prolarix, a roadmap for registration and market introduction of Larixyne® was developed. The roadmap is a prerequisite for any investment and development decision to be taken by the commercial partners and investors. The roadmap includes a risk/benefit analysis, an analysis of necessary investments over time, and an implementation strategy. The study focused on the European market as the primary target in order to comply with the overall objectives of the European Union. From the
regulatory point of view, registration of Larixyne® seems feasible, especially since the available data do not suggest a problematic toxicological profile. Profit margins of botanical based plant protection products are notoriously small as compared to synthetized materials, due to high production costs. The assessment reveals that profitable production of Larixyne® will be feasible in the future, provided that a range of processes can be made more cost-efficient. This includes logistics as well as manufacturing processes. Necessary investments including registration costs, additional R&D as well setting up logistics and manufacturing lines were estimated 5-10 m Euro. In a best case scenario, Larixyne® enters the European market in 2022, taking into account that once the full dossier is compiled and submitted, the evaluation of Larixyne® as an active ingredient at EU level will take at least 27 months. Following approval of the active ingredient, the formulated product needs to be registered in the member states. An application needs to be submitted to a zonal Rapporteur Member State. At this stage, further data on efficacy are required for product registration.

The road map demonstrated that the market introduction of Larixyne® is indeed feasible from the technical and economic point of view, and an appropriate risk management strategy can be developed. Next to product related parameters, agricultural policy and the general development of the pesticide market, agricultural production and the availability of low-cost raw material are further key drivers affecting the overall profitability of a novel botanical based plant protection product.

To protect background and foreground IP related to Larixyne®, a protection scheme was developed and implemented. IP specialists and attorneys were consulted throughout the project, The strategy included (i) protection of background IP developed by patent submission, (ii) the option to keep foreground developed under ProLarix as trade secrets accessible to partners/licensees only, (iii) the need to protect the envisaged brand name ‘Larixyne®’ by appropriate means, including the protection of internet domain names, (iv) the development of contractual framework between partners ensuring the legal use of background and foreground IP (Including data generated by subcontractors) by the licensor. Prolarix was aimed at providing the base for a commercial exploitation of Larixyne®. Therefore, dissemination was restricted to information that does not infringe in any way patenting or chances of overall success.

Potential Impact:
The expected impacts of Work Programme 2013 (WP2013) were to (i) reinforce the EU’s science base in the bio-economy by building on Knowledge Based Bio Economy and (ii) by providing tools to maximize the impact of research and innovation on European societies and economies consistent with the common strategic priorities of Horizon 2020: focus on societal challenges, competitiveness and excellent research. The main objective of KBBE.2013.1.4-07: ‘Boosting the translation of FP projects’ results into innovative applications in the field of agriculture, forestry, fisheries and aquaculture’ was to tackle the ‘paradox of EU research’: Even if highly promising candidate products or technologies were identified, the further development was discontinued. The expected specific impacts in relation to the overall topic were (i) to pave the way from the development of scientific knowledge and technologies to the market by stimulating the development of new patents, dedicated business plans and innovative marketable applications, and (ii) to contribute to the creation of economic growth in Europe. The EU has invested substantial financial resources into the development of sustainable plant protection products based on micro-organisms, invertebrates and plant extracts in past and ongoing Framework Programmes. These innovations will also help to replace problematic plant protection products such as copper in organic and other low input farming systems in order to facilitate long-term development of these high value food sectors. Prolarix provides a significant contribution towards the main impacts intended by the European Union
since the main objective of ProLarix was to facilitate the translation of an innovation developed under the FP7 project ForestSpeCs from an intriguing concept to a business model for European SMEs in forestry and the agricultural sector.

