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Opportunities and Challenges

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Executive Summary

The main objective of this study was to identify drivers, prospects, advantages and challenges of plant molecular farming (PM farming) with a particular focus on the EU. The report considers techno-economic, regulatory and wider policy aspects including stakeholder and public perception. It covers PM farming for producing biopharmaceuticals and vaccines, subsequently referred to as plant-made pharmaceuticals (PMPs) and plant-made vaccines (PMVs), and for plant-made industrials (PMIs) intended to be used for food and feed purposes (food supplements, food and feed additives). The study is based on literature reviews, document analysis and interviews.

Technology

A broad range of plants, including crops, vegetables and fruits have been investigated for their applicability in PM farming over the last fifteen years. At present stage mainly maize, rice, tobacco and safflower are used in open field production, for greenhouse production tobacco is preferred. Contained bioreactor-type systems focus on moss, duckweed (Lemna), algae and plant-cell culture. Expression systems include stable transformation of plant genomes (nuclear or plastid), which are also used in the first generation of GM crops, plant-viruses and transient expression. Each plant and each expression system (production platform) – offers different advantages and disadvantages which makes it difficult to think in terms of a dominant technology design. Platform choice is case-specific and depends on a broad range of criteria.

R&D activities, product pipeline and commercial actors

With the exception of a veterinary vaccine produced from plant cell culture no PMP or PMV has jet received market authorisation and not more than 7% of all biopharmaceuticals presently in clinical trials come from PM farming with a very few in advanced stage. Products targeted are antibodies, vaccines, interferons, hormones, and therapeutic enzymes. Commercial R&D activities in PM farming centre in USA, Canada and the EU. A comparative analysis of PM farming field trials, patents, PMPs in clinical trials, companies active in the field, and scientific publications clearly show a dominant position of the USA in advanced stage commercial R&D. In earlier stage R&D, the differences between the EU and the USA seems to be less striking and in case of publicly funded R&D there seems to be little difference. EU researchers and entrepreneurs have apparently started at a later stage compared to North America to exploit the technology for commercial purposes with a dynamic development over the recent years. Within the EU Member States which are strong in pharmaceuticals, Germany, Italy, Spain, France and UK, capture the majority of scientific publications, with Germany having by far the most companies active in the EU.

A small number of PMIs are already available from US companies for technical purposes, research and diagnostics. A few products aiming at the food supplement, and feed additive market are in advances stages. With respect to PMIs targeting food/feed application there is generally much less activity and fewer products developed compared to PMPs. As with PMPs the USA holds a similarly strong position.

Advantages and business drivers

In principle most advantages anticipated for PM farming boil down to direct or indirect savings in production costs and to large and even unlimited production scale of PMPs and PMIs. While it is acknowledged that cost savings would be case specific many analysts have published general estimates in the range of 75 to 99% compared to mammalian cell lines. Most cost estimates are not based on commercial process data and seem to be overly optimistic, as they are no based on real process data, underestimate or ignore downstream purification and do not consider extra compliance costs for agricultural biotechnology regulations. Open field cultivation would also allow delaying business decisions about production scale to later stages of clinical trials which will lower the risk of under- or overestimating production capacity needed. Savings are likely to be lower in case of contained production such as moss or Lemna is envisaged. For a model vaccine produced in tobacco in greenhouses calculations result in lower prices for subunit vaccines compared to yeast production.

Despite these (anticipated) advantages PM farming appears to be largely pushed by academics and technology providers. So far, there seems to be little demand from pharmaceutical companies and public health systems. Provided that the anticipated cost savings would actually materialize, this might, however, change if high-dose antibodies and non-parenteral administration routes, e.g. topical, nasal, mucosal would require higher production volumes. PM farming could also provide an alternative production platform for proteins difficult to express in presently used systems. Recently developed methods in PM farming for transient production could speed up drug and vaccine development. Pressure from public health systems on drug prices could also render PM farming a more attractive option.

There is definitely a demand for affordable and easily available drugs and vaccines. Whether PM farming could make a significant contribution to improve health care in low-income and developing countries e.g. by setting up domestic PM farming production remains to be seen. The same applies whether a potentially cheaper production in industrialised countries would improve availability of drugs and vaccines targeting indications relevant to these countries.

Provided that PM farming will successfully turn into a large-scale and low-cost production method this would enable the production of PMIs e.g. as food supplements and feed additives the costs for which would be prohibitive if depending on mammalian cell lines.

Challenges for PM farming

PM farming regulators and policymakers are facing a broad range of challenges including technical, economic, safety, regulatory, business strategic aspects as well as public acceptance which need to be tackled if this technology shall go ahead. Most challenges are linked to the use of food and feed crops and/or open field production.

In order to strengthen its competitiveness PM farming needs to further increase yield and to improve in-planta engineering and humanizing of the plant-specific glycosylation which is potentially immunogenic to human. A stronger focus on the downstream purification process will be important to overcome the problems linked to large scale biomass processing and to remove plant-specific compounds and contaminants (e.g. phenolic compounds, pigments, plant proteases). Innovations and improvements in the established production technologies mammalian cell lines and microbial systems and the advent

of first products from new technological platforms such as insect cell lines and transgenic animals are, however, steadily raising the bar for PM farming.

Drug regulators in the USA and the EU consider PMPs and PMVs to pose novel problems for market authorisation. Especially the less controlled environment of agricultural production seems to require a regulatory paradigm change. Key challenges include quality assurance for upstream production, choice of adequate agricultural practices including monitoring and control measures, and an appropriate banking system. More controlled production environment, e.g. greenhouse, bioreactor production with moss, Lemna, algae are deemed less difficult

In case of open field production the developers of PMPs have to consider environmental and health impacts in the context of the established regulatory framework for agricultural biotechnology. High concentrations in plant tissue of proteins intended to be pharmacologically active in humans or higher animals sparks health and environmental concerns. Unintended exposure can occur from accidental contamination by pharm crops of the food/feed supply (inadvertent admixture pollen flow etc.). Economic and liability risks include compensation for recalls and reduced value of food/feed products and damage to domestic and export markets for agricultural food/feed products. The key risk mitigation challenge, therefore, is to design and police a system of physical, organisational and molecular confinement measures.

The specifics of PM farming pose challenges to the EU regulatory regime which was essentially developed for first generation GM crops and normal agricultural practice. Key risk assessment concepts such as substantial equivalence and familiarity appear to be of limited use for PM farming. Assessing confinement might become a new focus of the risk assessment. In order to manage accidental contamination of the food/feed supply, EU harmonised substance-specific limits and liability rules have to be considered for both domestic PM farming and import from countries with significant PM farming activities. A separate authorisation track might be considered under Directive 2001/18/EC for PM farming as these crops will not be traded and cultivated by contract farming on limited acreage and under constant regulatory oversight only. Other regulatory challenges include transboundary movements of pharm crops, the different characteristics of field trials and the harmonisation of containment criteria across the EU.

In case of a wider adoption of this technology additional cost are likely to arise not only from contamination accidents but also from the need of food/feed control and from controlling confinement measures. A simultaneous production of various types of PMIs for food, feed or industrial use might render the avoidance of trace contamination of food and feed supply much more complex and costly. Measures and costs are likely to depend on scale and confinement measures applied. The first wave of PMPs will perhaps be produced on limited acreages only and not exceed 1,000 hectares per product. The high value of the products would justify strict, redundant and therefore costly confinement and monitoring regimes. A possible second wave of large-volume PMPs would require much larger acreage and would perhaps not allow for the same level of confinement.

A particular challenge to PM farming developers is the reluctance of large pharmaceutical industry to invest into PM farming. They seem to be discouraged by technological problems (glycosylation, downstream processing, lack of speed) and higher business risks due to uncertainties (market authorisation, GM crop regulations, stakeholder campaigning, and the policy climate for agricultural biotechnology in the EU). This has created serious financing problems for PM farming developers which might not be able to proceed with advanced stage clinical trials based on public funds or venture capital. Public research groups developing PMVs for non-commercial purposes are facing similar problems.

Public and stakeholder perception

Awareness of PM farming is largely limited to stakeholder groups in North America while there seems to be little awareness among EU stakeholders and general publics. In the EU awareness and activities are limited to national groups in Member States where field trials have been conducted. Public perception studies suggest a higher acceptance for PM farming compared to GM food and for PMPs compared to PMIs.

As a result from policy analysis and public perception studies the possible contamination of the food/feed chain by pharm crops is the key issue. In the USA a coalition of public interest groups (environmental, consumer, food safety, other), conventional farmer's associations, the food industry and regional groups has been campaigning for tightening regulations, against open field production, the use of food crops. Public interest groups highlight human health and environmental risks while farmer groups and the food industry point to liability and economic risks. Patience organisations are a novel actor which could bring in new arguments. However, these groups have not been very vocal so far. In the USA and Canada there seem to be little confidence in confinement measures and the regulatory framework As confirmed by public perception studies non-food crops and contained production would be considered much more acceptable but might nevertheless be critically perceived by some EU Member States.

Impacts on innovation and company strategies

The challenges for PM farming described above affect innovation and business strategies. Within a few years, there has been a striking shift from major food crops and open field production to non-food crops and/or more contained systems. As a result of the recent market consolidation only one company is still developing its product in rice plants. On the other hand the economics of producing PMIs is likely to renew the interest in open field production. Another shift occurred from blockbuster type and novel type drugs as well as novel indications to lower profile PMPs such as veterinary vaccines and antibodies, biosimilars and orphan drugs because of a shorter timeline of and lower costs for the regulatory procedure. For similar reasons, developers are diversifying into non-pharma products including nutraceuticals to be used as food supplements or feed additives. The third shift is on downstream processing. Companies offering innovative and cost-saving downstream processing solutions seem to have a competitive advantage, for instance, the oilbody based system in safflower and the secreted proteins in moss bioreactors.

Points to consider for policy development

From the analyses in this report a range of issues can be identified which would require further consideration by policy maker at the European Commission and the national level. A policy framework for PM farming would be helpful to clarify some general questions which would set the scene for regulatory and commercial activities. The need to adapt the EU regulatory framework on agricultural biotechnology should be investigated. For a more participatory development of this policy framework an open and well-informed debate would be required, including for instance, awareness raising, research into public perception, and public consultations. In order to explore and secure the development of less controversial technological options in PM farming the suitability of non-food plants and the use of contained systems for PM farming should be further explored. For further reducing risks of open field production confinement systems and assessment method should be further developed. In order to ensure further innovation in PM farming possible gaps and problems in R&D funding should be considered.

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Boxes, Figures and Tables

Acronyms

APHIS	Animal and Plant Health Inspection Service at USDA
BIO	Biotechnology Industry Organization
BRS	Biotechnology Regulatory Services Division at USDA-APHIS
CAP	Common Agricultural Policy
CFIA	Canadian Food Inspection Agency
CHMP	Committee for Medicinal Products for Human Use
CPMP	Committee for Proprietary Medicinal Products
DEFRA	Department for Environment Food and Rural Affairs
EC	European Commission
EFSA	European Food Safety Authority
EMEA	European Medicine Evaluation Agency
EPA	Environmental Protection Agency
EU	European Union
FDA	U.S. Food and Drug Administration
R&D	Research and Development
GMP	Good Manufacturing Practice
GM	Genetically modified
GMO	Genetically modified organisms
IAPO	International Alliance of Patients' Organizations
ICH	International Conference on Harmonisation
IPR	Intellectual Property Rights
IPTS	Institute for Prospective Technology Studies
Mab	Monoclonal Antibody
PM farming	Plant Molecular Farming
PMI	Plant-Made-Industrials
PMP	Plant-Made Pharmaceuticals
PMV	Plant-Made Vaccine
PNT	Plants with Novel Traits
USDA	United States Department of Agriculture
WHO	World Health Organization

1 Introduction

In January 2002, the Commission adopted a Strategy for Europe on Life Sciences and Biotechnology (EC 2002), which proposes a comprehensive roadmap up to 2010 and puts the sector at the forefront of those frontier technologies which are helping to take the European Union towards its long-term strategic goal established by the Lisbon European Council in March 2000, namely to make the EU the most competitive economy in the world and to achieve full employment by 2010 alongside inclusive social and environmental policies. The document highlights the potential of non-food crops as source for industrial feedstocks and new materials, including pharmaceuticals.

The sustainable application of crops for non-food purposes was identified as a focal area for European R&D in particular for the Seventh Framework Programme (Plants for the Future 2004, 2005, 2007; EC 2005) and recently reaffirmed as promising emerging application in a Reference Report by the Institute for Prospective Technology Studies (IPTS) (Zika et al. 2007). The latter study also identified the production of biopharmaceuticals from genetically modified (GM) crops as a particularly interesting area while at the same time expressing a cautious view on the technical and economic prospects.

The use of GM crops in the production of substances of industrial interests (plant molecular farming, PM farming), especially biopharmaceuticals, holds several promises including savings in production costs, possibility to realise large-scale production for high-dose drugs, guaranteed animal and human virus-free products, easier storage and transportation of drugs, e.g. as kernels, oral applicability (e.g. edible vaccines) etc. These prospects have sparked R&D activities especially in USA, Canada and the EU. A small number of plant-made pharmaceuticals (PMPs) are meanwhile close to market stage and very recently the first PMP, a chicken vaccine, was granted regulatory approval in the USA.

Production of PMPs is frequently envisaged on open-fields using major food crops such as maize and rice. With these crops, health and environmental risks are anticipated by many commentators to differ compared to first generation GM crops, modified for herbicide tolerance or insect resistance. As can be observed in the public debate and policy development on PM farming in the USA and in Canada, the possible contamination of the food and feed chain by pharm crops, e.g. via out-crossing or commingling, is a key issue that needs to be resolved before continuing with large scale open-field cultivation of PMPs. Confronted with strong resistance especially from the food industry and in the absence of a suitable regulatory framework at both the process and the product level, commercial actors are still manoeuvring in a difficult terrain.

Beyond pharmaceuticals and vaccines, PM farming developers also aim at the production of industrial products for other purposes (subsequently designated as plant-made industrials or PMIs), e.g. collagen for the cosmetic industry, spider silk proteins and enzymes for various technical applications, enzymes and antibodies as diagnostics and research chemicals, and a range of substances used as food supplements, food additives or feed additives. These applications suggest fewer challenges in terms of regulation and acceptability. Nevertheless, as will be discussed in this report, the larger acreage and the preference for food/feed crops envisaged for certain applications pose a number of challenges which are largely unattended so far.

2 This study

The overall objective of the study was to identify possible advantages and challenges in the area of plant molecular farming – in particular for the EU. The study covers PM farming applications for producing biopharmaceuticals and vaccines and for food and feed purposes (food supplements, food and feed additives), subsequently referred to as plant-made pharmaceuticals (PMPs), plant-made vaccines (PMVs) and plant-made industrials (PMIs). The overall focus is on techno-economic, regulatory and wider policy challenges including stakeholder and public perception.

The study is part of the AGRITECH activities of the Institute for Prospective Technological Studies (IPTS) and intends to inform the European Commission (for more details on AGRITECH see http://agrilife.jrc.es).

The study draws on literature and document analysis and 40 interviews as well as on material gathered in the course of two previous research projects on molecular farming (Spök 2007; Spök & Klade 2005; Spök et al. 2004) conducted by the authors of this study.

Phone interviews were conducted with a wide range of stakeholders including representatives from PM farming companies, pharma companies, industry associations, regulatory bodies, environmental organisations, consumer organisations, as well as academic experts from the USA, Canada and the EU (for a more comprehensive list see Annex 5: List of Interviews).

As there is much less activity in and very little material available on PMIs for food and feed purposes, the study largely focuses on PMPs. Wherever pertinent, similarities and differences are mentioned between PMPs and PMIs.

The report is structured as follows. Chapter 3 provides an introduction into the PM farming technology focussing on the plants and expression system used. Chapter 4 describes R&D activities, the product pipeline and commercial actors. It includes a comprehensive list of companies with a brief description of their technology and products developed in Annex 1: PM farming developers and selected public research and an overview of PM farming products that are already commercially available or in more advanced stages of (clinical) development. A discussion of potential advantages of PM farming compared to presently used technologies and PM farming business drivers is included in Chapter 5. Chapter 6 discusses challenges to policy makers and companies active in PM farming. Stakeholder and wider public perception have become a key issue for first generation agricultural biotechnology. Chapter 7 is therefore dedicated to this topic. Chapter 8 describes strategies of PM farming developers to cope with the challenges mentioned. On the basis of the preceding Chapters, the final Chapter 9 draws overall conclusions for policy development in the EU.

