European Cooperation in the field of Scientific and Technical Research - COST -

Secretariat

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MEMORANDUM OF UNDERSTANDING

Subject : Memorandum of Understanding for the implementation of a European Concerted Research Action designated as COST Action FA0804: Molecular farming: plants as a production platform for high value proteins

Delegations will find attached the Memorandum of Understanding for COST Action FA0804 as approved by the COST Committee of Senior Officials (CSO) at its 171st meeting on 18-19 June 2008.

MEMORANDUM OF UNDERSTANDING

For the implementation of a European Concerted Research Action designated as

COST Action FA0804

MOLECULAR FARMING: PLANTS AS A PRODUCTION PLATFORM FOR HIGH VALUE PROTEINS

The Parties to this Memorandum of Understanding, declaring their common intention to participate in the concerted Action referred to above and described in the technical Annex to the Memorandum, have reached the following understanding:

1. The Action will be carried out in accordance with the provisions of document COST 270/07 "Rules and Procedures for Implementing COST Actions", or in any new document amending or replacing it, the contents of which the Parties are fully aware of.

2. The main objective of the Action is to co-ordinate European efforts in Molecular Farming (MF) and to ensure the rapid development and commercialization of products as well as the efficient establishment of a pipeline of second and third generation products that will sustain the industry for the next two decades.

3. The economic dimension of the activities carried out under the Action has been estimated, on the basis of information available during the planning of the Action, at EUR 27 million in 2007 prices.

4. The Memorandum of Understanding will take effect on being accepted by at least five Parties.

5. The Memorandum of Understanding will remain in force for a period of 4 years, calculated from the date of the first meeting of the Management Committee, unless the duration of the Action is modified according to the provisions of Chapter V of the document referred to in Point 1 above.

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A. ABSTRACT AND KEYWORDS

Proof-of-principle for Molecular Farming (MF) has been established over the last 15 years through sustained efforts of a growing number of European research groups. This work has been supported by the strategic decision of the EU to fund several initiatives through FPs 4-6 resulting in an impressive volume of generated knowledge. The aim of the Action is to leverage fruits of earlier EU, national and industrial investments in Molecular Farming to reach the next level, i.e. to move from R&D to applications, to develop product-oriented platforms, to enable new classes of products, to lower the costs and ultimately to commercialize the products. This Action will create new opportunities for European agriculture, horticulture and related technology sectors as the plants dedicated to Molecular Farming constitute new high-value crops. The Action brings the key players together and will increase European momentum, capacity and infrastructure. It will also expand activities to countries that have not thus far been able to participate, including developing countries. The concrete outcome will be a sustainable European Molecular Farming community with a clear vision, and links and input into scientific, regulatory, biosafety, intellectual property (IP), dissemination and public engagement activities.

Keywords: Plant-made recombinant proteins, Scale-up and downstream processing, Contained growth or in-field production, Path to commercialization, Intellectual Property Rights, regulatory framework and biosafety

B. BACKGROUND

B.1 General background

One of the current major challenges is the provision of safe, efficacious and affordable pharmaceuticals on a global level for the treatment and prevention of disease. It is also very important to provide Europe with a competitive platform to strengthen the European pharmaceutical sector. A crucial question is how medicines for major largely ignored diseases, including emerging diseases, can be made affordable and in sufficiently large volumes and how they can be supplied to low-income populations.

The global pharmaceutical industry is a multibillion dollar business (about USD 500 billion) growing at 10% per year. The final drug products consist of one or more active pharmaceutical ingredients (APIs). The APIs manufactured by chemical synthesis and biotransformation are typically small molecules, whereas APIs manufactured by fermentation or cell culture can either be small molecules (secondary metabolites) or biological molecules (i.e. proteins). Recombinant pharmaceuticals are the fastest growing class of novel medicine with monoclonal antibodies, cytokines and blood products as major drivers. At the moment they represent approximately 30% of all marketed drugs in the US and EU. Many of these novel protein and peptide drugs cannot be produced by classical chemistry or microbial fermentation.

Molecular Farming (MF) in plants or plant cell cultures offers a viable alternative technology that has great potential to fulfill requirements specific for the production of complex recombinant proteins, including pharmaceuticals and other commercially valuable target proteins like diagnostics, veterinary vaccines and industrial proteins. The first recombinant plant-derived vaccine for veterinary use was licensed in 2006, and several plant-produced pharmaceuticals are now in clinical trials and approaching commercial release within the next few years, mostly in the US. However, there are still many issues that need to be addressed by the scientific and regulatory communities, e.g. technical and manufacturing issues; regulatory, intellectual property (IP) and technology transfer aspects; and the co-development of MF in developing countries. In Europe, an equally important aspect is the establishment of a coherent strategy for the development of MF that encompasses the reconciliation of scientific, political and public engagement. This Action provides the ideal and most cost-effective forum for this purpose, as it leverages and benefits from a sustained and continuous investment through FPs 4-6, national and industrial funding. The EU is expected to continue funding MF related research with increased vigour through FP7. The Action will bring much-needed coordination and interaction among scientists with expertise/funded activities and scientists who are just initiating programs in MF. Therefore this COST Action provides the best forum for these activities involving the majority of European countries. Importantly, it will allow the participation of states from Eastern Europe, who have generated considerable expertise in the field, but have had limited opportunities to work together with their colleagues from Western Europe.