A range of technical bottlenecks were overcome by R&D in ProLarix and transferred to the industry partner. These included the optimization of extraction and up-scaled production of standardized technical grade Larix extract (‘Larixyne®’). Analytical methodology and protocols were developed to quantify Larixyne® components and co-constituents in raw material, technical extracts and formulated products. Potential high-yield sources for extraction of Larixyne® constituents were identified in Europe, demonstrating that raw material for Larixyne® extraction is available in large quantities, suitable for extraction at commercial scale. Larch bark, which is a low- or zero value waste product of the wood industry, was identified as a valuable source of raw material. Scalable extraction protocols were developed to produce high quality technical grade extract from a range of sources of raw material. The evaluation process demonstrated that a resource-efficient, scalable and environmentally safe extraction protocol is feasible. Commercially feasible formulations of Larixyne®, a prerequisite to marketing, were developed to achieve solubility in spray solutions, optimum spread on leaf surfaces, protection against degradation by UV as well as to provide rain fastness and long shelf life. Efficacy of formulated Larixyne® was explored on grapevines under a wide range of pedo-climatic conditions and consistent and significant activity against downy mildew was demonstrated alone and in combination in organic and IPM control strategies, showing that implementation of Larixyne® in a spray programme with reduced amounts of other fungicides is a promising strategy. Larixyne® also significantly reduced diseases in additional horticultural crops, thus elucidating additional potential markets for its commercialization.

The IP developed in ForestSpeCs and ProLarix was protected by filing a patent. The envisaged brand name ‘Larixyne®’ was protected as a brand name in European countries as well as in additional target markets including the Americas, Russia and China. The IP protection strategy was developed in close collaboration between the industry partner and the technology transfer offices of the involved academic partners.

As one of the core outputs of ProLarix, a roadmap for registration and market introduction of Larixyne® was developed. The roadmap is a prerequisite for any investment and development decision to be taken by the commercial partners and investors. The roadmap includes a risk/benefit analysis, an analysis of necessary investments over time, and an implementation strategy. The study focused on the European market as the primary target in order to comply with the overall objectives of European Union. From the regulatory point of view, registration of Larixyne® seems feasible, especially since the available data do not suggest a problematic toxicological profile. Furthermore, the assessment revealed that profitable production of Larixyne® will be feasible in the future, provided that a range of processes can be made more cost-efficient. This includes logistics as well as manufacturing processes.

Necessary investments including registration costs, additional R&D as well setting up logistics and manufacturing lines were estimated 5-10 m Euro. In a best case scenario, Larixyne® enters the European market in 2022, taking into account that once the full dossier is compiled and submitted, the evaluation of Larixyne® as an active ingredient at EU level will take at least 27 months. Following approval of the active ingredient, the formulated product needs to be registered in the member states. An application needs to be submitted to a zonal Rapporteur Member State.

The road map demonstrated that the market introduction of Larixyne® is indeed feasible from the technical and economic point of view, and an appropriate risk management strategy can be developed. Next to product related parameters, agricultural policy and the general development of the pesticide
market, agricultural production and the availability of low-cost raw material are further key drivers affecting the overall profitability of a novel botanical based plant protection product.

Impact on the plant protection and forest industry

World-wide, the total value of fungicides sold in 2010 was estimated at 9,910 million USD. In the EU, 141,000 tonnes active ingredient (a.i.) of fungicides were used in 2003, representing 49% of total pesticide use. France, Italy, Spain, Germany and the United Kingdom account for approximately 75% of all fungicides used. Grapevine is by far the largest market for fungicides, and accounted for 70,000 tonnes of a.i. followed by fruit (10,000 tonnes a.i.) and vegetables (5,000 tonnes a.i.).

Grapevines are cultivated on 3,374,459 ha in the EU, of which 216,867 ha (6.4%) are organic certified. However, the plant protection scheme is expected to change in the near future since the transition to integrated pest management is under way as a consequence of the ‘pesticide package’ adopted by the European Parliament (Directive 2009/128/EC).