3 Description of the technology

In 1988 genetic engineering was for the first time applied to a plant in order to use this plant as bioreactor for producing a protein (Curtiss 1999; Curtiss & Cardineau 1990). Since then the technology has rapidly developed and diversified to comprise a variety of production platforms and target proteins, mostly biopharmaceuticals. The basic technological concept is relatively straightforward and combines molecular genetics developed for agricultural biotechnology and biopharmaceutical production. Genes for high-value proteins are expressed in crops which can easily be grown on a large scale and the protein is then extracted and purified from plant tissue. Besides open field cultivation, various plant production systems have been developed for greenhouse and contained production. This Chapter provides a brief description of the different types of production platforms developed for PM farming, i. e. the plant and the molecular expression system.

3.1 Plants for open-field and/or greenhouse production

A broad range of plant species have been used for PM farming including alfalfa, Arabidopsis, banana, barley, carrot, false flax, flax, lettuce, maize, pea, peanut, pigeon pea, potato, rice, rape, safflower, spinach, soybean, sugar beet, sugar cane, tobacco, tomato, wheat, white clover, and white mustard (for a review see e.g. Twyman et al. 2005; Twyman 2004). Field trials have been conducted with a smaller range of plants, the most relevant of which are maize, tobacco, rice, and safflower (see Table 3, p. 23).

For the purpose of PM farming, these plants are differentiated into dry seed crops (including cereals and grain legumes), leafy crops, fruits, vegetable crops, and oil crops.

Leafy crops are favourable in terms of biomass production. As a general disadvantage, proteins are synthesised in an aqueous environment and are subject to rapid proteolytic degradation after harvest. High yields can, thus, only be accomplished if the material is immediately processed on site or transported as dried or frozen material which adds to production costs. Expression of target protein in vegetative tissues has the theoretical potential to interfere with plant metabolisms.

In case of cereals and grain legumes (e.g. maize, rice), the protein is directed to the seeds allowing long-term storage of the target protein, often at room temperature. Storage up to three years has been demonstrated for antibodies without detectable loss of activity (Stoger et al. in press, c. f. Twyman et al. 2005). Downstream processing can therefore take place on batches of harvested material. The processing is improved as no oxidising compounds are present compared to leafy crops like tobacco and alfalfa leaves. From a regulatory perspective, seeds for PM farming are regarded GMOs in their own right.

Fruit and vegetable crops (e.g. tomatoes, bananas) are being investigated mainly for production of oral vaccines, because the raw plant material is edible. Oilcrops (e.g. safflower) can direct target proteins into oilbodies in the seeds which facilitates downstream processing.

A brief description of most frequently used crops for PM farming is given in the following:

Tobacco

Tobacco is the most widely used leafy crop because of massive biomasses yield and well established procedures for gene transfer, expression and farm scale handling. It is particularly attractive because it is not a food crop. Specific disadvantages of tobacco are the

Table 1: Proposed ratings for selected crop types as suitable protein production systems

Crop Type	Product Safety	Environmental Safety	Lab Ease	Growing Ease	Harvest Transport Storage	Puri-fication Process	By-Product Credits
Maize	A	B	B	A	A	A	A
Rapeseed	B	C	A	A	A	B	B
Soybeans	B	B	C	A	A	A	B
Tobacco	C	A	A	B	C	B	C
Tomato	A	B	A	B	C	C	C

Source: Adapted from Hood 2004; A score: best performance B score: moderate performance C score: least desirable performance.

presence of toxic alkaloids and the heterogeneous glycan structures produced by tobacco cells. For PM farming Nicotiniana tabacum (conventional tobacco plants) and N. benthaminiana (a non-cultivated tobacco species) are used.

Maize

Maize is easy to transform and use in the laboratory, has the largest biomass yield of all major cereals and grain legumes tested and is the easiest to scale-up in the field. In terms of production costs and efficiency, and without considering regulatory or environmental issues, maize is still considered by many developers to be the best available option for large scale production of proteins (company interviews).[1]

Rice

Similar to maize, rice is easy to transform and manipulate in the laboratory. Field operations and scale-up can be easily handled. Rice has a lower annual grain yield compared to maize. Producer prices for rice are significantly higher compared to maize. Rice is a self-pollinating crop and is therefore considered by some developers a better choice in terms of biosafety compared to maize.

Safflower

Safflower is a highly productive oilseed crop that can be easily transformed and scaled-up in production, and that has a plus regarding confinement: there are no weedy relatives in the USA and Canada, it is self-pollinating, and the seeds show minimal dormancy. Safflower is a minor food crop, which in North America is grown on 50,000 hectares and limited to California only. In Europe there is essentially no safflower cultivation.

Commercial scale production with these four crops is usually envisaged in the open field. Only with tobacco greenhouse production is being considered.

As briefly described above, each crop has particular characteristics in technical, economic, and environmental terms. Ratings of the different crops have been proposed by some authors (e.g. Table 1) but have been subjected to changes as technology progresses and the focus of crop developers for PM farming becomes wider to include more aspects.

3.2 Expression systems

A number of expression systems have been developed and used by commercial actors. An overview is provided in the following (based mainly on Fischer et al. 2004; Twyman et al. 2005; Twyman 2004). An overview including a brief assessment of

1 By applying a narrower focus on techno-economic aspects and ignoring wider regulatory and economic constraints.

strengths and weaknesses of each system is given in Table 2 based on Fischer et al. (2004).[2]

Stable transformation

The dominant system used in PM farming is the stable integration of the target gene into the plant genome; routine transformation protocols are available for a broad range of plants. Transgenic plants usually contain the target genes incorporated into the plant genome. Such plants are considered stable over many generations allowing for easy scale-up and low-cost production. Major disadvantages are the timescale for developing the plants (up to two years) and biosafety concerns of biotechnology regulators. Genetic stability is on the other hand the very reason why pharmaceutical regulators, appear to have less concerns compared to e.g. transient expression (interview regulators). Stable transformation is presently the most widespread system used in commercially available GM crops.

Transplastomic plants are generated by introducing DNA into the chloroplast genome. The high copy number of chloroplasts in plant cells allow for high expression levels (25% and 31% of total soluble protein (TSP); see Daniell et al. 2005; Fischer et al. 2004). As a confinement plus, out-crossing via pollen is strongly inhibited because pollen usually do not contain chloroplast DNA. The major disadvantage is that chloroplast proteins are not glycosylated (glycosylation, i.e. the attachment of sugar residues to the protein backbone, is a frequent characteristic of human proteins; see also Section 6.1.3). Chloroplast transformation is routinely used only in tobacco, while research is being conducted on a variety of other plant species including chromoplast[3] transformation of carrots and tomatoes.

Virus-infected plants

Recombinant plant viruses, such as the Tobacco Mosaic Virus, can also be used as expression vectors. Virus-infected plants could be grown on the same scale as transgenic plants; the development of producer lines is much quicker because virus infections take days or weeks to establish compared with the months required to produce stable transgenic plants. High level expression is possible as viral replication is prodigious and infections are systemic. Virus-infected plants have been developed as a platform technology by several companies. A similar technology platform involves the use of plant virus particles to display the epitopes of animal viruses and other pathogens as coat fusion proteins. Plant-based vaccines are frequently developed using this technology (reviewed in Mor & Mason 2004).

Transient expression

Transient expression is mainly being used for early stages of process development and in case there is a need for quickly obtaining gram amounts of the target protein, although it has meanwhile been developed for scale-up and production. One example of this is the transient expression of recombinant proteins in tobacco and alfalfa leaves through agroinfiltration, a process in which recombinant Agrobacterium tumefaciens is introduced into the gaps between leaf cells by vacuum infiltration, resulting in the short-term production of recombinant proteins. Researchers at Medicago have described how the agroinfiltration of alfalfa leaves can be scaled up to 7,500 leaves per week, for the production of micrograms of recombinant protein. Similarly, it has been shown that 25-50 kg of tobacco leaves can be batch-processed by agroinfiltration resulting in the production of several hundred milligrams of protein.

High-throughput systems have been developed with Nicotinana benthamiana using the Tobacco Mosaic Virus (TMV) as vector. Gleba et al. (2004) and Marillonnet et al. (2004) described extreme expression levels of 80% of

2 As with the ranking of crops for PM farming above, the assessment might be subject to changes depending on technical progress, policy frameworks and regulatory requirements etc.

3 Chromoplasts are plastids responsible for pigment synthesis and storage.

Table 2: Advantages and disadvantages of different plant-based production systems.

System	Advantages	Disadvantages
Transgenic plants, accumulation within plant	Yield, economy scalability, establishment of permanent lines	Production timescale, regulatory compliance
Transplastomic plants	Yield, multiple gene expression, low toxicity, containment	Absence of glycosylation, some evidence of horizontal gene transfer
Virus-infected plants	Yield, timescale, mixed infections	Biosafety, construct-size limitations
Transient expression by agroinfiltration	Timescale	Cost
Transgenic plants, secretion from roots or leaves	Containment, purification	Scale, yield, cost of production facilities
Cell or tissue culture	Timescale, containment, secretion into medium (purification), regulatory compliance	Cost

Source: Fischer et al. 2004. http://www.pharma-planta.org/COPB%202004.pdf

total soluble protein (TSP) or 5 g/per kilogram of fresh leaf biomass within 3-14 days.

Given its speed advantage transient expression is presently the most widely used system applied by academic groups and industry researchers for producing and evaluating plant-made proteins in the R&D process.

While, in principle, all expression systems can be used for both greenhouse and open field systems, there are two alternative systems which are envisaged to be used in-house only. In both cases the target protein will be recovered from a liquid medium:

Hydroponic cultures

As an alternative to extracting the target proteins from plant tissue, the protein can be directed to the secretory pathway and recovered from root exudates (rhizosceretion) or leaf guttation fluid (phyllosecretion). This technology has for instance, been used for producing antibodies.

Hairy roots

The formation of hairy roots can be induced by following transformation with Agrobacterium rhizogenes and enable root tissue to be cultured in liquid medium. A variety of plant metabolites have been produced from hairy roots and excreted into the liquid medium, which makes purification easier. Proteins produced so far include antibodies, phosphatase, and ricin B fusion protein (Fitzgerald 2003; Gleba 1999; Guillon et al. 2006).

3.3 Bioreactor-based systems

Plant production platforms are also developed using plant-cell culture, moss, Lemna, and algae, usually in fully contained bioreactors.

Plant cell culture

Suspension cell cultures derived from whole plants (e.g. tobacco, rice, carrots) possess many of the advantages of whole plants in terms of safety and capacity for the folding and modification of human proteins (Doran 2000; Fischer et al. 1999; Hellwig et al. 2004). They can be grown in a very similar way as mammalian cell lines but are cheaper to maintain because they require a relatively simple, synthetic growth medium, and ideally they allow the product to be secreted into the medium for purification. Current challenges that need to be addressed include the relatively low yields and the genetic instability of many plant cultures (Hellwig et al. 2004). In the last fifteen years the production of more than 20 different recombinant proteins has been demonstrated, including antibodies,

hormones, growth factors, and cytokines. While some consider cost savings in plant cell culture as low compared to mammalian cell lines, if there are any savings at all, others claim savings in capital costs of about 80% (company interviews). Purification of the target protein might be simpler compared to agricultural-scale production (Doran 2000; Hellwig et al. 2004). The first commercially approved PMP, a poultry vaccine, is being produced from plant cell culture (Dow Agro Sciences). Protalix Biotherapeutics is working with cell culture from carrots and recently received FDA agreement for abbreviated clinical testing in Phase 3 of their glucocerebrosidase.

Moss

Physcomitrella patens, a moss variety which is very susceptible to transformation with recombinant DNA, has been used as a model organisms over more than three decades. Physcomitrella can be modified by homologous recombination allowing for the elimination of unwanted side effects of the transformation. Plant specific glycosylation can easily be knocked out – and can be humanized via additional genetic modification. Physcomitrella can easily be cultured under phototropic conditions in bioreactors and have a high level of purity and rapid growth rates. Proteins can be secreted into the medium and purification is therefore facilitated. Genes controlling sexual reproduction are presently being identified – the genetic simplicity of the organisms might allow for simpler genetic bioconfinement strategies (Decker et al. 2003; Schaaf et al. 2005; Decker & Reski 2004; Hohe & Reski 2005; Huether et al. 2005; Koprivova et al. 2003, 2004; Hohe et al. 2002a, b).

The German company Greenovation BioTech is presently developing a commercial production system based on Physcomitrella. Physcomitrella has been used for proof of concept and feasibility studies of several biopharmaceutical proteins, especially antibodies. A transient system is used for feasibility studies and a stable integrated system for production. The company is presently developing a 100 l full-GMP production facility. Up-scaling can be done by establishing serial batteries of bioreactors of the same size and identical conditions. Yield, however, is in the range of 30 mg per litre per day. This corresponds to the yield of a typical fed-batch culture over 20 days of 600 mg per litre. Notwithstanding the low yield the company is claiming total savings to be in the range of 50% compared to mammalian cell culture because of the savings for purifications, quality control, and glycosylation (company website, interviews).

Duckweed (Lemna)

Lemnaceae are small, free-floating aquatic plants, the most common of which is duckweed or Lemna. Duckweed is growing on the surface of ponds, lakes and rivers. Lemna minor is used for food and feed in Asian countries and used for wastewater management in North America. The plant has been genetically modified to produce twelve monoclonal antibodies including small peptides and large multimeric enzymes (Fitzgerald 2003; Gasdaska et al. 2003).

For PM farming Lemna is grown in water-based reactors. Lemna has biomass doubling times of 48 – 72 hours in controlled systems (according to the company Biolex even 36 hours). Two companies are developing Lemna systems; recently the US company Biolex acquired its competitor LemnaGene (France).

According to company information a Lex facility allows for 8-fold reduction in start-up costs with total costs of US$ 50 million and can be established within three years compared to mammalian systems (the start-up of which costs some US$ 400 million and may take up to five years).

Although Lemna might be attractive for reasons of containment, the rapid reproduction rate, and the fact that Lemna is flowering and produces pollen raises concerns. It might be very difficult to eradicate Lemna that has escaped, e.g.

via waste water, thus a strict containment system is considered pivotal (Dunwell & Ford 2005).

Algae

Algae can generally be easily transformed and have short-life cycles. The possible application of algae for PM farming has been reviewed by El-Sheekh (2005); Franklin & Mayfield (2004, 2005); Walker et al. (2005). Among single cell species Chlamomydomonas reinhardtii is used. Single cell algae can be grown under high density and large volumes. Downstream processing might be easier and therefore less costly compared to higher plants because algae are much simpler organism (Walker 2005). These systems have been tested to express a broad range of biopharmaceutical proteins including antibodies, interleukins, neurotrophic factors, and cholera toxin B unit (Mera Pharmaceuticals, c. f. Dunwell & Ford 2005; Sun et al. 2003).

Algae are considered as natural colonisers and some species have a tremendous capacity to disperse and persist in natural habitats. Together with their short generation time and high growth rates concerns about escape are being raised. So far there is no sufficiently reliable method available to control algae reproduction; hence containment would need to be very strict.

3.4 Platform choice

As described above, each plant and each expression system (both aspects combined are often referred to in the literature as technology or production platform) offer different advantages and disadvantages which makes it difficult to think of dominant technology design. Rather, it depends on the particular case which technology platform might be the best choice.

Platform choice depends on a broad range of criteria including the nature of the protein and the required posttranslational processing (e.g. chloroplast expression for non-glycosylated proteins only), scale of production (e.g. greenhouse and bioreactor based systems might be more difficult for very large scale production), downstream processing requirements (e.g. are different for leafy crops and seeds; different purity requirements for oral vaccines and biopharmaceuticals which will be injected; lower purity requirements for non-pharmaceutical applications), overall costs (e.g. for a given protein an economically viable production cannot be set up with each production system; low cost systems would be especially important for non-pharmaceutical applications), speed (e.g. key for vaccine and for evaluating a larger number of substances), environmental issues (e.g. additional biosafety requirements for open field production), confinement and containment (e.g. in case of risks of accidental contamination of the food supply), regulatory requirements for drug authorisation (difficulties with open field production and transient expression), and on the developers IPR status. For non-pharmaceutical applications and with the possible exception of low-volume fine chemicals selling at high-prices, the feasibility of large scale production and low costs will be of key importance.