B.2 Current state of knowledge

In Europe, research in plant MF has always been internationally competitive, starting from the first description of monoclonal antibody expression in plants two decades ago, through FPs 4-6. These efforts have culminated in an impressive volume of knowledge, as well as several potential products developed by the private sector already in Phase II clinical trials, and projected Phase I trials by the EU FP6-funded Pharma-Planta consortium. A wide range of recombinant proteins has been produced by MF, ranging from antibodies, antigens/vaccines, cytokines and hormones to industrial enzymes and protein polymers. Recombinant proteins have been expressed successfully in plants, on occasion at high levels. Much still needs to be done to maximize expression levels and the quality of recombinant proteins produced in plants, but we are now beginning to develop a good understanding of the factors which control the yield and stability of recombinant proteins. In addition, it will also be necessary to develop novel plant biomass processing and purification systems that safeguard API functionality. The production of plant-made pharmaceuticals therefore requires the integration of expertise present in diverse fields: agricultural and horticultural plant production practices, quality control and cGMP procedures from pharmaceutical industry and management systems.

Substantial progress has also been made in aspects such as biosafety, regulatory compliance and public engagement. Much still needs to be done in these areas as well. However, it is encouraging to note that the two key EU regulatory agencies, EFSA (European Food Safety Authority) and EMEA (The European Medicines Evaluation Agency), have made remarkable progress in establishing a regulatory framework specifically for MF applications. Both agencies have established working groups of experts who have been charged with the development of comprehensive guidance documents, establishing the rules and codes of conduct for MF product developers in terms of submitting comprehensive dossiers for regulatory approval. A number of participants in this Action are directly involved with these working groups; consequently the Action will have direct input and benefit from activities in the regulatory domain and vice versa. It is also very encouraging to see that the International Alliance of Patients Organizations (IAPO) in 2005 launched a Briefing Paper on the topic of plant-made pharmaceuticals providing the public and especially patients with accurate and independent information based on evidence-based research.

This allows patients organizations and patient advocates worldwide to evaluate the potential benefits of the technology from an accurate scientific, technological and related social, ethical, economic and environmental perspective.

In the US and Canada, the development of MF has been catalyzed primarily by small start-up companies, whereas in Europe, the bulk of R&D has been performed by academic institutions, which have established a sound scientific knowledge base for further development. In the subsequent sections key remaining bottlenecks are outlined that need to be overcome before the technology can reach its full potential and deliver e.g. affordable medicine to everyone in both the developed and developing world. A vision is set out to propose how these bottlenecks should be tackled within the stipulations of this specific COST Action.

B.3 Reasons for the Action

Significant progress has been made over the years in MF, and it has been shown that plants can provide a unique opportunity for economic and safe production of commercially valuable complex proteins, amongst which important pharmaceuticals used for human health. This guiding principle will be a key driver for further development of the technology in Europe over the next 25 years, as discussed in the European Technology Platform vision document "Plants for the future" and in the corresponding Strategic Research Agenda (SRA). Five years ago, the tandem baculovirus/insect cells was a widely practiced and efficient lab tool - today, it is a validated production host that proved itself valuable for antigens for human vaccines (GSK, Protein Sciences) and more useful applications are coming. This is where plant-factories stand today, at the dawn of product approval for human and animal therapeutics. It is worth noting this is one of the fields where Europe excels, and where continued investment is the most likely to produce exemplary scientific and societal results.

There are a number of compelling reasons to produce complex recombinant proteins in plants:

1. As higher eukaryotes, plant cells resemble mammalian cells in possessing an endomembrane system, that allows the folding, assembly and post-translational modification of complex proteins (this is often not possible with prokaryotic cells).
2. Plants are easy, versatile and economical to grow.

3. The latest expression technologies in plants allow very rapid production of large amounts of recombinant protein. This speed and scale of production now rivals the capacity of the best conventional technologies currently available.
4. Scale-up technology is available for harvesting and processing plants or plant products on a large scale.
5. The purification requirement is simplified. It is possible to use only partially processed plant products if the recombinant protein is used topically or orally.
6. Plants are not infected by potential human pathogens, e.g. prions or viruses. This significantly reduces production costs, and eliminates health hazards.

Ultimately, plants represent versatile expression systems for a wide variety of recombinant proteins, and they offer rapid and economical production scale-up. Early experiments were carried out in model plant species, such as Arabidopsis and tobacco, but important crop plants (e.g. rice, corn, barley and other crops important for European agriculture) with well established agronomic, harvesting, transport, storage and processing practices, have now been shown to be effective production platforms. Furthermore, plant cell cultures can offer another alternative production system.

In order to maximize the potential of MF to deliver valuable products that take advantage of specific needs or market opportunities, like affordable medicines to developed and developing countries, a number of hurdles need to be addressed. A virtual co-ordination centre will be established, in which all the major European players in this field can join. Through this centre, efforts in key areas such as dedicated infrastructures for plant biomass production, manufacturing, downstream processing, purification, product validation and quality control, clinical trials, IP and regulatory issues will be coordinated by this Action in order to sustain and broaden the scientific basis of European plant research. In addition, an element dealing with co-development of plant MF in developing countries is incorporated. The centre will also act as a first port of call for anyone interested in MF, from within or outside the EU, from industry, academia or any other agency.

The outcome of the Action will be a sustainable European plant MF community with clear frameworks for regulatory, biosafety and IP issues. Eventually the Action will allow the establishment of a **European Committee of Molecular Farming**. This Committee would be established in order to influence policy in Europe for MF in a more positive direction, which would

guarantee the continuity of this COST Action in the fast developing field of complex recombinant proteins, including biopharmaceuticals.