Plasmopara viticola, the downy mildew of grapevine, is one of the most devastating plant diseases worldwide. Based on our current knowledge and plausibility analysis, we expect that Larixyne® fits into the category of contact fungicides (rather than translaminar or systemic fungicides). There is a range of contact fungicides in the market against oomycetes, including (i) copper-based products, (ii) dithiocarbamates (metiram, zineb (phased out) and mancozeb), (iii) phthalimide (captan), (iv) chloronitriles (chlorothalonil), and (v) anthraquinone (dithianon ‘Delan’). These fungicides are quite old. However, they are still used in large quantities either as stand-alone products or in tank mixtures with systemic fungicides in order to prevent development of resistant pathogen populations. Larixyne will be positioned in this market segment in the conventional/IPM production systems. In organic viticulture, copper-based fungicides are so far the only highly effective means to control P. viticola, but copper use is controversial, and there is a general agreement that it should be replaced by more sustainable alternatives as soon as possible. We expect that Larixyne® will be adopted by this market readily.

A conservative estimate of the market potential of Larixyne® indicates that (i) Larixyne® will have a market size in European agriculture of several million Euro per annum (total sales), and (ii) a substantial amount of the available larch bark from the forest industry can be used to produce a high-value product. If an end user price of 100 Euro per application per ha is considered correct the full market potential can be expected to be generated within 5 years after the registration of the product provided that the end product is economically competitive. The production costs obviously depend on the costs for raw material and processing. There is room for improvement with respect to production costs, but there is also room for higher end user prices, as 100 Euro per ha and application is competitive when compared to alternatives. ProLarix will pave the way for other innovative botanicals as well, as the compilation of an information package for registration purposes will not only benefit the manufacturer of Larixyne®, but also other industries developing innovative botanicals as plant protection agents and biocides. Plant protection products derived from plants have to be approved under Regulation (EC) No 1107/2009, and a dossier has to be compiled according to the data requirements as laid down in Regulation (EC) No 544/2011 (active substance) and Regulation (EC) No 545/2011 (plant protection product). Revised data requirements are applicable since 1 January 2014. ProLarix will make use of the improved avenue to registration by compiling a state-of-the-art information package, thus providing a showcase for the novel registration process of botanicals. Larixyne® is an ideal candidate as the active compounds are present in the European environment already in vast amounts, and since there is a long history of use of Larix products in households and industry.
Impact on agriculture and environment
Bringing Larixyne successfully to the market will bring tangible and substantial economic benefits to farmers and forest owners in Europe, as well as to central European sawmills handling Larix timber. Farmers will be more competitive and will be able to produce higher quality (priced) products (e.g. organic wines), and will need to deal less with synthetic chemical pesticides (health and environmental benefits to growers). The development of novel, environmentally safe plant protection products is fully in line with the current Agricultural policy of the EC. Larixyne® has the potential to replace a substantial amount of old fungicides with problematic ecotoxicological profiles. High biodegradability can be expected and, as a consequence, exposure of soil, ground water, and air to residues will be acceptable (Larixyne® compounds enter naturally the soil and water systems in vast quantities in larch forests). Within a reasonably short period of time, farmers will have access to an additional, urgently needed plant protection tool that will contribute to the transition towards environmentally friendly and economically feasible IPM and organic production systems. ProLarix has thus also the potential to make a significant contribution to sustainable growth of European agriculture by providing a ‘green’ plant protection tool to farmers, made from a renewable source (by-products of the forestry industry) at a competitive price. This is also in line with the objectives of many national action plans (e.g. Eco-Phyto 2018 in France, IPM demonstrations-brug in Denmark) and NGO activities.

Dissemination activities
ProLarix was aimed at providing the base for a commercial exploitation of Larixyne®. Therefore, dissemination was restricted to information that does not infringe in any way patenting or chances of overall success. A more intensive dissemination strategy will be developed prior to market entry of Larixyne®. Communication will also take place as part of the dissemination of the activities to replace copper in organic farming.

Exploitation of results
The industry partners involved in ProLarix are committed to proceed with the development Larixyne. Therefore, results and outcomes of ProLarix will be fully exploited.

List of Websites:
Website: www.prolarix.eu

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