For instance, for industrial feedstock, selecting a major crop that already is used in industrial applications would have benefits. For orally delivered therapeutic proteins or vaccines, a food crop that has GRAS (Generally Recognized as Safe) status would be a convenient choice. For protein stability and ease of transport a grain (e.g. maize, rice, and soybean) would be a good choice. For avoiding the risk of contaminating the food or feed chain tobacco, while maintaining the advantages of open field production, might be best. Food crops, however, still seems to be the preferred option from a technical and efficiency point of view. Transient expression might be a very good system if speed is key (e.g. vaccines), but regulators favour genetically stable systems. (e.g. Twyman et al. 2005; Hood 2004; company interviews).

Some of the issues related to platform choice will be revisited in the subsequent sections.

3.5 Summary

A broad range of plants and expression systems have been developed over the last fifteen years. For open field production maize, rice, tobacco and safflower seems to be most widespread in commercial contexts, for greenhouse production tobacco is the preferred choice. Contained bioreactor type systems include moss, duckweed (Lemna), algae, and plant-cell culture. Expression systems included stable transformation of plant genomes (nuclear or plastid), plant-viruses, and transient expression. Each plant and each expression system – often referred to as technology or production platform – offer different advantages and disadvantages, which makes it difficult to think of a dominant technology design. Rather, it depends on the particular case which technology platform might be the best choice. Platform choice depends on a broad range of criteria, including the nature of the protein, posttranslational processing, scale of production, downstream processing requirements, overall costs, purity needed and delivery route of the drug, speed, environmental concerns, confinement and containment issues, regulatory requirements, IPR. For non-pharmaceutical applications large scale and costs will be of key importance.

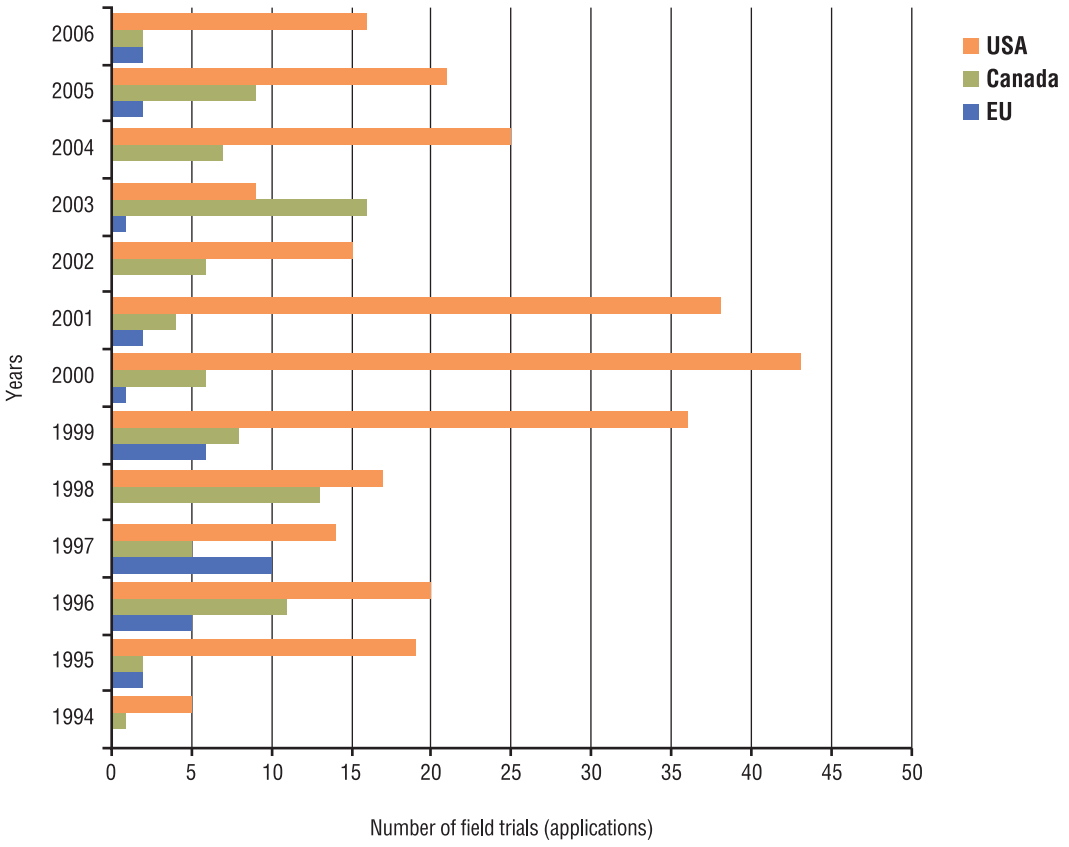
4 R&D Activities, Actors and Product Pipeline

R&D related to PM farming is being pursued in the USA, Canada, the EU, Israel, Australia, South-Korea, Singapore, Japan, South Africa, China and Cuba. The vast majority of activities centred in the USA, Canada, and the EU and there is very little information publicly available on Asian countries. Therefore, the overview of commercial and public R&D provided in this Chapter focuses on the USA, Canada and the EU. Section 4.1 to 4.5 analyses commercial and public R&D activities over time and across countries based on a number of indicators: field trials (Section 4.1), scientific publications (Section 4.2), patents (Section 4.3), companies active (Section 4.4), and products in the pipeline (Section 4.5). Based on these analyses a comparison between the USA and the EU is provided in Section 4.6. In addition, Annex 1: PM farming developers and selected public research provides a comprehensive overview of companies active in PM farming worldwide including some academic groups that have been very visible in the scientific literature.

4.1 PM farming Field trials

Field trials for PM farming generally comprise only a very small segment of about 1–3% of total field trials with GM crops (Sauter 2006). The vast majority of field trials have been conducted in USA (237 field trials until 2005) compared to Canada (88) and Europe (30) (Bauer 2006). A similar picture emerges from the analyses of other authors (Sauter & Hüsing 2006; Spök & Klade 2005). Even

Figure 1: PM farming field trials 1996-2006.



Data between 1991 and 1993 were only available for the USA and therefore omitted from the chart. No data are available for the EU before 1995. US data were based on field trial application, which does not fully correspond with field trial conducted. This is also true for data from the EU. Source: Bauer (2006), updated and modified.

Table 3: Plant species used for plant molecular farming.

Plant	Number of applications for field trials	
	Up to 2003	Update from 2004 onwards
Maize	72	14
Tobacco	33	19
Rapeseed	16	-
Soybean	12	-
Tobacco Mosaic Virus (TMV)	9	1
Rice	8	18
Safflower (Carthamus tinctorius L.)	6	27
Flax	4	-
White mustard	2	-
Alfalfa	1	-
Barley	1	3
Sugar beet	1	-
Sugar cane	1	-
Tobacco Etch Virus (TEV)	1	-
Tomato	1	-
Wheat	1	-
White Clover	1	-
Pea	N.i.	3
Potato	N.i.	3

Source: Hüsing 2004 c.f. Sauter and Hüsing (2006) (based on USA: http://www.nbiap.vt.edu 1987-2003, Canada: http://www.inspection.gc.ca 1988-2003, EU: http://www.rki.de http://biotech.jrc.it 1991-2003, Argentine: http://www.sagpya.mecon.gov.ar 1991-2002, South Africa: http://www.nda.agric.za 1999-2003) adapted and updated (updates include data from the USA 2004-2007, Canada 2004-2006, and EU 2004-2006).

Abbreviations: N.i.: not investigated.

more striking is the difference in total field size: in the USA a total area of more than 6200 hectare was dedicated to PM farming so far compared to some 200 hectare in the EU (Bauer 2006).

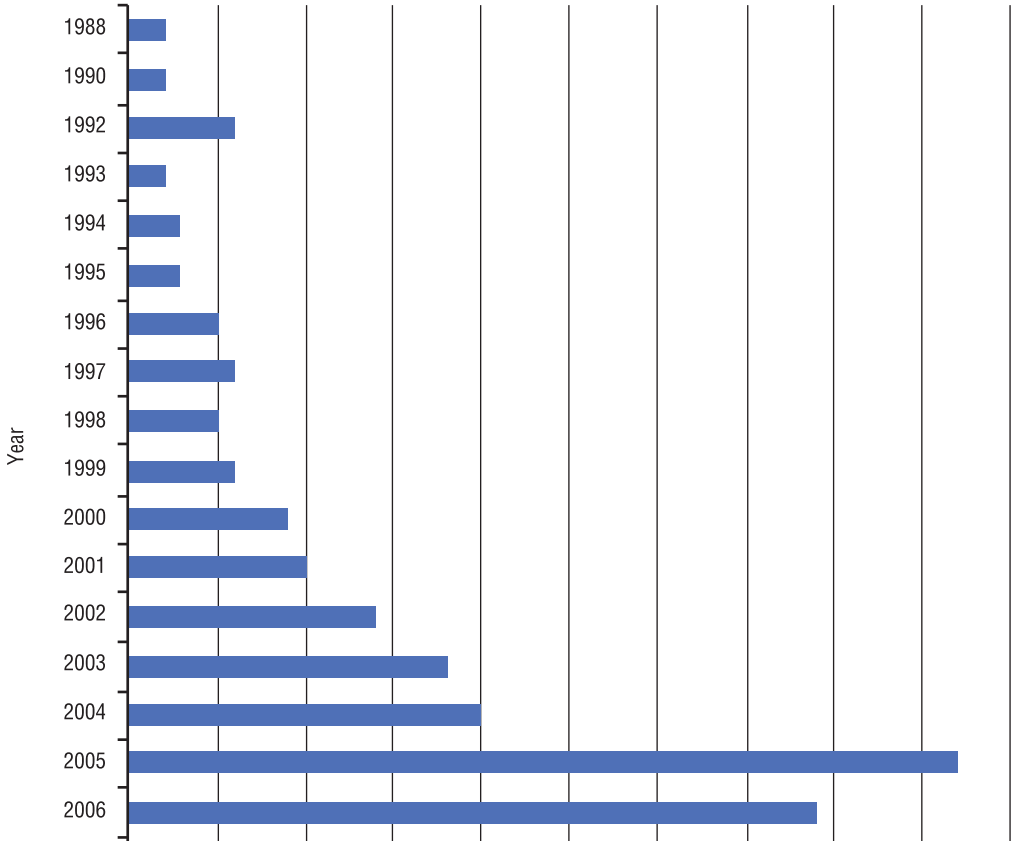
Figure 1 shows the number of field trials over time. The sharp decline in numbers in the USA after 2001 is generally interpreted as a consequence of the ProdiGene incident where volunteer pharm maize was discovered in fields dedicated to food production.

Field trials have been conducted with a broad range of plants, the most relevant of which are maize, tobacco, rice, and safflower. In recent years the trend in crop choice seems to shift towards non-food (tobacco) or minor food crops (safflower), with the possible exception of rice (see Table 3).

4.2 Public sector research

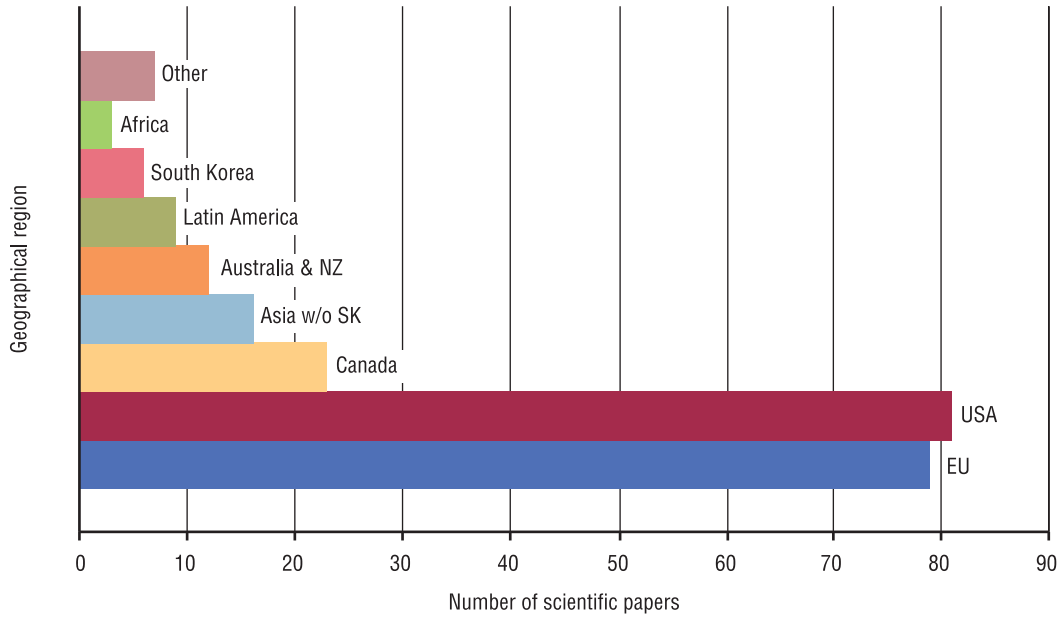
Field trial statistics give a first impression of commercial R&D activities but they do not consider R&D that is solely conducted in laboratories and greenhouses, i.e. early stage R&D which will eventually proceed to field trials but also R&D on production platforms not intended for the open field. Thereby, most of public sector research activities are ignored as they usually include much less field trial activities. As an indicator for public sector research activities the number of scientific publications about PM farming is analysed. Figure 2 shows the development over time and Figure 3 the geographical distribution. After a lag of about ten years following the first publication in this area the research activities sharply increased from early 2000 onwards. While confirming the overall picture from the field trial statistics – that

Figure 2: Scientific publications in PM farming from 1988 to 2006.



Source: Keyword analysis from the ISI Web of Science.

Figure 3: Scientific publications related to PM farming.



The numbers are slightly skewed because they include some 10% industry publications mostly from North American companies and about 5% of papers are cited twice because of shared authorship. Acronyms: SK: South Korea, NZ: New Zealand; source: Keyword analysis from the ISI Web of Science.

Table 4: PM farming research projects in the course of the EU Framework Programmes.

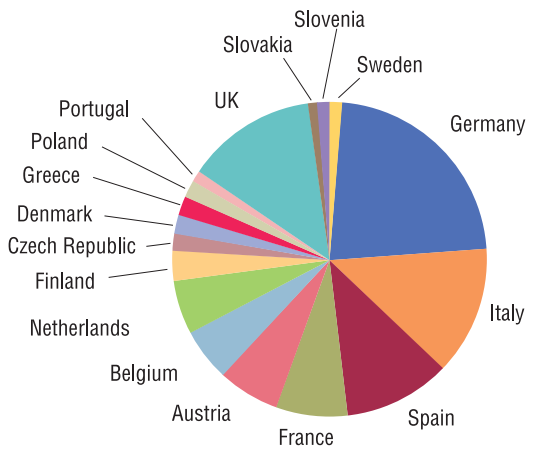
Project No.	Project Title
4th Framework Programme	
FAIR-CT96-5068	Molecular farming of therapeutic antibodies in plants
FAIR-CT96-3110	Production of diagnostic and therapeutic antibodies in plants by molecular farming
FAIR-CT96-3046	Production of recombinant immune complexes in transgenic plants for systemic and mucosal vaccines
FAIR-CT95-1039	Processing Technology for Recovery of Recombinant Antibody Produced in Crop Plants
FAIR-CT95-0720	The Plant as a Factory for the Production of Oral Vaccines and Diagnostics
5th Framework Programme	
QLK3-CT-1999-00692	The Plastid Factory
QLK2-CT-2000-00739	Immunotherapy of enteric infections by rotaviruses and coronaviruses using plantibodies
QLK4-CT-2002-51547	Metabolic engineering of plant cells for the production of pharmaceuticals
6th Framework Programme	
N.i.	Pharma-Planta

Source: updated from Pickardt and de Kathen (2004, p. 52); N.i.: not investigated.

most activities concentrate in the USA, Canada and the EU – the analysis suggests little differences between the USA and the EU in terms of public sector research. It also shows some activity in Australia and New Zealand, and Asia (mainly Japan, China, and India). In contrast, very little activity takes place in other countries; almost no activity can be related to developing countries.