In addition the Action will create new opportunities for European agriculture and horticulture and the related technology sectors as the plants dedicated to MF constitute new high-value crops that may generate significant investments in modern greenhouses and agricultural systems.

Although the funding of members of this Action is secured from national or EU resources the Action will nevertheless endeavour to engage and involve key institutions from developing countries, at least by opening our annual WG meetings or workshops to them. The attempt is to solicit additional funding for this purpose from national and philanthropic agencies and organizations committed to improving the quality of life and living standards in the developing world. Through the identification of lead institutions in particular geographical areas, the Action could be expanded to accomplish this objective.

One of the first activities of this Action will be the establishment of a Road Map as a tool to facilitate productive joint research among the groups. A preliminary inventory of activities and fields of expertise of the participants to this Action show promising future trends in MF. At first glance, a rich and diversified toolbox is available. A second lecture shows that at least half of the groups have a clear orientation toward a family of products. With minimal coordination, the Action will form three to five groups of interest, each developing a product-specific production-platform to answer unmet-medical needs (e.g. oral-administration vaccines and antimicrobials; enzymes; efficient allergens; antibodies). In addition, the Action will allow collaborating in pioneer work on targeting, control of plant-produced recombinant proteins and characterization, essential building blocks for an eventual third generation of product classes.

Coordinated Action at the European level is critically needed in order to overcome the bottlenecks in MF.

These include:

- an overwhelming number of potential alternative plant-based production platforms, including many different intact plant and cell-based systems and a lack of targeted and commercially viable plant production systems (e.g. contained systems)
- lack of strong, direct and committed corporate involvement and investment

- challenges in terms of downstream processing and purification of clinical grade recombinant pharmaceuticals
- poor product launch and pipeline
- regulatory burden
- public acceptance
- fragmentation and redundancy of research effort

This is an interesting mix of scientific and socio-political issues, which together have frightened off the major commercial players out of Europe, to North America and south east Asia where the development of the technology can be pursued in a more certain environment. However, commercial activities have not stalled completely in Europe, and the activities of organizations such as Icon Genetics, Cobento and Meristem are testament to the fact that on the basis of good scientific principles, progress in this field can be achieved also in Europe.

Most of the above challenges will be addressed as discussed in more detail in subsequent sections of this Action and by doing so we expect to facilitate at least in part the advancement of MF from R&D to the clinic and commercialization by private sector entities. Importantly, the activities and knowledge of European scientists and industry working in the MF field will be coordinated to pave the way for a sustainable and competitive plant-based production platform. This will clearly provide new possibilities and market opportunities for European agri- and horticulture as well.

B.4 Complementarity with other research programmes

The Action will be complementary with several ongoing projects and initiatives and provides excellent links with them. These include FP6 integrated projects PHARMA-PLANTA and SAGE as well as the FP7 initiative FLUPLANT Production and preclinical evaluation of a plant-derived pandemic influenza vaccine (HEALTH). Also a recently opened call GREEN FACTORY The expression and accumulation of valuable industrial compounds in plants (KBBE) is complementary to this Action. It reflects possibilities to use plants as production hosts for important non-food compounds. In addition, two other calls have been launched in the FP7 2008 round to specifically support the development of contained, plant-based platforms for the production of pharmaceutical products and other high-value industrial compounds.

The mission of PHARMA-PLANTA project is to build a plant-based production platform for pharmaceuticals in Europe, and to enter the first candidate pharmaceuticals into human clinical trials. These efforts can be combined with this Action particularly in the area of regulatory issues, and together with PHARMA-PLANTA scientists we can work with EU regulatory authorities in order to ensure safety and acceptance of plant-produced recombinant proteins. The aim of the SAGE project is to determine the most suitable plant-based expression platform for the production of therapeutic antibodies and to determine which glycan structures give antibodies superior properties in a clinical setting. Project results will be exploited to develop safer and more active glycoform varieties for therapeutic applications. The purpose of this Action also has links to the FLUPLANT project proposal, which focus entirely on animal health.

Several research groups and scientists are involved in two or more of the above mentioned projects or initiatives and this facilitates the realisation of the aims and will ensure the lack of redundancy.

C. OBJECTIVES AND BENEFITS

C.1 Main/primary objectives

The main objective of the Action is to co-ordinate European efforts in MF and to ensure the rapid development and commercialization of products as well as the efficient establishment of a pipeline of second and third generation products that will sustain the industry for the next two decades.

C.2 Secondary objectives

The secondary objectives of the Action are to:

1. Set out a long term strategy for European plant MF. The outcome of this will be a clear vision which direction European MF should take and its priorities.

2. Effectively integrate relevant expertise and knowledge from other domains such as agriculture and horticulture to bring the many proof-of-concept platforms developed in the EU at the lab scale closer to commercial production level.

3. Identify pharmaceutical, veterinary and industrial needs allowing the development of new targets. It is very important to carry out a thorough survey of European and global recombinant protein needs in order to prioritize new targets. Currently the pharmaceutical needs are assessed by industry

on a commercial basis that bears little or no relationship to actual health needs.

4. Further develop and refine the enabling technologies. MF tools can be considered as generic and can be applied to several research problems. Thus a network with combined efforts will facilitate the development of the MF technology platform. In addition, the costs of this development work are then at least partly shared.

5. Support evolving regulatory frameworks. The regulatory framework for MF has advanced, but is still in its infancy. There is no doubt that the regulatory oversight for e.g. biopharmaceuticals will evolve as more experience is gained from both plant biology and medicine production perspectives. The experience arises along as a diverse pipeline of products enters into the regulatory approval process.

6. Address IP issues. Intellectual property management should be dealt with in a constructive and forward-looking way. This is important not only for commercial interest but also for the improvement of global health and especially for the co-development of MF in developing countries. (see also Statement of Intent Humaritarian Use earlier signed by Pharma-Planta partners)

7. Expand collaborations with countries in the developing world. The collaboration between Europe and research institutes from developing countries (especially from India and China) should be carried out in all key areas of MF such as infrastructure, manufacturing, downstream processing, purification, clinical trials, IP and regulatory issues.

8. Training and mobility of early-stage scientists. The future development of European MF lies in the hands of young scientists. This should be taken into consideration when research agendas are drawn in order to support the education of the next generation of plant scientists including early age school education.

C.3 How will the objectives be achieved?

The deliverables of this Action are:

- Position and vision papers for FPs, Strategic Research Agendas and regulatory bodies
    - Through the interaction with the European Technology Platform Plants for the future (Launch of the Strategic Research Agenda, SRA, was at 25th June, 2007 in European Parliament the SRA includes the topic plant MF)

    - Through European Plant Science organization (EPSO): two experts interested to participate in the Action are board members and several institutes interested to join the Action are institutional EPSO members

- Scientific reviews, special issue of MF in journals such as Phytochemistry Reviews, Transgenic Research, Current Opinion of Biotechnology and Trends in Plant Science
- Joint congress with organizations such as EPSO, Phytochemical Society of Europe (PSE), Society of Medicinal Plant Research (GA), European Federation of Immunological Societies, or National Immunological Societies (e.g. British Society for Immunology) on MF
- Consultations with governments, regulatory authorities, consumer organizations, patient groups, farmers, industry and other stakeholders
- Implementation of collaborative initiatives with new EU members and developing countries
- SOPs for plant-based protein production, manufacturing, downstream processing, purification, quality control and assurance
- A database enclosing all relevant EU players (research groups, industry, non-governmental, regulatory bodies etc.) involved in recombinant protein production, its applications and connected activities

C.4 Benefits of the Action

The development of plant production platforms for recombinant molecules such as biopharmaceuticals has been identified and supported as a key area by the EU in FPs 4-6. As a result significant progress has been made and proof-of-concept has been achieved. It is now shown and accepted that plants can compete favourably with other expression systems for the safe and economic production of complex recombinant proteins like important. Plants provide a unique opportunity to establish production platforms with real advantages for specific biomolecules (See Section B3). However, there are many hurdles which need to be solved before full profit can be taken from MF. This Action will largely contribute on this.

The benefits from activities and research of participating laboratories within the Action will include the exchange of ideas, knowledge, results, tangible materials and know-how, aiming to minimize and ultimately eliminate redundancy and wasteful duplication of efforts and resources. At the same time, joint access to expensive infrastructure, facilities and equipment would thus allow additional European and developing country groups to participate in and benefit from this Action. A direct consequence of this effort will be the streamlining of production platforms and production technologies, and increasing the level of competence and awareness of the current state of the art in the field throughout the Action. Through discussions, dedicated workshops and targeted Working Groups it is expected that the Action will catalyze decision making in aspects of downstream processing and purification, Good Manufacturing Practice (GMP) production, clinical testing, the preparation of Standard Operating Procedures (SOPs) for production and even regulatory submission dossiers.

Amongst the different areas of plant biotechnology, MF has received the lions share of attention concerning biosafety and environmental impact. With appropriate public engagement, the specific development of plants for the production of safe and valuable drugs against major human diseases will contribute to public understanding on GMOs and provide evidence of how genetic modification can benefit human health and welfare.

The potential direct impact of this project is multifaceted and wide in scope. There is clearly the potential for direct health benefits, scientific benefits through the creation of new knowledge as well as maintaining a strong science base in Europe. It is generally accepted that plant-based recombinant pharmaceutical production will have significant impact in developing countries, in delivering affordable modern medicines to the countries that have the highest levels of disease. Europe will benefit from developing a technology that has tremendous potential for economic and social stability and development. In addition the further development of MF will result in new market opportunities and niches for the specialized agricultural and horticultural sector in Europe.

C.5 Target groups/end users

This COST Action will serve as a compelling example to the wider public that plant biotechnology has the potential to impact positively in a multitude of ways, with health benefits as the most direct example. Moreover, it will provide guidelines enabling academic and industrial partners to carry out competitive MF projects.

In addition, novel production platforms e.g. based on closed greenhouses might provide new economic options for European agricultural and horticultural industries including SMEs, when they provide the facilities for producing valuable recombinant proteins like biopharmaceuticals.

D. SCIENTIFIC PROGRAMM

D.1 Scientific focus

The key steps towards maintaining and expanding European plant MF investment with a view to maintaining competitiveness and sustainability include:

- The development of novel tools (e.g. new transformation techniques)
- Refinement and optimization of effective platforms for plant MF, particularly for 2nd and 3rd generation targets
- Support existing regulatory and IP frameworks with sound scientific information
- Strengthen SME involvement by securing strong IPR

D.2 Scientific work plan – methods and means

The scientific program of the Action will be pursued through three main topics. These show significant overlap and interaction, and the overall success of the Action relies on strong interactions between the different topics. The scientific plan for the three main topics, each being designated as a Working Group (WG, see Section E) is as follows:

Strategic development of Molecular Farming (WG1)

This WG aims to provide a broad and global overview of the state of MF in the world today. Its primary purpose is to survey the global MF sector, identifying the main contributors, the technologies that are being used, the products that are being developed, the financial implications of these strategies, the contributions from academia and government research organizations, the involvement of SMEs and large companies, the IP framework and the juxtaposition with developing regulatory guidelines.