Within the EU, the concentration of public sector research activities on Germany, France, Italy, Spain, and UK correlates with the relative strength of these countries in the manufacturing of pharmaceuticals (Zika et al. 2007).

Figure 4: Proportion of scientific publications related to PM farming. EU internal distribution of authorship.



Source: Keyword analysis from the ISI Web of Science.

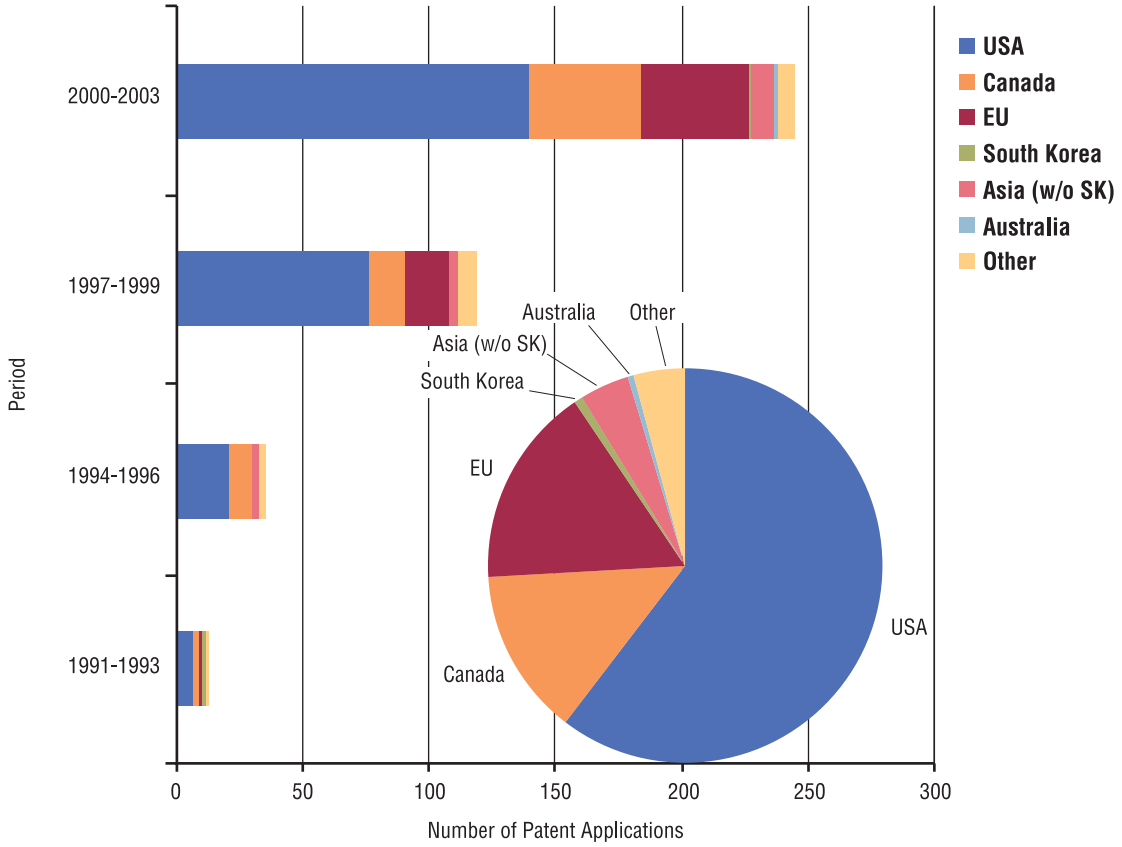
EU based research in PM farming was partly conducted in the course of the EU Framework Programmes (see Table 4). Of particular interest is Pharma-Planta, a research consortium under the European Commission's 6th Framework Programme that is pioneering academic research activities and also striving to clear the regulatory path for PMPs in the EU in partnership with a small number of European firms.[4]

Following the research policy advice of the European Technology Platform "Plants for the Future"[5] (Plants for the Future 2004, 2005, 2007) and as indicated by the first calls for research proposals, the recently started 7th Framework Programme is likely to set a particular focus on industrial crops which will

4 www.pharma-planta.org

5 EU Technology Platforms are led by industry and serve as frameworks for stakeholders, to define research and development priorities, timeframes and action plans on a number of strategically important issues where achieving Europe's future growth, competitiveness and sustainability objectives is dependent upon major research and technological advances in the medium to long term. The European Technology Platform "Plants for the Future" is coordinated by European Plant Science Organisations and EuropaBio and is advising the European Commission on biotechnology and plant genomics.

Figure 5: Geographical distribution of patent applications related to PM farming over time and total up to 2003 (pie chart).



Other: Argentina, Russia, Israel, Switzerland). Source: adopted from Arcand & Arnison (2004).

include PM farming for both pharmaceutical and non-pharmaceutical products.

4.3 Patents in PM farming

An analysis of Arcand & Arnison (2004) of patents related to PM farming show again a dynamic development over time in all countries with relevant activities and a strong position of the USA and Canada with both countries holding about 75% of patents versus 17% of EU Member States (see Figure 5).

4.4 Commercial actors

At least 60 companies worldwide are conducting R&D in PM farming. Most companies are start-ups or of SME-type founded between early 1990s and early 2000 and are specialised into this technology. Presently there are only three multinational companies active in PM farming, only one of which has a substantial pharmaceutical business (Bayer, Germany). The largest number of companies can be found in the USA, with the EU catching up. Fewer companies are active in Canada and much less activities are reported from other countries.

Companies are usually developing their own proprietary technology platform, including crop choice and expression system, conducting proof of concept and feasibility studies both with their own products and – as technology providers – also for other companies.

The majority of companies are working on public funds and venture capital, some companies are meanwhile publicly traded (e.g. Medicago,

SemBioSys). So far, none of the smaller companies could create a return for their investors – although this seems to be a general characteristic of many biotech companies. Therefore, it is perhaps not surprising that a substantial number of companies has dropped out of business over the recent years. Some companies failed to secure further funds (e.g. CropTech Development (USA), Axis Genetics PLC (UK), MPB-Cologne GmbH (Germany), Large Scale Biology Corp. (USA), ProdiGene (USA). Monsanto and Syngenta, for a couple of years the only multinational companies besides Dow AgroSciences active in PM farming, abandoned the business in 2003 and 2005, respectively. The decisions were portrayed as pure internal priority settings but implied that this technology was not expected to deliver any profits in the short and medium time range (company interviews).

Conversely, two other multinationals, Bayer and BASF (both Germany), started R&D activities and got access to proprietary technology partly by buying promising start-ups such as Icon Genetics (Germany, bought by Bayer) and CropDesign (Belgium, bought by BASF). SunGene (Germany) established as Joint Venture of BASF, the Institute of Plant Genetics and Crop Plant Research (Gaterleben) and others (now fully owned by BASF).

An extensive list of companies, including a brief description of their technology platforms and products is provided in Annex 1: PM farming developers and selected public research .

Besides companies, a large number of universities and other public research institutions as well as NPOs, are conducting research in PM farming. Only a few of them – which have been more visible in the scientific literature and in discussions related to PM farming, and which are also aiming to bring products closer to market stage (e.g. the EU FP6 Research Consortium Pharma-Planta including the IME Fraunhofer (Germany), the Arizona State University (AZBIO, USA), the Squipps Research Institute (USA), and the Centro de Ingeniería Genética y Biotecnología (CIGB, Cuba) – are included in the Annex.

The technology platforms used are very diverse, mirroring the broad range of crops and expression systems available (see previous chapter). Presently, about one third of the companies are developing technology platforms in containment (including greenhouses), another third is aiming at open field cultivation at least with some of their products. Tobacco appears to be to the most frequent choice of a non-food crop, companies using major food crops (maize, rice, barley, and rape) are only a few, with only one company left to use maize (Meristem Therapeutics, France; for one product only).

4.5 What's in the pipeline

The majority of the companies focus on biopharmaceuticals and vaccines for human use, especially on antibodies with some of them recently broadening their portfolio to include PMIs for non-pharma applications.

PMPs – biopharmaceuticals and vaccines

Although company information on products and advancements in clinical trials cannot be considered as comprehensive and complete it seems that there are less than 20 products in clinical trials (see Table 5 as well as Table 14 in Annex 1). About 90% all clinical trials with PMPs are being pursued by US companies. This strong position of the USA contrasts a total of 109 (EU) and 190 biopharmaceuticals (USA) which were in clinical trials in 2005 (Zika et a. 2007).

With the possible exception of a chicken vaccine against Newcastle disease produced from plant cell culture (Dow AgroSciences),[6] no PMP or PMV has been granted authorisation for market commercialisation. A number of products are in clinical trials and a small number of products are

6 Dow received market authorisation by the USDA in 2006 but is not considering commercialisation. According to company officials, the vaccine was only used as a proof of concept but never intended to be commercialised.

already in Phase 2. Only one product has already arrived in Phase 3 (see Table 5).

Among the most advanced products are therapeutic enzymes, a human glucocerebrosidase from plant cell culture, a therapeutic enzyme from maize used for treating Cystic Fibrosis as

Table 5: Plant-made pharmaceuticals and vaccines in advanced stages of development[a]

Product	Application	Plant host(s)	Status[b]	Company/academic Group
Plant-made pharmaceuticals and vaccines – human use				
AB	AB cancer vaccine	Tobacco	Phase 2 clinical trials	Large Scale Biology Crop., USA[c]
B subunit of heat labile E.coli toxin LT-B	Oral vaccine against traveller's diarrhoea	Potato, maize	Phase 1 completed (potato: 1998)[d]	Tacket et al. 2004 USA
Capsid protein Norwalk virus	Vaccine	Potato	Phase 1 completed (2000)[d]	Tacket et al. 2000 ; USA
CaroRx™	AB carries prophylaxis	Tobacco	Phase 2 clinical trials, approved as medical device in the EU in 2003	Planet Biotechnology, USA
DoxoRx™ antibody	Side-effects of cancer therapy	N.sp.	Phase 1 completed	Planet Biotechnology, USA
Fusion protein including Epitopes from rabies	Vaccine against rabies	Spinach	Phase 1 completed[d]	Yusibov et a. 2002 ; USA
Gastric lipase	Cystic fibrosis	Maize	Phase 2 clinical trials, commercialisation expected for 2009/2010	Meristem Therapeutics, France
Hepatitis antigen	Oral vaccine against Hepatitis B	Potato	Phase 2 clinical trials	Azbio, Arizona State University, USA
Human glucocerebrosidase (prGCD),	Treatment of Gaucher disease	Plant cell culture	Received FDA approval for Phase 3 clinical trial of prGCD; marketing expected in early 2008	Protalix Biotherapeutics, Israel
Insulin	Diabetes	Safflower	Abbreviated path for clinical trials accepted by FDA, commercialisation expected for 2010	SemBioSys, Canada
Lactoferon™ (alpha interferon)	Hepatitis C	Lemna	Phase 2	Biolex, USA
RhinoRx™	Rhino viruses caused cold	Tobacco	Phase 1/2 planned for 2005[d]	Planet Biotechnology, USA
Plant-made pharmaceuticals and vaccines – animal use				
Antigen	Vaccine against feline parvovirus	Tobacco	Advanced	Large Scale Biology Corp., USA[c]
Antigen	Vaccines against papilloma virus	Tobacco	Early	Large Scale Biology Corp., USA[c]
HN protein of Newcastle Disease Virus	Poultry vaccine	Plant cell culture	Approved by USDA	Dow Agro Sciences, USA

a) This table cannot be considered a comprehensive list and does also not include PMPs and PMVs which are still in pre-clinical phase or very early phase resp.; b) For human biopharmaceuticals: phase of clinical trials; c) Large Scale Biology filed bankruptcy in 2006; d) no updated information available. Source: Spök (2007) updated and extended from company websites and literature.

well as antibodies from tobacco (cancer, carries prophylaxis), an oral Hepatitis B vaccine from potato and insulin from safflower. According to some interviewees glucocerebrosidase and insulin might be the first PMPs to reach market stage, expected for 2008 and 2010, respectively.

The insulin and the glucocerebrosidase also represent the first plant-derived biosimilar[7] approaching market stage.

This contrasts with more optimistic accounts, e.g. of Horn et al. (2004) who anticipated market approval for 12 PMPs including vaccines, antibodies, and enzymes by 2009.

PMIs for food and feed use

Given the lower regulatory barrier to market entry, non-pharmaceutical products are much closer to market stage of even commercially available already (Spök 2007).

Companies are also aiming at food supplements and feed additives, though (see Table 6). Some of these products can be considered as nutraceuticals and might also be used as a pharmaceutical at a later stage (e.g. human intrinsic factor. The carp somatotropin from safflower and the human intrinsic factor from Arabidopsis seem to be closest to commercial application.

Field production for somatotropin which is used to stimulate immunedefence in shrimps, has already been scaled-up to 120 hectares in Chile. Given its expected application in the major shrimps producing regions in Latin America and Asia, market entry regulatory requirements might be lower than in the USA, Canada or the EU. According to company representatives only import permits would be needed in the USA, Canada and the EU for the food products for which the additive had been used. As the additive is not detectable and no longer present in the final food, these permits are expected to be easily granted. Thus, commercialization is expected in 2008.

The human intrinsic factor intended to be used as a food supplement for patients suffering from vitamin B12 deficiency is produced from Arabidopsis grown in greenhouses. According to their self-portrayal – as the first company world-wide, Cobento received a permit for commercial production of the human intrinsic factor from Arabidopsis in greenhouses from the national authorities and it also received authorisation of its use as a food supplement in Poland.[8]

Not included in Table 6 but also active in this field are the German company BASF and US based Monsanto. BASF company is developing a range of products to be used as food supplements, food additives or feed additives including omega-3 and omega-6 fatty acids produced in rape (Brassica napus) as well as carotenoids, vitamins and amino acids produced in soybean and other crops. Field trials for these products have been conducted outside the EU. Only omega-3 and omega-6 fatty acids and carotenoids are intended to be extracted and used as supplements whereas the other GM crops would be directly processed giving rise to biofortified food.[9] Monsanto is

7 Biosimilar or follow-on biologics are generic products of biopharmaceuticals. For more information on this product category see also Sections 6.2, 6.5.

8 There is no harmonised authorisation regime established for food supplements in the EU. Any requirements are therefore governed by national law. In case of health claims Regulation (EC) No 1924/2006 of the European Parliament and of the Council of 20 December 2006 on nutrition and health claims made on foods.(OJ L 404, 30.12.2006, p. 9–25) applies and companies have to substantiate their claims with scientific evidence.

9 This points to the difficulty to discriminate molecular farming from other applications of agricultural biotechnology. Only the former case would be considered as PM farming. In case of overexpression of endogenous plant substances some commentators, including the authors of this report have not considered PM farming. If such crops would be used for both purposes extracting and direct processing as food/feed (according to company information envisaged by BASF) the distinction becomes difficult to maintain. Similarly, the phytase-rich maize which was repeatedly announced by Syngenta is intended for direct processing of feed only and was therefore not included in the Table.

Table 6: Plant-made industrials in advanced stages of development

Product	Application	Plant host(s)	Status	Company
Human intrinsic factor	Food supplement; vitamin B12 deficiency	Arabidopsis	Approval from Danish authorities for commercial production in greenhouse; market authorisation in Poland	Cobento Biotech AS, Denmark
Human lactoferrin	Developed as food supplement: anti-infection, anti-inflammatory and iron-binding properties	Rice	Advanced[a]	Ventria, USA
Human lysozyme	Developed as food supplement: anti-infection, anti-inflammatory and iron-binding properties	Rice	Advanced[a]	Ventria, USA
Immunosphere™	Carp somatotropin to be used as feed additive for shrimps	Safflower	Only import permits required for USA, Canada or the EU[b]; commercialisation expected for 2008	SemBioSys, Canada

a) Already commercially available as fine chemical; b) According to company officials the carp growth hormone will be used in major shrimp producing countries only (e.g. South America, China, Thailand) and has to seek market authorisation as a food additive in these countries only. Source: Spök (2007) updated and extended from company websites and literature.

developing a GM soybean producing omega-3 fatty acid (Powell 2007).