This broad overview will involve reciprocal interactions with the other WGs specifically in the areas of production systems and processing strategies (WG2) and target molecules (WG3) but will

also incorporate marketing, commercial development, clinical trials, regulatory approval, regulation, public acceptance, stakeholder involvement (particularly farmers, patient advocacy groups and the bioprocessing industry), available research infrastructure and the impact on research funding and opportunities for research scientists involved directly or peripherally with the MF area. One of the important roles of WG1 is to assess the impact of MF on developing countries and to develop a strategy for their active engagement, so that the technology can be co-utilized with developing-country organizations to mutual benefit, avoiding the impression that new technologies are being foisted upon unwilling countries for untested and unverified products and processes. This will involve the identification of strategies to facilitate technology transfer, training, IP donation/licensing for humanitarian purposes, skills development and engagement with local farming communities, and developing county industries and educational facilities.

The initial output from WG1 will be a **positional report** which summarizes the global state of MF and the position of European research within that global picture. This will lead to the development of a **strategic vision document** whose dual purpose will be to identify areas where European research and development effort can have the most significant and positive global impact, and set out a long term strategy detailing how these aims can be achieved. This will cover the scientific areas which have most development and deployment potential, key product candidates that will be suitable for fast-track development and a description of how these areas fit in the current and emerging IP and regulatory landscape.

Ultimately, the strategic vision document will act as a guide for relevant EU bodies and scientists to find science-based information that will help to focus European efforts, reduce redundancy in research and development, identify impact areas to enhance European competitiveness and identify a dissemination strategy to maximize stakeholder awareness, public acceptance and support and regulatory support for MF in Europe and beyond.

In contrast to established host systems like E. coli or mammalian cells, the regulatory requirements for plant-based therapeutics are not yet fully defined. However, both the US Food and Drug Administration (FDA) and EMEA have recently published draft guidance documents addressing this issue. Thus the future focus of the agencies concerns and activities in the field of manufacturing of biopharmaceuticals from genetically engineered plants has become clearer. WG1 will address open questions, for example at which step the process should be transferred to a GMP environment.

Production systems and process development (WG2)

This WG2 aims to produce a critical evaluation of all current systems for the cost-effective production of valuable recombinant proteins like pharmaceuticals in plants and plant cells. The aim is to create new and attractive options for moving from the R&D phase to the clinic and to create market opportunities for SMEs and other corporate entities interested in the field of MF. Before this is achieved the following manufacturing processes for plant material (leaves, kernels) should be defined:

- effective, robust and reproducible without negatively affecting the product
- scalable to an industrial level
- compliant with the GMP regulations for the production of active pharmaceutical ingredients

Specifically, WG2 will carry out an inventory and literature study to summarize the state-of-the-art in MF and identify major bottlenecks hindering commercial exploitation. Therefore all recently published MF reviews, scientific literature and published patent applications, issued EU, US, Japanese and other patents, information obtained from partners of this Action (Road map) and from SMEs (non-confidential) describing the current state-of-the-art and major bottlenecks will be brought together and integrated into **a summary document database**. This will be in a publishable form and will constitute one of the major early deliverables of this Action.

Discussions will be initiated to define and understand the key constraints that currently prevent or limit the commercial exploitation of plant-based production of complex recombinant proteins like biopharmaceuticals. Simultaneously with these activities the WG2 will attempt to investigate the reasons for the apparent limited success of commercial activities in the field of MF in Europe.

The WG2 intends to engage in discussions with SMEs and larger companies active in the field, both in the EU and elsewhere. It also intends to take advantage of other such initiatives contemplated within a number of collaborative projects.

Another key deliverable will be a set of concrete recommendations for the production of valuable recombinant proteins in the best suited plant hosts for the major targets which will be identified in WG3. WG1 and WG3 will work in close cooperation in this exercise. More specifically, SOPs for crop-based and model-based production of recombinant proteins like pharmaceuticals, downstream processing and purification also taking into account biosafety will be defined and implemented. It is

expected to reduce the current fragmentation in terms of the multitude of plant production platforms in use in many different labs. Members of WG2 will discuss with industry end-users, opportunities and constraints soon after commencement of the Action in order to define the best plant host systems and expression strategies primarily from a European point of view but also in a global context. This will provide a starting point to allow similar decisions to be taken for second generation products and beyond.

One of the most difficult challenges in the processing of plant-made pharmaceuticals is the development of suitable technologies for the early steps in downstream processing. The requirements for processing, independently whether whole plants or plant cells are in question, differ most markedly from those established in traditional fermentation-based microbial or mammalian cell systems for the production of recombinant therapeutic proteins. Furthermore, the design and engineering experience as well as process know-how are decades behind the established pharmaceutical technologies. Later process stages are product specific and less influenced by the expression platform. The evaluation for the best possible downstream processing system needs to consider the source of plant material and the minimum level of extraction and purification required for orally-delivered and injectable products to minimize processing costs making the technology sustainable and industrially exploitable. Additionally major steps to be analyzed include early process stages, subsequent purification steps and quality control and post-production monitoring which all may affect the final yield and quality. In consultation with WG1, regulatory requirements and the demands of the pharmaceutical industry regarding product quality will be considered as well.

Once plant production platforms have been defined, strategies will be worked out for contained and non-contained propagation of the selected host plants or plant cells. These strategies largely depend on the nature of the pharmaceutical compound. For the contained growth of GM plant cells/plants in bioreactors/greenhouses, agricultural and technical aspects will be worked out as to critically evaluate the economic feasibility to grow the chosen plants for the purpose of MF applications. A major deliverable of WG2 will be a list of recommendations for establishing a process system as well as waste management, quality control and quality assurance for plant-made pharmaceuticals. In addition options to tune the production of complex valuable recombinant proteins such as biopharmaceuticals in closed systems will be evaluated. All these recommendations will be used to define and implement SOPs for a manufacturing process of plant-produced pharmaceuticals. WG2

will rely heavily on ongoing and soon to be initiated funded projects in a number of laboratories participating in the Action to derive process and analyze this information.

Target molecules assessment of (clinical) need and production feasibility (WG3)

The production of complex valuable recombinant proteins such as biopharmaceuticals, including vaccines, in plants can potentially address many of the challenges posed by existing methods of production. The combination of low capital investment, low cost of goods, coupled with highly scalable manufacturing capability is particularly important for many products and will enable the development of new applications (such as passive immunotherapy with monoclonal antibodies) that are currently not achievable with conventional fermenter based production technologies.

The following principal advantages which plants can offer need to be evaluated case by case when choosing the best production system:

1. **Scalability.** No other production system offers the potential scalability of plants. Whilst some high-value products could be produced in sufficient amounts in plant cell culture in the future, contained technologies in greenhouses or growth at agricultural levels will allow product manufacture on a massive scale. This in turn will enable the design of new products and approaches in many areas, and in the medical arena, will offer the prospect of providing medicines and vaccines at a scale that could finally match the global health need.
2. **Costs.** Plants are cost-effective and easy to grow. The cost of raw goods will certainly be low. However, as this typically represents only a small percentage of the total cost of a product, this is not necessarily where the major financial savings are to be found. The major cost attraction of plants is that the initial investment into a production line is significantly lower compared with conventional fermenter facilities. Many observers have also noted that for a plant-derived pharmaceutical the requirement for a major capital investment can be delayed until much later in the product development line.
3. **Adaptability.** Plant cells are higher eukaryotes, and therefore possess, like mammalian cells, an endomembrane system that allows them to produce extremely complex proteins such as monoclonal antibodies that are currently not feasible in, for example, microbial systems. Indeed, all the generally recognized forms of antibody and related engineered molecules have been successfully expressed in plants. In addition, there are examples of proteins that, at present, can only be produced in plants (for example secretory IgA antibodies, and

recombinant immune complexes). Thus plants appear to be highly amenable to the production of a wide range of proteins.

4. **Speed.** The latest advances in plant biotechnology now allow large scale amounts of high quality recombinant proteins to be produced extremely rapidly. This has allowed at least three plant-based commercial ventures to develop technologies, which will allow them to compete, for example, with existing systems for the production of influenza vaccine, or for the requirement for rapid scalability of products to respond to bio-terrorist threats.

Of course, not all pharmaceuticals will be appropriate, or will need to be made in plant systems. Currently, those application areas that are thought likely to benefit most are:

1. Medicines that are required in very large quantities e.g. monoclonal antibodies, some sub-unit vaccines, HIV protein microbicides.
2. Medicines that can only be made in plants e.g. secretory IgA antibodies - at present this major class of antibody that is important for mucosal prevention of disease cannot be made efficiently by any other means.
3. Medicines that are specifically designed for production in plants e.g. recombinant immune complexes - with a growing understanding of the mechanisms of protein production in plants, has come the ability to engineer molecules with enhanced immunological properties.

However, it has always been the cases that as new technologies are developed; potential applications also develop to capitalize on the innovative aspects of the new technologies. This will undoubtedly also be the case for plant biotechnology and MF, and it will be extremely important to monitor potential targets for MF, with the latest plant biotechnological developments in mind.

E. ORGANISATION

E.1 Coordination and organisation

Overall management of the Action will be carried out by the MC led by the MC Chairperson. The MC Chairperson and the WG leaders will be nominated at the kick-off meeting. The WG leaders and the MC Chair and Vice-Chair will form the core group (CG) of the MC. This CG will prepare meeting formats, agendas and minutes. The MC Chair will act as a contact person between the

Action and the COST Office and the Domain Committee.

Each WG leader will be tasked with coordinating the activities within WG, ensuring that the objectives of the WG are met in a timely fashion and preparing reports for WG and MC meetings. They will also be expected to direct the organization of WG meetings and sessions as well to oversee the interaction with the other WGs as well as with the other relevant Actions and European projects.

The Short Time Scientific Missions (STSMs) form an important part of the Action and a STSM coordinator will be selected from one of the nominated MC members. A STSM program will be initiated to allow exchange of scientist. This will an effective way to start and energize collaborations, to make new equipment and methods familiar to the Action members, and to standardize experimental and analytical approaches so that large-scale tasks can be effectively organized.

The STSM program will apply to scientists from all four WGs, and will be seen in particular as a way of promoting the involvement of early-stage and promising scientists in international collaborative projects and in mobility for advanced training.

In order to get the dissemination of the Action into full power a Dissemination Coordinator will be selected among MC members. The Dissemination Coordinator will guide the dissemination activities and is also in charge of the development and maintenance of the specific Action website. This website will serve several purposes: explaining the Action to the general public and interested scientists, familiarizing potential but non-affliated researchers, disseminating Action deliverables to interested parties, and coordinating the Action and research undertaken by its members.

E.2 Working Groups

This Action will be organized into three interactive WGs, which are listed below. The WGs are established according to the types of tools they apply and by the types of data and analyses carried under the research projects and programs of the participants.