Also not included in the Table is an antibody from tobacco which was developed by the Cuban Genetic Engineering and Biotechnology Center (CIGB), authorised by national authorities in 2006 and sold under the trademark of Heberbiovac-HB (Roumeliotis 2006). This antibody cannot be regarded a pharmaceutical, rather it is applied in the manufacturing process of a subunit Hepatitis B vaccine for large scale affinity purification (Pujol 2005).

A small number of products are already commercially available on a small-scale for use as fine chemicals in research, diagnostics and manufacturing (Table 7). In the US and presumably also in other countries outside the EU, products from PM farming field trials can legally be commercialised as long as they comply with other relevant legislation such as chemical legislation. PM farming companies have increasingly used this option to market products that are being developed for medical or larger-scale technical applications. Interestingly, and in accordance with the focus of early PM farming, all these products are derived from open field production.

4.6 Comparing EU – North America

The picture emerging from comparative analysis of both field trials in PM farming and from PMPs in clinical trials suggests that almost all activity centres in North America and that there is very little activity in the EU. If Considering other indicators and taking a more careful look at these activities, however, this picture turns out not to be fully adequate:

First, most EU companies became active in PM farming within the last seven years, at a time when the opposition of North American stakeholder groups to the use of food crops and open field cultivation for PM farming was already very visible. EU companies did, therefore, to a lesser extent embark on such production platforms and developed a stronger focus on contained systems (tobacco and Arabidopsis in greenhouses, Lemna, moss, Camelina

Table 7: Commercially available products from PM farming.

Product	Trade Name	Pharm crop	Source of Genes	Commercial Purpose [a]	Company Producing	Company Selling [b] (product number)
Aprotinin	AproliZean	Corn	Cow	Research and manufacturing	ProdiGene	Not available
Aprotinin	Apronexin	Tobacco[c]	Cow	Research and manufacturing	Kentucky BioProcessing, LLC (formerly manufactured by Large Scale Biology)	Sigma Chemical Company (A6103)
Avidin	Recombinant avidin	Corn	Chicken	Research and diagnostic reagent	ProdiGene	Sigma Chemical Company (A8706)
β-glucuronidase (GUS)	Not available	Corn	Bacteria	Research and diagnostic reagent	ProdiGene	Not available
Trypsin	TrypZean	Corn	Cow	Research and manufacturing	ProdiGene	Sigma Chemical Company (T3568 and T3449)
Lactoferrin	Not available	Rice	Human	Research	Ventria Bioscience	Sigma Chemical Company (L4040)
Lysozyme	Not available	Rice	Human	Research	Ventria Bioscience	Sigma Chemical Company (L1667)

a) Information on specific commercial uses of pharmaceutical and industrial crop products is not available to the public. Some have potential applications for human or veterinary medicine but none has been approved by the Food and Drug Administration, which regulates drugs; b) Most of these products have been commercialized through Sigma Chemical Company, which specializes in products for research and diagnostic purposes. AproliZean and B-glucuronidase have been commercialized according to ProdiGene documents, but their current availability is unknown.; c) Unlike pharmaceutical corn, tobacco itself is not genetically engineered. Rather, a tobacco mosaic virus is engineered to contain a gene for aprotinin. The engineered virus then produces aprotinin in tobacco plants infected with the virus. Source: Adopted and updated from UCS http://www.ucsusa.org/food_and_environment/genetic_engineering/pharma-crops-on-the-market.html.

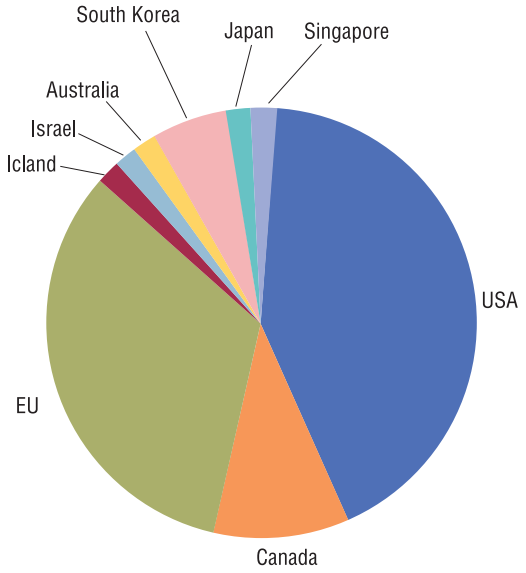
sprouts etc.). R&D activities and commercial application of PM farming in greenhouses or other types of containment is not included in EU or international databases. Furthermore, the geographical distribution of field trials is slightly skewed because EU-based companies aiming at open field cultivation of food crops were – and still are – conducting their field trials in USA, Chile and elsewhere (e .g. Meristem, Syngenta, Novoplant). Meristem (France) was in fact the only EU company that conducted substantial field trials in the EU (in maize), most of them in France.

Second, after 2002 the USA faced a strong backlash in terms of PM farming field trials and commercial interest following the ProdiGene incident, with a dramatic decrease of interest in maize as a technology platform and with the first companies that were going out of business and investors getting tired. The EU, in contrast, had a comparably quiet period where entrepreneurs were starting with new venture capital and could develop their platforms and products with little or no public discussions.

In fact, with 17 companies being now active in the EU, two of which are multinationals, the overall picture has changed (USA: 22 companies, Canada: 7)[10]. Within the EU there is a strong concentration of companies in Germany and of field trials in France. With the exception of Spain, Italy, Denmark, and Finland, with each of them having one active company (Spain: 2) there is little commercial R&D in other EU Member States(see Figure 6).

10 Public research organisations or private non-profit research organisations listed in Table 14 not included.

Figure 6: Geographical distribution of companies active in PM farming.



Note: Multinational companies were either included in the EU sector (two) or in the USA sector (one) according to the geographical focus of their R&D activities.

Most likely because of the later start of EU companies, most companies appear to be in earlier stages of their R&D activities. With the exception of Meristem (France) no EU company has any PMPs in the pipeline of products in advanced stages of development.

Third, public sector R&D activities as indicated by numbers of scientific publications, seem to be of similar scale in the USA and the EU, with Germany, Spain, Italy, and France being the most active within the EU.

A similar picture emerges from PMIs. With the exception of Cobento's human intrinsic factor (authorised as food supplement in Poland), no EU company has yet commercialised a product from PM farming for non-pharmaceutical purposes.

The reasons for the latter are partly caused by an important difference in the regulatory regime for agricultural biotechnology between the USA and the EU: in the USA companies are allowed, in principle, to commercialise products from their field trials as long as the particular, substance-specific regulations are respected. In the EU, in contrast, commercialisation from field trials is explicitly forbidden in the Directive 2001/18/EC (EPC 2001). In the EU commercialisation of products from open field cultivation requires a permit obtained in an EU centralised procedure. This procedure has already been proven not to facilitate commercialisation for first and second generation GM crops – and cannot be expected to be more efficient for PM farming. For Canada different reasons might apply: field trials in Canada are restricted to one hectare per province per year, whereas field trials in the EU or USA are not restricted in acreage. For instance, some of the field trials of first generation GM crops were in the range of thousands of hectares. Conversely, as costs might be key for non-pharmaceutical purposes, production from greenhouses or other types of containment might be probative for some substances. Small volumes of PMIs can be therefore produced more easily in the USA compared to the EU or Canada.

In terms of technology platforms a shift from open field to more contained production can be observed. While North American companies are still maintaining tobacco, rice, and safflower for open field production, EU-based companies seem to have a stronger interest in non-food crops and contained systems. With PMIs for non-pharma application, production economy is driving developers into open field production on both sides of the Atlantic (e.g. in case of Cobento which would like to move from greenhouse production in Arabidopsis into open field production with potatoes). Companies aiming for large-volume (and/or low-cost) products are only considering open field production (e.g. BASF, Maltagen in the EU, SemBioSys in Canada, and Ventria, USA).

5 Advantages and business drivers

This Chapter describes the advantages of PM farming compared to presently used production systems and the key aspects driving PM farming technology development. Section 5.1 provides a brief overview whereas Sections 5.2 to 5.10 discusses the business drivers in greater detail. Most of this Chapter is focussing on PMPs and PMVs because there are much less activities and information available on PMIs. Main differences to PMIs are summarised in Section 5.11.

5.1 Overview

Plant-based systems are considered to have a number of advantages over conventional production of pharmaceuticals in bacteria, yeast of mammalian cell lines. Table 8 provides an overview on anticipated advantages and some disadvantages of PM farming compared to well established production systems and also animal pharming. The ratings are derived from several authors and are remarkably consistent among them with timescale being the only controversial issue. Nevertheless, it has to be mentioned that most ratings came from PM farming proponents. With the exception of plant cell culture the ratings envisage PM farming rather as open field cultivation. Other reactor based systems, such as Lemna, moss or algae are so far ignored.

PM farming is anticipated to provide a broad range of technical advantages compared to other production systems (insertion gene size, yield, propagation, protein assembly and folding accuracy, product quality and homogeneity, distribution, and storage temperature) and scale-up capacity, all of which translate into cost savings in production and storage of the product. Other advantages frequently reiterated in the literature are the speed and flexibility to scale-up production, the potential to enable large-volume production for affordable high-dose pharmaceuticals and vaccines, and the potential to improve health care for developing countries.

According to this overview PM farming is also clearly out-competing animal pharming. Data monitoring and GMP conformity in production (open field) are seen as the only disadvantages of PM farming. The differences in plant specific glycosylation compared to mammalian glycosylation are largely deemed a technical problem that is about to be resolved by changing plant-specific glycosylation pathways and/or subsequent modification steps. The overall risks from PM farming are considered to be low – being merely a public perception and an ethical issue.

Given that there is virtually no practical experience with commercial processing in PM farming, these ratings are based on expectations, modelling and calculations. As such they are based on a number of assumptions about future developments, demand from the pharmaceutical industry and/or health care systems, costs structure of pharmaceutical production, acceptability by regulators and the general public etc.

Some of these underlying assumptions will be discussed in the subsequent critical discussion of key business drivers.

5.2 Cost savings

Potential savings in production costs were strongly emphasised until very recently (e.g. Dove 2002; Giddings 2001; Kusnadi et al. 1997; Seon et al. 2002). According to these estimates the production of the biomass containing the target protein is likely to be much cheaper in case of open field cultivation compared to microbes and mammalian cells. Recombinant proteins could be produced in plants at 2 to 10% of the cost of

Table 8: Comparison of production systems for biopharmaceuticals.

Costs	Bacteria	Yeast	Mammalian Cell Cultures	Transgenic Plants	Transgenic Animals	Plant cell culture	Plant viruses
Costs and Timescale							
Costs	Low	Medium	High	Low	High	Medium	Low
Storage cost	Moderate	Moderate	Expensive	Inexpensive	Expensive	Moderate (m,c)	N.sp.
Productivity	Medium	Medium	Medium	High	High	Medium	N.sp.
Timescale	Short	Medium	Medium	Controversial[a]	Very long	Medium	Low
Risks and Ethical Concerns							
Risks	Toxins	Low	Viruses prions	Low	Viruses prions	Low	N.sp.
Public perception of risks	Low	Medium	Medium	High	High	N.sp.	High
Safety	Low	Unknown	Medium	High	High	N.sp.	High
Contamination risks	Endotoxins	Low	Viruses, prions and oncogenic DNA	Low	Viruses, prions and oncogenic DNA	Low	N.sp.
Therapeutic risks	Yes	Unknown	Yes	Unknown	Yes	N.sp.	Unknown
Ethical concerns	Low	Low	Medium	Medium	High	Low	N.sp.
Scale-up							
Scale-up capacity	High	High	Very low	Very high	Low	Medium	N.sp.
Scale-up costs	High	High	High	Low	Medium (h,m)	High	Low
Technical Factors							
Gene size	Unknown	Unknown	Limited	Not limited	Limited	N.sp.	Limited
Protein yield	Medium	High	Medium-High	High	High	N.sp.	Very high
Propagation	Easy	Easy	Limited	Easy	Medium	Easy	N.sp.
Millimetres protein assembly	No	No	No	Yes	Yes	N.sp.	No
Protein folding accuracy	Low	Medium	High	High?	High	N.sp.	High?
Glycosylation	None	Incorrect	Correct	Minor differences	Correct	Minor differences	Minor differences
Product quality	Low	Medium	High	High	High	High	N.sp.
Protein homogeneity	Low	Medium	Medium	High?	High	N.sp.	Medium
Distribution	Feasible	Feasible	Difficult	Easy	Difficult	N.sp.	Easy
Data monitoring	Easy	Easy	Easy	Difficult	Difficult	Easy	N.sp.
GMP conformity	Possible	Possible	Possible	Difficult	Possible	Possible	N.sp.
Storage temp	-20°C	-20°C	Liquid nitrogen	Room temperature[b]	Liquid nitrogen	-20°C	N.sp.

Source: Adapted from Goldstein & Thomas (2004), Ma et al., (2003), Schillberg et al (2003). Colours are used to quickly identify areas of advantages or disadvantages. Uncertainty is thereby considered as disadvantage. a) Estimates differ among authors between short and long. N.sp.: Not specified; ?: Question mark added by the original authors; b) If proteins accumulates in kernel.

Table 9: Comparison of production costs of different platforms for biopharmaceuticals.

Production platform	Estimated costs [€ per g][a]	
	Upstream	Including downstream
Yeast	77	n.sp.
Mammalian cell culture	40-1,538	550-5,100
Transgenic plants	8-160	24-1,300
Transgenic animals	1-77	45-548

N.sp.: not specified. Source: Various authors cf de Kathen & Pickart (2004).

microbial fermentation systems and at 0.1% of the cost of mammalian cell cultures, although this depends on the product yield (Giddings 2001; similar Sala et al. 2003). Dove (2002) envisaged even lower production costs of 0.05 US$/g corresponding to 0.03% of the costs for mammalian cell lines. Some of the most optimistic estimates have been uncritically reiterated in many documents on PM farming, although they focussed on upstream production of biomass only and underestimated or ignored costs arising from downstream purification and formulation of the biopharmaceutical which amounts 50 to 80% of the total production costs. Perhaps more realistic but still hypothetical estimates are provided in Table 9. In case of maize, for instance, costs are assumed to be about 43 US$/g including downstream purification (Evangelista et al. 1998; Mison & Curling 2000).

Capital costs

Capital requirements for establishing a mammalian cell culture production unit are estimated to range from 77 to 500 million € (Arcand & Arnison 2004; Dove 2002; Thiel 2004). Innovation can drastically reduce capital requirements. Assuming an initial yield of 0.1 g/l, an annual production of 250 kg per year and a 10,000 l scale, an improvement to 1 g/l would lower capital requirements from 1.6 billion US$ to 100 million US$ (Werner 2004).

Industry estimates the capital costs for a unit capable of producing 100 kg protein to be about 25 to 40 million € (Fineman c.f. de Kathen & Pickardt 2004), which would be slightly lower compared to the numbers for mammalian cell lines reported above. Other industry representatives envisage a reduction in capital costs of 75 to 80% (DePalma 2004).

Case study on vaccines

The perhaps most comprehensive calculation published compares plant-based vaccines with yeast-derived vaccines (ProVacs 2006). Assuming facilities for producing 75 million doses per year of Hepatitis B vaccine (HBV) savings are envisaged to be in the range of 62% to 90% depending on the location of the facility (India, Korea, USA) and the dose packet (single dose or 10-dose packet). Cost of Goods (CoG) are in the range between 2.98 and 7.07 million US$ per year. This would result in total costs per finished dose of US$ 0.13 which would allow for a final price of US$ 0.15. Although the PMV is designed as an oral vaccine, implying much higher doses (2 mg/dose) and a total annual demand of 1,500 kg/year for 75 million doses, the costs and prices would hence be much lower compared to US$ 0.27 UNICEF is currently paying per dose of HBV from yeast production (UNICEF 2004).

Given the important role of cost savings from PM farming in the scientific literature, in discussions and shareholder communication over a long period it is perhaps pertinent to make few qualifications.

First, most estimates for plant-based production are not based on real process data and are therefore still hypothetical. This is also true for the case study on HBV mentioned above.

Second, most estimates come from the molecular farming industry, some of which appear to be optimistic to satisfy shareholders and investors. The assumptions on which these numbers are based are in almost all cases not transparent to outsiders.

Third, downstream purification costs are envisaged to be in the same range as for presently used microbial and mammalian systems. In contrast, however, it is increasingly evident that protein purification from plants, especially from green plant parts, poses challenges absent in microbial fermentation and cell culture (see 6.1).

Notwithstanding the level of purity needed, the plant production platform, the particular plant tissue to which the protein is targeted (e.g. seeds or leaves), and the properties of the target protein will greatly impact the actual cost savings. It is generally believed that production in maize kernel will be cheaper compared to open field production systems based on green biomass (company interviews) and that products of lower degree of purity (e.g. oral vaccines, antibodies, products for non-pharmaceutical applications) would offer more savings compared to high purity and sterile biopharmaceuticals for intravenous administration.

Forth, higher total compliance costs are usually not considered. This is especially relevant in case of open field production using food/feed crops, e.g. extra costs for authorisation and monitoring of the GM crop plus possibly higher costs for market authorisation of the PMP. Regulatory requirements from biotechnology regulators to protect human and animal health and the environment have already emerged from the US debate (see Section 6.4.2). While, so far, no costs estimates have been published for the proposed regulatory requirements and measures, recently published figures on first generation herbicide tolerant and insect resistant GM crops indicating a range of 6 to 15.4 million US$ might be instructive (Kalaitzandonakes et al. 2007).[11] For PMPs market authorisation extra costs may arise from uncertainty in what particular way regulatory requirements widely accepted for biopharmaceuticals from microbial fermentation or mammalian cell lines would be applicable to PMPs and at what costs, e.g. GMP production for agricultural production systems. The latter type of compliance costs may, however, reach normal levels after the regulatory pathway has become entirely clear.

Fifth, existing production systems are being improved at a considerable pace and productivity is further increasing: standards for commercial processes moving from 1 g/l to 2 g/1 to 4 g/l and up to 5 g/l have been reported for mammalian cell lines (Scott 2007; Langer 2007; interview biopharmaceutical supplier). "Theoretical" limits of 20 g/l are already discussed (Gottschalk 2007) while work on human cell lines yielding 10 g/l is already underway (company interview). Second generation molecules with a higher affinity for the target, higher efficiency and longer half-life in the blood are contributing to lower production volumes at the same time (Werner 2004).

With its initial emphasis on the cost savings PM farming proponents were also assuming that this would be the key issue. According to interviewees from the pharmaceutical industry the cost savings that might be realistically achieved with PM farming does not seem to play a major role – at least for products which are presently on the market in industrialised countries.

Furthermore, most costs savings are estimates for open field production. Savings might be considerably lower for contained production systems: especially bioreactor

11 These costs include items which will not be relevant for pharm crops such as fees for other national authorities, it can be assumed that at least in the case of food crops the same level of scrutiny might be applied under the assumption that confinement measures fail. More likely, additional costs will have to be faced for confinement measures and more extensive stewardship.

systems such as Lemna, moss, and algae require a complex infrastructure and much more control and monitoring measures. With these systems, however, other expenses might be lower compared to open field cultivation, e.g. analysis for contaminants and compliance costs.

These arguments have partly been raised in recent discussion – it is thus perhaps not surprising that emphasis in most recent literature and communication is no longer on cost savings.

On the other hand, these systems might be favourable because they are contained and the production environment can be much better controlled compared to open field or greenhouse production. Advantages in downstream processing including quality control and in total compliance costs might also materialise as cost reduction. For instance, the moss system would allow for 50% savings of total production costs despite the low yield because of the massive savings in downstream processing, quality control, and glycosylation (according to company information).

Nevertheless, the cost argument might play a key role in medium and long term view. Especially if envisaging biopharmaceuticals which require high doses and therefore large production volumes (see also Section 5.4)

5.3 Flexibility and speed to scale-up production

Pharmaceutical companies have to anticipate market demand for a prospective biopharmaceutical at a very early stage – i.e. while the product is still in clinical trials – mainly because of the time needed and the huge capital costs to set up a production plant for mammalian cell culture or fermentation. Any errors could lead to expensive overcapacities or shortages.

While this is a generally acknowledged business risk, manufacturers are meanwhile more accurately predicting demands. Contract manufacturing and sharing of manufacturing capacities have further alleviated this problem. Moreover, the only case documented so far of a shortage of manufacturing capacities (Enbrel, see also Section 5.5) has proven to be an exemption rather than the top of an iceberg.

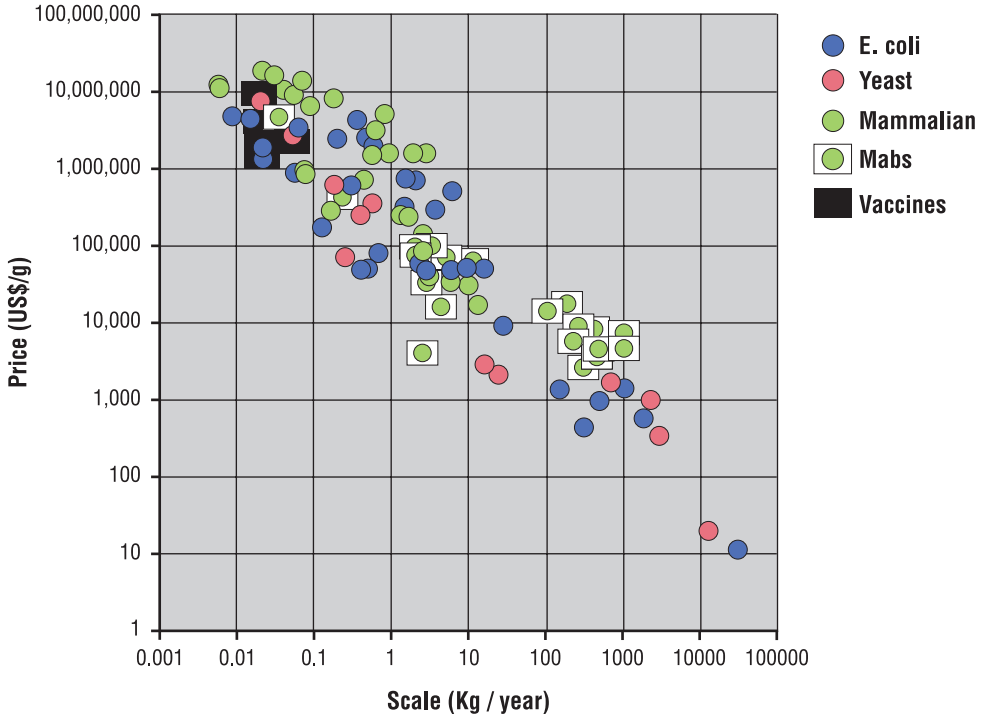
Despite these improvements the scale-up of PM farming in case of open field production or in greenhouses is anticipated to be much more flexible and much cheaper compared to mammalian cell culture. Flexibility is increased because business decisions can be delayed until further data from clinical trials are available providing a better basis for anticipating production capacity needed. Costs are expected to be lower because of lower capital requirements and because of better avoiding errors in anticipating production capacity.

This might also be true in case of greenhouse production. Increasing levels of containment in PM farming are, however, likely to gradually reduce these advantages, for instances in case of PM farming underground, e.g. in mines, and even more so in case of Lemna in bioreactor-type facilities. Especially, plant-cell culture is likely to be little or no different in terms of scale-up flexibility and costs to mammalian cell culture.

5.4 Products that would be applied in high-doses

The vast majority of presently used biopharmaceuticals are produced in volumes bellow 1,000 kg per year. Only a very few substances are produced at larger volumes with Human Serum Albumin and Bovine Growth Hormone to be outliers with production amounts beyond 10,000 kg (Steiner 2005, see Figure 7).

Figure 7: Price and Sales of 89 therapeutic proteins presently marketed.



Source: Steiner (2005).

PM farming would also provide sufficient capacity to manufacture high-volume biopharmaceuticals, well beyond 10,000 kg/year. This is considered by industry as especially important for novel high-dose antibodies that would be required in annual tonnages up to 50,000 kg and more. For this kind of antibodies a shortage of production capacities has been anticipated by some authors if relying on production in bioreactors only (Ko & Koprowski 2005; see also Section 5.5).

Developments towards alternative routes of administration of biopharmaceuticals and vaccines might spark a demand for even higher production amounts and lower costs. Besides systemic application there are numerous attempts to explore topical, oral, nasal, mucosal or inhalative administration. In these cases proteins are often subjected to proteolytic degradation (especially if the proteins need to pass the gastro-intestinal tract) and absorption rates might also be very low. Therefore, these products need to be applied in much higher doses compared to systemic administration.

Examples mentioned by interviewees are needle-free administration of insulin (e.g. via inhalation) and generally topical and mucosal application of antibodies.

For insulin a 5–12 fold increase demand is expected from new routes of administration. These developments and additional demand from newly industrialised and developing countries is expected to push up demand from today 6 tons/year to 16 tons/year in 2012 (SemBioSys 2007).

The US company Planet Biotechnology specialised in the development of IgA antibodies specifically adapted to interact with pathogens and toxins before they disseminate throughout the body. Products under development are intended for topical preventive administration (CaroRx™; tooth decay), nasal (RhinoRx™, impeding rhinovirus infection) and topical or oral

(DoxoRx™, neutralization of chemotherapeutic drug toxicity).

The Pharma-Planta consortium is developing an antibody against HIV which would be applied topically in a vaginal cream. According to estimates for such a similar antibody and the same applications and assuming 10 mg per dose, 52 doses per year, and 1 billion patients, about 520 tons of the antibody would be required per year (Slater 2006).

5.5 Shortage in biomanufacturing capacities?

The PM farming literature frequently refers to a shortage in manufacturing capacity when justifying demand for PM farming as an alternative production system (e.g. Arcand & Arnison 2004; Elbheri 2005; Peterson & Arntzen 2004).

In fact, a world-wide capacity crisis for manufacturing biopharmaceuticals was diagnosed by many analysts following the Enbrel case (e.g. Dove 2002).Within six months after the launch of the soluble tumour necrosis factor Enbrel in 1998 the demand for the drug outstripped its supply (Kamarck 2006) forcing the company to make large capital investments in the construction of new production facilities and to seek for partnerships with other companies that might provide additional manufacturing capacity. The subsequent acquisition by Amgen of Immunex was perceived by some as monopolizing world capacity for biopharmaceuticals. A 2001 report form industry analysts estimated that by 2005 demand would exceed worldwide manufacturing capacity by a factor of four (Molawa 2001, c.f. Thiel 2004). The planning ahead and availability of sufficient manufacturing capacity is a key issue as a commercial facility costs between 77 to 500 million € and takes 4–5 year to be built, validated and licensed (Arcand & Arnison 2004; Dove 2002; Thiel 2004).

The Enbrel case was readily taken by PM farming proponents: "if Enbrel were produced in corn [Immunex] could have just planted more acres, which would have been much less expensive than building new, larger facilities" (BIO 2004, c.f. Thiel 2004).

More recent analyses, in contrast, do no longer anticipate such a bottleneck. The Enbrel case sparked contract manufacturers to drastically increase their capacity, with an expected doubling by 2010. In 2004 there were already considerations of excess manufacturing capacity (Thiel 2004; In-pharma Technologist.com 2004). In 2006 capacity utilisation declined to 64% compared to 76% in 2003 for mammalian cell culture and 62% compared to 71% for microbial fermentation (Langer 2007). Nevertheless, possible capacity constraints are anticipated by some to materialise by 2012 (51% of responding biopharmaceutical and contract manufacturing facilities[12]) might continue to trigger further extensions of manufacturing capacity.

According to interviewees from the biopharmaceutical industry even high-dose antibodies are unlikely to lead to another manufacturing bottleneck in the near future. Although market demand is always difficult to predict there seem to be no products in the pipeline that would have to be produced at tonnages clearly exceeding the present maximum of 3 to 10 tons/year. Furthermore, company strategies in antibody production tend to lower capacity demands for a given antibody. In order to minimise market risks companies tend to come up with new antibodies if there is a clear indication and if other antibodies have already been proven successful. Consequently, there is a fierce competition between a range of antibodies for a given indication and a single product or company only gets a share of the market. Hence,

12 Problems are not only related to fermentation equipment capacities but also to hiring production staff (Langer 2007).

tonnages for a particular product tend to be lower. At the same time antibodies are becoming more and more efficient thereby reducing the amount that needs to be applied. Production efficiency is also increasing and is expected to double within the next couple of years (see also 5.2).

From the present point of view, bottlenecks in manufacturing capacities do not seem to be a powerful driver of PM farming any longer. In the long run it could nevertheless revive as an issue if very broad indications are envisaged or in case of novel administration routes for biopharmaceuticals and vaccines, e.g. oral or topical which would need much larger amounts of protein (interview non PM farming pharmaceutical company; see also preceding Section 5.4).

5.6 Product safety

In the manufacturing process of biopharmaceuticals human or animal pathogens and toxins can contaminate the product via the production organism, source material or media ingredients. For mammalian cell line viruses, prions, and Mycoplasma are of most concern. For microbial fermentation contaminating pathogenic bacteria and fungi as well as endotoxins are considered a thread. For animal pharming viruses and prions are perceived as a risk.

Plant viruses, in contrast, are not known to infect humans (Commandeur et al. 2003). In case of open field production animal or human pathogens can contaminate biomass via excrements from birds and mammals, carcasses, organic fertilizer or farm worker-shed material (EMEA 2006). The range of contaminating viruses which are distributed by rodent excreta includes for instance Hantaviruses, Minute Virus of Mice (MVM), avian influenza virus and Hepatitis A virus (HAV) all of which are relevant to man. Nevertheless, EMEA contents that in the "event of contamination of the starting material or the manufacturing process with a mammalian virus of concern, it should be borne in mind that the virus would not be amplified, as it might be for example in a bioreactor containing mammalian cells" (EMEA 2006: 11).

Whether this additional safety argument actually translates into a competitive advantage might eventually depend on the safety measures and the monitoring required by the regulators. As EMEA stated, the likelihood of viral contamination will be a function of the extent and nature of the operations involved, including the environments in which they are performed, the containment measures applied, the quality and good practice systems in place, and the personnel involved (ibid.). EMEA is therefore asking for a risk analysis of the contamination potential and for an "integrated step-wise strategy that reliably ensures the virus safety of each batch of medicinal product and batch-by-batch analysis" (ibid: 11).

In this regards, more contained systems might be advantageous and could therefore save costs on quality control. Greenhouse systems might be designed in a way to further minimize animal and human virus contamination. In fully contained systems, such as moss and Lemna this kind of virus contamination can be excluded.

5.7 Speeding up R&D?

Speed in the development process has hardly been referred to as a driving force for PM farming in the first place. In fact, the development of stably transformed GM plants has always suffered from very long developing times because of the inherently long life cycles and complex genetics associated with identifying and stabilising transgenic lines. For many commonly used crops, such as maize, the process can take years (Hiatt & Pauly 2006) and interviewees from biopharmaceutical companies frequently consider this to be a drawback of PM farming.

Table 10: Comparison of different production platforms in terms of speed to first grams[a]

Expression system	Time to milligrams of Mab	Time to grams of Mab
Mammalian cell culture*	2–6 months	6–12 months
Transgenic animals	> 12 months	> 12 months
Stable transgenic plants	12 months	> 24 months
Magnifection (viral transient expression)[b]	14 days	14–20 days

a) Values are cited from Hiatt and Pauly (2006) and are based on direct quotes from contract manufacturers; b) magnification is special form of transient expression; Mab: monoclonal antibody.

Recently developed viral plant production platforms might have the potential to change this and enable to set up small scale production sufficient for pre-clinical trials' quantities within weeks (Arntzen 2007; see also Table 10). The transient expression system indicated in the Table has been used to successfully produce a variety of proteins including antibodies and vaccines within two weeks. Moreover, viral transient expression has been demonstrated to yield very high amounts of protein (Gleba et al. 2004; Marillonnet et al. 2005).