WG1: Strategic development of Molecular Farming in Europe (visions, planning infrastructure, regulatory oversight, public engagement, training and engagement with developing country organizations).

WG2: Production systems and process development, e.g. plant cell cultures and plants, open field or contained production, hydroponics (scale-up, harvesting tools, downstream processing and purification, waste management).

WG3: Target molecules assessment of (clinical) need and production feasibility (including regulatory oversight).

WG1 is established as a think tank, with a global overview of plant MF. Several members of MC are involved with this WG. The purpose of WG1 is to define the areas where European efforts can make the most significant impact, to provide relevant EU bodies with science based input on MF and to establish a long-term visionary strategy that will place Europe at the forefront of research and development, and commercialization of MF. Training and dissemination activities form a very central part of this WG. In addition, WG1 will ensure that the appropriate regulatory oversight is in place in Europe for this expanding technology. European regulators (EMEA and EFSA) have only started to develop their guidance in this area.

WG2 and WG3 will address technical issues, which represent the key constraints to be solved to further mature the technology.

WG2 will critically evaluate all current plant-based production systems to produce new recombinant pharmaceuticals in a cost-efficient way. The aim is to move from the R&D phase to the clinic and finally to real products to create market opportunities for corporate entities interested in the field of MF. WG2 will identify and develop the process systems and manufacturing technologies required for plant derived pharmaceuticals. Many of these differ significantly from those already established for cell fermentation systems. Key issues will involve the handling of vast volumes of plant material, extraction, concentration, purification, removal of plant products including secondary metabolites and waste management.

WG3 addresses the selection of potential pharmaceutical targets. Much emphasis is placed presently on monoclonal antibodies. The challenge now is to identify the next pharmaceutical targets, which will represent the 2nd and 3rd generation of products. Cost calculations and scalability vs needs are important to be made already in the early-stage. Regulatory issues belong also to this WG. It is essential to establish the pipeline of MF targets, which will sustain and expand

the technology and the industry through the next 25 years.

E.3 Liaison and interAction with other research programmes

This COST Action has synergies with several running EU programs as described earlier in section B.4. Liaisons and interactions will be coordinated by the MC when appropriate.

E.4 Gender balance and involvement of early-stage researchers

This COST Action will respect an appropriate gender balance in all its activities and the Management Committee will place this as a standard item on all its MC agendas. This Action will also be committed to considerably involve early-stage researchers. This item will also be placed as a standard item on all MC agendas.

At the level below Principal Investigator (PI), this network is expected to approach a gender balance of 50%. It is the intention that early-stage researchers form the predominant group in this proposal, under the guidance of the PIs. This is an excellent opportunity to train early-stage scientists in plant biotechnology, to develop them into the next generation of plant biotechnology PIs, and not to lose them to other disciplines, or to research laboratories or industry outside Europe.

F. TIMETABLE

The Action will last for four years. This Action will comprise several activities such as kick-off meeting, WG meetings, MC meetings, conferences, STSMs and reports as well as writing statements and vision papers. The position of each activity is shown in the Table 1. At the kick-off meeting the MC Chairperson, the WG leaders, the STSM Coordinator and the Dissemination Coordinator will be selected and nominated. The first WG and MC meetings will take place four to five months after the kick-off meeting in order to permit enough time to get organized. The WG and MC meetings (that will coincide with WG meetings) will take place annually. The WG meetings for all four WGs (annual workshops) are held together in order to maximize the interactions between different WGs. The length of these meetings will be from two to three days. In addition, if the WGs consider useful they may organize separate one day gatherings once a year (optional). During the Action, one conference will be arranged where all the WGs are present and which will be open for non-Action participants as well.

Table 1. Timetable for MolFarmGlob Action

Activity	Year 1	Year 2	Year 3	Year 4
Kick-off meeting	**			
Annual workhops	**	**	**	**
MC meetings	**	**	**	**
STSMs	**********	**********	**********	**********
Conference			**	
Reports	**	**	**	**

G. ECONOMIC DIMENSION

The following 21 COST countries have actively participated in the preparation of this Action or otherwise indicated their interest: Austria, Belgium, Bulgaria, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Iceland, Italy, Lithuania, The Netherlands, Norway, Poland, Romania, Slovenia, Spain, Switzerland and United Kingdom.

On the basis of national estimates, the economic dimension of the activities to be carried out under this Action has been estimated at EUR 27 million for the total duration of the Action. This estimate is valid under the assumption that all the countries mentioned above but no other countries will participate in this Action. Any departure from this will change the total cost accordingly.

H. DISSEMINATION PLAN

H.1 Who?

The aim of the Action is to identify and address key bottlenecks in MF to promote the translation of results from R&D into affordable medical products for widespread clinical application and

commercialization. As outlined above, these bottlenecks include a scientific and technical component, but also strategic, regulatory, economic and IP-related challenges, as well as issues related to public acceptance. This defines a diverse target audience for the expected outcomes of the Action in the different focus areas.

At the scientific and technical level, the Action will establish a robust international framework for internal and external communication to promote collaboration and avoid unnecessary competition, duplication and redundancy. The Action plan comprises a scientific expert team that includes most, if not all European key players in the area of MF. All the participants have excellent records in collaborative science and there are many examples of groups of scientists who are already involved in EU funded projects and networks demonstrating their willingness to collaborate and share expertise, facilities and knowledge. A scientific network of such magnitude will be in a unique position to generate a sound public knowledge base for further technology development.