Whether this advantage in speed will actually translate into an economic advantage in drug development will depend on several aspects. Transient expression is presently considered by regulators to be less stable and reliable compared to stable transgenic plants and might therefore face difficulties in the process of regulatory approval. EMEA even did not consider transient expression in its most recent guidance document on PM farming (EMEA 2006). If regulatory problems persist, this might confront developers with the need to switch to stably transformed plants in subsequent stages of drug development (see also Section 6.2). Switching production systems might, however, raise additional regulatory hurdles for developers – the extent of which would most likely depend on when the switching takes place during clinical trials.

Unless a regulatory route to market commercialisation for PM farming in general and for transient expression systems in particular is clarified and as long as the presently used expression systems are properly working for a particular protein, it appears to be unlikely that pharmaceutical companies would be willing to use these systems (company interviews).

On the other hand more and more researchers are using transient expression in early stages of drug development as their standard system because of its simplicity and speed. Some experts are therefore expecting this technology to impact the early phase of drug discovery and pre-clinical development, which would then "set the stage" for and diffuse into PM farming (Arntzen 2007).

A stronger demand might come from applications where speed would be key, such as vaccines for rapidly mutating viruses, pandemic diseases and bio-terrorist attacks, where such PM farming systems might be attractive (e.g. Santi et al. 2006; Arntzen 2007). Influenza vaccines, for example, are normally produced in specially bred hen's eggs. Manufacturers have to order eggs up to 12 months in advance. Given that one to two eggs are needed per dose a reasonable reserve for pandemic vaccine production would comprise several million of eggs and be very expensive (Sheridan 2007).

5.8 Difficult-to-express proteins

PM farming is also considered an interesting alternative for proteins that are difficult or impossible to be produced in presently established production systems. For example, Cobento's

Human Intrinsic Factor, a Vitamin B12 binding protein presently produced from Arabidopsis is considered a too complex protein to be produced in microbial systems. And, because it would interfere with their metabolism, mammalian cells are no alternative, either. Plants do not need or synthesise Vitamin B12, hence they are the only feasible production platform.

Another example are the avian influenza strains that are most likely to give rise to a human pandemic strain: these viruses are toxic to eggs used for cultivating epidemic influenza strains (Sheridan 2007).

5.9 Improvements of health care for developing countries

In the preceding Sections potential advantages and drivers of PM farming were discussed with a focus on the production of and markets for biopharmaceuticals in industrialised countries, suggesting that there is no urgent but only a rather long-term demand for it. If developing or low income countries are considered the situation might however be different: despite conducting some large vaccination programmes already the costs of vaccines and their distribution in developing countries remain a major hurdle for their extension. Yet, AIDS, tuberculosis, malaria and diarrhoeal disease still account for 30 to 50% of all deaths in low-income countries (Ratzan et al. 2000).

Throughout the 1990s some researchers proposed widespread and local production of PMVs, conjuring images of edible vaccines through fresh produced obtained from selected farmers or even from their own garden (Prakash 1996). Later on researcher became more cautious about the prospects of simply using unprocessed fruits or vegetable for immunization programmes. Potential benefits to developing countries are however still maintained: developers point to possible improvements in the availability and applicability of vaccines and biopharmaceuticals, e.g. local acreage, with anticipated cost reduction, oral application, storage conditions in case of PMPs in kernels (Daar et al. 2002; Acharya et al. 2003; Vermij 2004; Ma et al. 2005).

PMPs and PMVs for use in the developing world seem to be targeted by public research organisations rather than companies. For instance, Pharma-Planta (36 of 39 partners are university laboratories), a research consortium in the context of the EU's 6th Framework Programme (www.pharma-planta.org) is developing an HIV antibody in a joint collaboration with scientists from South Africa. Mexican researchers are developing rotavirus antigens as edible vaccine in banana (Morales 2007). The Pharma-Planta consortium even issued a statement to underline its humanitarian aspects (Pharma-Planta 2005).

In fact, the potential benefits for countries of the global South could be huge if the technology delivers on it's promises in case of infectious diseases with a large prevalence in the global South. Castle and Dalgleish (2005) claimed that the time has already come to facilitate the putative global health benefits of PMVs, others are less optimistic though. No PMVs have yet progressed into Phase 2 clinical trials and there is still uncertainty about commercial feasibility and scientific and technical hurdles in terms of the efficacy of oral PMVs. Robert et al. (2006) therefore concluded that "any proposal for broad acceptance of this technology is grossly premature without significant improvements in technical and economic feasibility" (p 33). Furthermore, open field production of PMPs in such countries raises important questions. For instance, it is unlikely that the same level of regulatory oversight and enforcement which can be expected in industrialised countries can be maintained in these countries. In case of any significant open field production, the occurrence – and even the hypothetical possibility only – of admixture could be detrimental to food exports, which, in turn, could jeopardize the economy of many countries.

Nevertheless, humanitarian aspects may continue to inspire and guide public sector research relating to PM farming. Public funding will continue to play a key role. If manufacturing of biopharmaceuticals and vaccines is primarily determined by market forces, developers will rather target diseases that also have a high prevalence in industrialised countries, such as Hepatitis B and HIV.

While the Third Global Vaccine Research Forum mentions PMVs as a potentially important issue (WHO 2002), there was little further activity by the WHO beyond a consultation of the scientific basis for regulatory evaluation of PMVs (WHO 2006). Definitely missing, though, is a serious analysis of the potential impacts of PMVs for and in such countries.

5.10 Some remarks about absent drivers

From the discussion in this Chapter and from Chapter 4, two interesting observations can be made in terms of apparently absent drivers.

First, there is very little engagement of the pharmaceutical industry. Second, it is difficult to identify a market demand driving this technology development.

The first aspect has meanwhile also been identified and acknowledged as a challenge by PM farming promoters and is being discussed in more detail in Section 6.5).

The apparent absence of market demand – at least in short and medium term view – was also confirmed by interviewees from the pharmaceutical industry.

PM farming entrepreneurs are developing alternative production platforms to presently used systems, which might allow for lower production costs and higher tonnage. However, the literature and company interviews conducted suggest that both aspects are of limited relevance for products presently on the market or close to commercialisation stage: producers have invested in extending fermentation capacity to avoid further capacity crunches and are still able to sell their biopharmaceuticals at high prices. Producing biopharmaceuticals and vaccines at lower costs to be affordable for developing countries is definitely something that everybody would agree with for humanitarian reasons. Still, as economic prospects for commercial applications are limited, this is not being translated into market demand.

Developers in the field of PM farming are rather anticipating possible changes that might come from several parallel developments: the possibility to produce high volume at lower costs might render the commercial exploitation of certain biopharmaceuticals, which are needed in high amounts to become viable products, more realistic. Demand for higher volumes of presently used biopharmaceuticals could also come from novel routes of administration (topical, oral, mucosal, etc.). Moreover, the pressure on pharmaceutical prices may be rising. In industrialised countries national health care systems face more and more difficulties to handle the ever increasing costs of pharmaceuticals and, therefore, might exert more pressure on manufacturers. For drugs that are no longer protected by IPR the newly established marketing routes for biosimilars might spark competition between companies which is expected to lower prices, thus again increasing pressure on the price of pharmaceuticals.

An entirely different picture emerges from lower income countries. Many biopharmaceuticals available in industrialised countries might not be affordable for their domestic health care systems. In order not to loose market shares to emerging pharmaceutical industries, e.g. in Asia, global producers might see a need to lower costs.

5.11 Non-pharmaceutical applications

For PMIs considered in this report the driving forces differ from the pharmaceutical business. Until recently, non-pharmaceutical applications (research chemicals, diagnostics) were largely considered by PM farming developers as an opportunity to put their technology to work in a commercial product much earlier than would be possible for PMVs, and to generate cash flow in a much shorter time period. Recently it has become more attractive to target the food supplement and feed additive market to achieve these objectives.

For food supplements and even more so for food or feed additives and enzymes production costs comprise a relatively bigger chunk in the overall costs compared to biopharmaceuticals, because purity requirements are lower, R&D is less costly and time consuming and compliance costs are much lower.

For products selling at lower prices the costs for production in mammalian cell lines have been prohibitively high before and microbial fermentation and extraction from plant and animal tissue was the usual way of production. This might be even true for food supplements claiming to have additional health benefits which might represent the highest value products in this segment. For such products lower costs, very large scales and flexible scale-up would therefore be the most important advantage. The use of food or feed crops would allow for additional cost savings on purification as it might be possible to market certain products with little downstream processing as crude preparations. Consequently, open field cultivation and crops that would allow for high yield and simple agricultural practice would be key – and is in fact envisaged in all cases investigated in this report: the food supplement omega 3 and omega 6 fatty acids (BASF, Germany) to be produced in Brassica sp., the food additive thaumatin developed in barley (Maltagene, Germany, http://www.maltagen.de/PDF/Products.pdf), a carp somatotropin from safflower (SemBioSys, Canada) and an antibody (Novoplant, Germany) – the latter two are intended to be used as feed additives. Cobento is presently producing its human intrinsic factor intended to be used as a food supplement from Arabidopsis in greenhouses but is eventually aiming to move into potatoes in the open field. Whether in certain cases the higher prices for food supplements would allow for greenhouse production is still unclear, though.

Earlier PM farming literature claims that bulk products such as enzymes for food, feed and technical purposes that are presently produced in large-scale fermentation from microbes, would also represent interesting targets (Hood et al. 1999; Hood and Jilka 1999). Enzyme producers, however, does not seem to be active in PM farming. According to one interviewee there is little interest to produce an enzyme that needs to be extracted and purified as long as it can (more easily) be produced from microbes. A much more interesting option seem to be to produce enzymes in crops for applications where no extraction would be required, for instance amylase in maize for the production of biofuel. Otherwise, these enzymes would have to be produced in huge amounts from microbes and then applied in the process. Given the huge amounts needed they represent a considerable cost factor in bioconversion.[13] Another theoretical option are enzymes which would be difficult to produce in microorganisms. (company interview).

5.12 Summary

In principle most anticipated advantages of PM farming boil down to direct or indirect cost savings and to large-scale (and even unlimited) production of PMPs and PMIs.

13 This is neither considered to be PM farming as understood by the authors of this report nor is it in the scope of the PM farming applications investigated.

For PMPs savings in production costs including downstream processing are predicted to be in the range of 75 to 80% compared to costs of mammalian cell lines. Most of these estimates, however, are still hypothetical as they are not based on commercial process data. They might still be overly optimistic as they come from PM farming developers, who are frequently lacking experience in the pharmaceutical business. Downstream purifications costs and compliance costs – and in case of open field production – also compliance to agricultural biotechnology regulations costs are either not or not properly considered. Furthermore, productivity of mammalian cell lines is rapidly increasing. On the other hand, open field cultivation would also allow to delay business decisions about scale-up of production to later stages of clinical trials which would lower the risk for costly errors of under- or overestimating the needed production capacity. Real process costs of PM farming and the amount of savings compared to mammalian cell culture is therefore likely to be case-specific and depending on the time such a process will be introduced. Savings are likely to be lower in case of contained production such as moss or Lemna. For a model vaccines produced in tobacco in greenhouses calculations result in lower prices for subunit vaccines compared to yeast production.

If large-scale production at lower costs actually materialises PM farming can be important to allow the production of antibodies that are only effective in higher doses and of biopharmaceuticals and vaccines that are administered via the topical, nasal, mucosal, or oral route in which cases higher doses have to compensate a lower rate of uptake. PM farming could also provide an alternative solution for proteins difficult to express in presently used systems.

Recently developed methods in PM farming for transient production could speed up drug development. However, transient production is presently not accepted by EMEA for commercial production.

Notwithstanding these anticipated advantages, PM farming appears to be largely pushed by academics and technology providers. So far there seems to be little demand from pharmaceutical companies and health care systems. This might however change over time, depending on technological progress in other areas (e.g. when novel types of biopharmaceuticals and alternative routes of administration become established) and on the increasing pressure on drug prices and, hence, costs.

For PMIs used as food supplements and feed additives there will be even more pressure on costs. This would drive production towards open field cultivation and the use of major food or feed crops. Greenhouse production for this type of PMIs might perhaps be economically feasible only in case of certain high-price food supplements.

Whether PM farming will represent an interesting option for low-income or developing countries also remains to be seen. There is definitely a demand for affordable and easily available drugs and vaccines, and the idea of PMPs and PMVs is therefore likely to continue to attract investments from the public sector and private humanitarian funds. Vaccines against diseases which have also a high prevalence in industrialised countries such as Hepatitis B and HIV, will be of greater interest for commercial companies.

6 Challenges for PM farming

This Chapter discusses challenges from two angles. One angle is about the challenges that need to be tackled in order to improve and eventually establish PM farming as an alternative production technology. The other angle attempts to identify the challenges which are likely to arise from further development and commercialisation of the technology. Both angles are interrelated and include technical, economic, socioeconomic, regulatory and wider policy aspects.

The first part (Sections 6.1 and 6.2) is dedicated to techno-economic aspects and the competitive environment. The second part focuses on regulatory aspects. Sections 6.3 discusses market authorisation of PMPs and PMVs. Section 6.4 aims at identifying the challenges for the EU regulatory regime for agricultural biotechnology. The third Part (Section 6.5) speculates about challenges from managing large scale PM farming while Part four (Section 6.6) discusses the interrelated problem of securing funding for R&D and the apparently slow adoption of the technology by large pharmaceutical companies. Stakeholder and public perception of PM farming might be of particular importance for EU policy development in these areas and are therefore discussed in a separate Chapter (1).

6.1 Techno-economic challenges

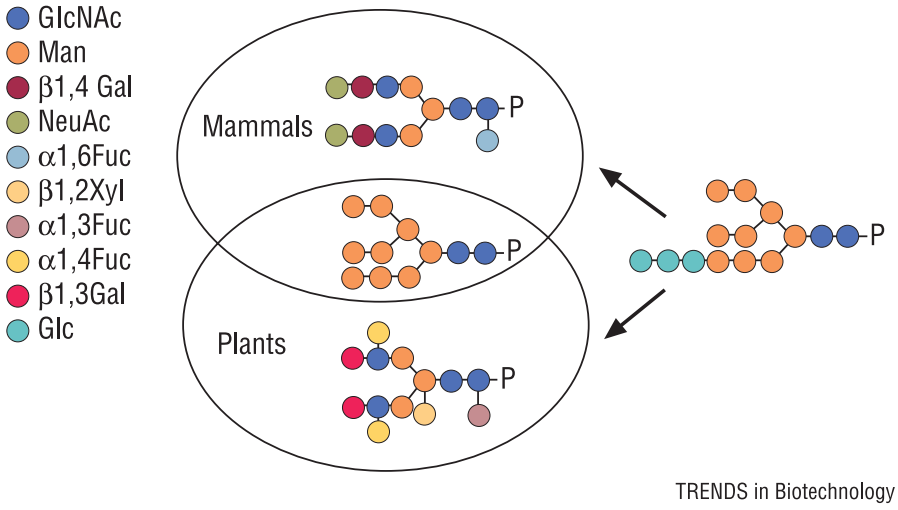
6.1.1 Expression of the protein

The technology of PM farming has tremendously improved over the last decade. While with transient production in tobacco leaves (Icon Genetics, Germany) yields have been achieved of five grams of the target protein per kilogram of plant biomass and reportedly also with rice kernel (Ventria, c.f. Arcand 2007) there is still a broadly acknowledged need to further improve yield to strengthen competitiveness vis-à-vis improved mammalian cell lines and microbial fermentations (Arcand 2007).

6.1.2 Downstream processing

Perhaps most important, however, is to improve the downstream processing and purification which had been a neglected area for a long time although it could constitute up to 80% of total production costs (e.g. Gottschalk 2007). While efforts to reduce these costs have been increasing over the last five years (Nikolov & Woodard 2004), there is still a number of hurdles to be tackled. Some substances are creating problems in downstream processing, including lignin, fibres, swelling substances in general, waxes, phenolic compounds, pigments, and endogenous proteases. Yet, all of them needed to be addressed for setting up commercial production. The sheer amount of biomass is thereby posing sizeable technical and economic problems. For instance, fibre rich tissue can clog up chromatography columns, or pigments can make it more difficult to clean them (Drossard 2004; company interview; Nikolov pers. comm.). Another example is protein A affinity chromatography which is a key step in antibody purification. Protein A columns for purifying antibodies from a 10,000 l fermenter could cost about 4 million € (Rathore et al. 2004). Hence, there is a strong incentive to reuse these columns as often as possible. Valdes et al. (2003), describe the difficulties experienced in removing plant pigments and phenolics from a monoclonal antibody pool after protein A expanded-bed adsorption. Attempts to remove the yellow colour from a purified antibody pool by ion exchange, gel filtration, ultrafiltration, and precipitation were unsuccessful. Protein A resin in expanded-bed mode performed poorly when used without the removal of residual suspended particles from centrifuged tobacco extract.