One important and vital group of stakeholders includes corporate entities, in particular SMEs. Many of those are already in collaboration with partners of the Action through other European research frameworks. A key role will be assumed by research institutes whose mission is to bridge the gap between academic research and industrial exploitation of results.

The strategic choice of sensible target molecules for Molecular Farming requires close interaction with clinicians and pharmaceutical industry. This will be one of the aims of WG3, which includes leading medical experts.

The Action aims at establishing a clear framework for IP issues, in particular with respect to the co-development of Plant Molecular Farming in developing countries. To this end, legal advice and exchange of expertise will be sought through further links with patent lawyers and IP experts in the field of plant biotechnology and pharmaceutical development.

A continuing dialogue between the scientific research team and members of the national and European regulatory authorities will also be supported. As a consequence of this and through establishing the **European Committee of Molecular Farming** the Action will exert a direct influence on national and European level policy makers for Molecular Farming towards a more positive direction to promote the fast developing field of biopharmaceuticals.

A key to the management of public concerns about Molecular Farming and GM plants will be the

dissemination of factual information, so that any concerns should be evidence-based, rather than based on gut-feelings. Thus an important part of the Action is the principal aim of engaging the public in a two-way debate and consultation process throughout the lifetime of the project.

H.2 What?

For internal and external networking clear channels of communications between the project partners as well as with the wider scientific community will be established. Internal electronic mailing lists will be defined by the WGs for project communications. Existing mailing lists will be utilized for external dissemination and exchange of knowledge, and the possibility of establishing a new overarching list will be explored.

In addition, the Action will establish a website including information about the project, contact details, background information, selected presentations (seminars, workshops, conferences) and links to related websites and articles in scientific and technical journals. The public website will also include instructional materials that will be made available for teaching at schools and universities. For internal communication, password protected pages of the web site will be used as the principal means of distributing administrative, policy, and procedural documents for use by members of the consortium. In particular this will include SOPs, IP databases, regulatory draft documents and scientific news and updates.

In addition, the communication in the consortium will work through various carefully focused groups and committees through formal and informal mechanisms.

Focus groups will serve as a mechanism for external communication in the areas of target protein selection, biosafety, IP management, developing country policy and regulatory principles. The purpose of these groups will be to provide a feedback loop for formative evaluation, as a means of involving all the stakeholders in the project and as a means of communication and dissemination. Regular focus groups will be organized to solicit input from the wider community.

Within the frame of previous and ongoing international projects relevant links to expert groups and regulatory agencies have already been made and will serve as a valuable basis. For example, a strong interface to the key EU regulatory agencies EFSA and EMEA exists already since a number of the participants in this Action are directly involved with these agencies in a consulting function thus facilitating direct input and benefit from activities in the regulatory domain. Similarly, cumulative experience in the field of IP management in the context of developing countries health

needs and humanitarian use of biopharmaceuticals has been accrued in the context of FP6 EU projects and relevant existing links will be exploited.

Finally, the **European Committee of Molecular Farming** will be the most important instrument for communicating the knowledge generated within the Action to policy makers at the national and European level, also after the Action is closed.

Conferences will be organized to raise awareness about Molecular Farming activities and to exchange scientific news. They will also act as training venues for disseminating instructional material for stakeholder communities and as forum for a more public discussion of research, development and strategic issues of interest to the wider community. The meetings will be scheduled over 3 days, in order to accommodate extensive scientific discussion and necessary committee meetings. This will help to minimise the time needed to implement management decisions and ensure that the maximum number of participants is available. In some instances, it may also be possible to discuss committee business by telephone conference.

Scientific results will be disseminated in annual reports and publications in scientific and technical journals that will be summarized in a database on the public website.

Of paramount importance though, will be for the participants to reach out and engage with the agricultural and horticultural sector as well as the public, in order to discuss areas of concern, disseminate knowledge and awareness and generally involve these in thinking about biotechnology. Many of the scientists involved in the Action are already very active on these fronts through public talks and media discussions. An additional source of information will be provided by the Action in the form of instructional material on the public website and through regular press releases.

H.3 How?

The Action is by nature, multifaceted and multidisciplinary, comprising coherent and tightly interdependent activities. The Action will generate knowledge useful to policy makers, ethicists, regulators, environmental researchers, public interest groups and others. It can be used to help formulate a more general and coherent framework to encompass the integration of plant-based pharmaceutical production systems into human healthcare and quality of life, in a safe and acceptable manner. Thus, the Action affords a substantial opportunity for innovation and scientific excellence.

The overall Communications Strategy is multi-layered. A first port of call is internal discussion and presentations at the meetings. In close consultation with the IP partners, it will be determined whether results constitute inventions that may be valuable and patentable. After such a determination is made, and appropriate steps to protect such IP are taken, the preferred means of knowledge dissemination would be through high calibre peer reviewed publications. Because of the nature of any scientific program, such activities will continue well beyond the duration of the lifetime of the project. Additional means for disseminating knowledge would be through seminars and lectures at national and international meetings and through press releases. In addition, important messages that come out of our work will be articulated in a manner that can go into the project website that will be accessible to the wider community. Through close interactions with European Commission services, pertinent knowledge generated in the project will be made available to SMEs in the hope that they will be willing to take these on board thus allowing them to benefit from this Action. This will be done after IP protection is secured.

This COST Action will serve as an example to the wider public that plant biotechnology has the potential to impact positively in a multitude of ways on health. Indeed, all of the senior scientists involved have already been actively engaged in the public GM debate, both nationally and on an European level, and this Action could illustrate potential benefits from GM plant technology.