Figure 8: Plant and mammalian complex N-glycans differ in their structure



Source: Gomord et al. (2005).In plant and mammalian cells, two main classes of N-glycans are added to proteins. A first class of high-mannose-type N-glycans have the same structure in plant and mammalian glycoproteins and contain two N-acetylglucosamine and 5–9 mannosyl residues. The second class of N-glycans, the complex type N-glycans, is more specific for the organism producing the glycoprotein. As a result, complex type N-glycans are structurally different in plants and mammals. Abbreviation: P, protein.

Other challenges include the scale-up of filtration steps (huge volumes), proteolytic degradation of the target protein during downstream processing, the designing of an appropriate virus clearance strategy, or the handling of variable expression levels (Gottschalk 2007).

6.1.3 Glycosylation

More than half of the human proteins and more than a third of approved biopharmaceuticals are glycosylated. Glycosylation could affect their function, including plasma half-life, tissue targeting and/or biological activity. Glycoproteins are therefore produced in mammalian cell lines. Unlike bacteria or yeast, plants also glycosylate proteins but the carbohydrate pattern differs from human and/or mammalian glycosylation (see Figure 8). Plant specific glycosylation is immunogenic in animal experiments and elicits glycan-specific antibodies in humans (Aalberse et al. 1981a; 1981b, 2001; Bardor et al. 2003; Jin et al. 2006). Immunogenic glycans could lead to a faster and unwanted clearance of PMPs circulating in the blood stream. The relevance of the immunogenic potential is still controversial. All kind of presently authorised antibodies with varying degrees of similarity or even fully human glycosylation, have been seen to be immunogenic in a portion of patients (0.1 to 72%) (Amin & Carter 2004). The presence of antibodies has in many cases little or no biological and clinical consequences. However, the loss of efficacy and the neutralization of endogenous proteins followed by major clinical impacts have also been described (Kessler et al. 2006).

On the other hand, plant-specific glycans could also act as a kind of adjuvant in case of PMVs (Mari 2002). Proper glycosylation, i. e. "humanized" glycans, is therefore an important requirement in terms of safety and efficacy (Gomord et al. 2005; Saint-Jore-Dupas et al. 2007; Werner et al. 2006).

Regulators require tests for immunogenicity in animal models. Evidence for immunogenicity might not exclude clinical application of PMPs but would bring about additional testing requirements

in subsequent steps of the development process and might represent an higher risk of attrition (Gomord et al. 2005).

PMPs have therefore frequently been subjected to in planta or in vitro glycoengineering, including the knock-out elimination of unwanted sugars and/or knock-in to "humanize" PMP glycosylation (reviewed in Gomord et al. 2004; Saint-Jore-Dupas et al. 2007). Glycoengineering is a particularly difficult in tobacco because tobacco-derived glycan structures are highly heterogeneous, which might result in a mixture of different glyco-variants. Yet, humanization of glycoproteins, avoidance of immunogenic properties or loss of efficacy is not only a problem for PMPs but also for biopharmaceuticals derived from mammalian systems (Kessler et al. 2006; Werner et al. 2007).

As some experts see it the plant specific "handicap" could also turn in an advantage: efforts in glycoengineering have generated strategies for generating a large diversity of PMP glycoforms (Saint-Jore-Dupas et al. 2007). Thereby, modified glycan structure can not only be tested for lower immunogenicity but also for improved efficacy.

6.2 Competitive environment

Innovations and improvements in presently established production systems are also challenging PM farming. Yield, for instance, is constantly increasing: currently, mammalian cell lines routinely reach 2 to 4 g/l cell suspension, and up to 5 g/l have been reported (Scott 2007; Langer 2007; interview biopharmaceutical supplier). The maximal potential for mammalian cell is estimated to be some 20 g/l (Gottschalk 2007) and about 30 g/l for Pichia pastoris (Werner et al. 2007). Yeasts, such as Pichia pastoris, have been successfully engineered to allow for the expression of complex proteins including glycosylation (Li et al. 2006; Gasser & Mattanovich 2007; Werner et al. 2007). Recently, a cervical cancer vaccine from insect cell lines (bacaulovirus system) won for the first time regulatory approval and might pave the way for more products. Second generation molecules with a higher affinity for the target, higher efficiency and longer half-life in the blood are contributing to lower production volumes at the same time (Werner 2004).

As another alternative system along with PM farming, transgenic animals are being developed for commercial production of biopharmaceuticals (animal pharming).

Animal pharming

Transgenic animals can produce biopharmaceuticals in their body fluids, providing a production system without the need to kill the animals, for instance in the milk of mammals or in chicken eggs (animal pharming). This technology is presently being pursued as an alternative – and presumably more cost effective – option for the production of biopharmaceuticals compared to mammalian cell lines. It is at a similar stage of development and marketability like PM farming. Very recently, the first the first biopharmaceutical from transgenic animals, a human antithrombin from goats (ATryn), has recently been approved in the EU and a C1 inhibitor from rabbits is already in Phase 3 clinical trials (Schmidt 2006). Commercial attention has so far focussed on rabbits, cows, pigs, sheep, goats, and chickens.

Proponents of animal pharming claim a number of advantages – similar to those put forward for PM farming – compared to presently used methods: cost savings in scale-up of production, correct posttranslational modification (vis-à-vis microbial systems), no requirements of constant monitoring and sampling. A general advantage of animal pharming might be the simpler downstream purification requirements because the target proteins are passed through the milk and are present in high concentrations (Patel et al. (2007).

Table 11: Selected products currently in development for production in animal bioreactors.

Company	Product	Indication	Production platform	Development stage
GTC Biotherapeutics (USA)	Recombinant human antithrombin, ATryn	Hereditary antithrombin deficiency	Goat	Approved in EU; phase 3 in the USA
Pharming (The Netherlands)	C1 inhibitor	Hereditary angiodema	Rabbit	Phase 3
	Human lactoferrin	Infection and inflammation	Rabbit	Preclinical
	Human fibrinogen	Tissue sealant	Rabbit	Preclinical
BioProtein Technologies (France)	Rotavirus virus-like particles	Rotovirus infection vaccine	Rabbit	Preclinical
PharmAthene (USA)	Version of human butyrylcholinesterase (BChE), Protexia	Treatment for chemical nerve agents	Goat	Preclinical

Source: adapted from Schmidt 2006.

Although productivity in animal pharming is high, the process to generate transgenic animals is time consuming and costly. Furthermore, the pharmaceutical proteins and the process leading to to transgenic animals might affect the health and physiology of the animals thereby creating problems of animal welfare (Patel et al. 2007; Twyman et al. 2005). Production in chicken eggs seems to be more competitive in terms of timescales and production costs but is still in earlier stages of development (Lillico et al. 2005; Patel et al. 2007).

Innovations in established production systems are constantly raising the bar for PM farming. Animal Pharming might not be a threat to PM farming – but if regulatory and technical obstacles continue to slow down commercialisation of PM farming, animal pharming might establish itself as a routine production technology in some niches of the biopharmaceutical market.

6.3 Market authorisation

Biopharmaceuticals and vaccines have to undergo an extensive assessment of their efficacy, safety, and quality before market authorisation will eventually be granted. This assessment procedure includes pre-clinical and clinical trials involving studies on animals and human subjects and accounts for a major proportion of total R&D costs.

Regulatory authorities in the EU, USA, Canada, and elsewhere have accumulated considerable experience in dealing with biopharmaceuticals from bacteria, yeast and mammalian cell culture, whereas no PMP or PMV has passed through the regulatory procedure and has been granted market approval.[14] Regulators have repeatedly pointed out that existing guidance and experience are applicable to PMPs (e.g. WHO 2006; FDA & USDA 2002), especially on

- Biopharmaceuticals and vaccines derived by recombinant DNA technology
- Quality control methods for medicinal plant material
- Good agriculture and collection practices for medicinal plants.

The challenge nevertheless is to adapt or supplement the existing guidance documents and regulatory requirements, which were

14 The only exemption to this, a poultry vaccine authorised by the USDA in 2006, is derived from plant-cell culture.

established for contained production using microbes or mammalian cell lines in tightly controlled and sterile production environments, to less predictable, non-sterile conditions of greenhouse and agricultural production using crops. Downstream processing of plant tissue, in contrast, is perceived to be fairly similar and much less difficult compared to presently used approaches.

After developers of PMPs were approaching the clinical trial stage in the USA and Canada regulators started to work on guidance for PMPs. In 2002 the FDA issued a comprehensive Draft Guidance for PMPs for human and veterinary use (FDA, USDA 2002). EMEA published a "Points to Consider"' document on "quality aspects of medicinal products containing active substances produced by stable transgene expression in higher plants" (EMEA 2002), which was further developed as a guideline and is currently available as a second draft (EMEA 2006).[15] Health Canada is presently in the process of developing a position on PM farming and did not issue any guidance documents so far (interview regulators). Furthermore, an informal WHO consultation in 2005 discussed aspects specific to PMVs in 2005 (WHO 2006).

Generally PM farming approaches are the easier to handle for regulators the more similar they are compared to well established production methods and the better controlled the production environments are. Therefore, plant-cell culture is likely to be most similar to mammalian cell lines and also algae, moss, and Lemna sp. all of which are produced in full containment with more controlled conditions might be considered to be more analogous. Production in greenhouses and even more so in the open field is considered to be different and to pose more difficulties (interviews regulators).

In case of crops in open field production, consistency is a particular challenge as the expression of the target protein as well as the nature and amount of by-products and contaminants can differ between geographical regions, seasons, fields, and even between individual plants. Other potential sources of variability are handling and storage of seeds and plant materials as well as agricultural practices and primary processing steps of harvested plant material. While variability of the latter aspects can be limited by Standard Operating Procedures (SOPs), the inherent variability of the former causes difficulties for validating processes and for establishing a production under Good Manufacturing Practices (GMP), which are both standard requirements for producing biopharmaceuticals.

Another challenge is the different profiles of possible contaminants compared to existing production technology. New contaminants have to be considered: plant metabolites (e.g. toxic alkaloids from tobacco, anti-nutrients), aflatoxin, mycotoxins, pesticides, herbicides, fungicides, and fertilizers. Contamination by animal viruses – a frequently quoted safety advantage of PM farming compared to mammalian cell lines – cannot be entirely excluded due to possible contamination by workers, field insects, birds, animal excreta, carcases, organic fertiliser residues, etc. For instance, the human pathogen Hantavirus can be distributed by rodents' excreta. Other possible contaminants could be avian flu virus and Hepatitis A.

Open field production will generally be more susceptible to variations in climate, weather, and soil compared to greenhouse cultivation. In addition, pest invasion and plant diseases as well as the use of pesticides might be easier to avoid in greenhouses. Thus, process validation under GMP (or a similar quality assurance system) might generally be more feasible under greenhouse conditions. These advantages led a recent informal WHO consultation on PMVs

15 The scope of the Guidance includes higher plants only, and does therefore not cover moss, algae, and plant-cell culture.

conclude that "greenhouse cultivation should therefore be recommended for the production of vaccines from plants" (WHO 2006: 12).

Any change in protein glycosylation of the plant-derived protein compared to the original protein (in case of human-derived proteins and vaccines) or more broadly – any change in post-translational processing – is an issue that has to be thoroughly investigated and described (see also Section 6.1.3). However, at least the FDA does not require equivalence in glycosylation as long as efficacy and safety of the protein can be assured in pre-clinical and clinical tests.

Therefore, key challenges for regulators include (interviewed regulators):

- The establishment of an appropriate quality assurance system, ideally GMP, for upstream production to facilitate the establishment of a consistent production.

- The choice of adequate cultivation, harvest, storage, and primary processing procedures including in-process monitoring control measures.

- The establishment of an appropriate banking system (cell bank, seed bank, virus bank).

The FDA seems to take a more flexible view and sees "ways and means to address those adequately" in consultations with industry. For the EMEA, these points are largely unresolved (EMEA 2006, interviewed regulators). In the view of the FDA regulatory uncertainty seems to persist in case of edible vaccines (an issue not being addressed so far by EMEA) where batch uniformity and consistency of dose cannot be ensured, especially if there is little or no processing of the plant tissue before oral administration.

The more flexible view of the FDA is also illustrated by the scope of the 2002 Draft Guidance, which includes all PM farming production systems, whereas the EMEA Guidance only covers higher plants. GMP provisions are interpreted more broadly by the FDA to be applicable to PM farming whereas neither open field cultivation nor greenhouse production would qualify for "real GMP" in the view of EMEA. The FDA also envisages the use of virus-based transient production systems while EMEA exempted them from the scope of their guidance because of a lack of stability (interviewed regulators).

Both EMEA and the FDA are developing their guidance along applications from industry. While the FDA is handling a few cases from different platform (corn, tobacco, Lemna sp., etc.), there is apparently little interest to obtain an EU authorisation. Consequently, the process of developing guidance in the EU is continuing.

The regulatory uncertainty associated with this policymaking-in-progress status is definitely discouraging R&D, further investments, and adoption of PM farming by large pharmaceutical companies (interviews PM farming and pharmaceutical companies). In the absence of a first approved product, PMP developers are confronted with difficulties to predict not only the time frame but also the associated costs.

6.4 Managing GMO risks

6.4.1 Why risks might differ from first generation GM crops

Possible risks of and risk assessment in open field PM farming has been discussed in number of reports issued by governmental authorities and public interest groups[16] and more recently in the scientific literature (Kirk et al. 2005; Peterson & Arntzen 2004; Spök 2007; Wolt et al. 2007). In principle most of the potential risks discussed for first generation GM crops[17] would apply

16 References are provided in Chapter 1.
17 Mostly herbicide tolerant and insect resistant crops.

to PM farming as well, i. e. gene-flow to other agricultural, feral and wild plants, invasiveness, effects on non-target organisms, potential allergenic, and toxic properties of introduced protein for humans, etc. Nevertheless, following Spök (2007) four reasons are suggested here as to why risks associated with PM farming could have additional characteristics:

First, unlike first generation GM crops, PMPs are designed to have a biological effect on man and/or higher animals; hence the hazard characteristics of the introduced protein might be of concern. Human exposure might occur via inadvertent admixture to the food chain and to workers handling the plant material. In case of long term low-level exposure immune tolerance might be of concern in case of PMVs (Kirk et al. 2005; Streatfield 2005c).

Secondly, an entirely different breeding rationale applies. Plants will be optimised, e.g. for maximum yield, special morphology, and growth habit suited to a specific harvesting method that can be used with the PMP application, absence of metabolites that may compromise product integrity or quality during bioprocessing (Davies 2005). Pharm crops are considered production facilities that have to be optimised for maximum yield of the target substance. Human and environmental exposure could therefore be increased compared to first generation GM crops. Depending on the expression system, maximum yields of up to 25 and 31% of total soluble protein (TSP) (Daniell et al. 2005; Fischer et al. 2004) and 80% TSP (Gleba et al. 2004; Marillonnet et al. 2004) have been achieved (the latter of which in greenhouse experiments). This would constitute a 700 to 5,000 fold increase in transgene products compared to first generation GM crops (Spök 2006).[18]

Thirdly, the likelihood of unintended secondary effects might be higher, and the hazard characteristics of GM plants might thus be of concern. Unintended secondary effects are already an issue with single gene insertions of first generation GM crops, but the number and significance of genomic changes in the forthcoming generation of crops increase the likelihood of unintended effects and the associated uncertainties, all of which will need to be addressed in regulation. This is since these plants are likely to include several genetic modifications at the same time. Resistance genes might be introduced to avoid problems with pests, pathogens, and weeds which would otherwise require applying pesticides and herbicides. These substances might cause concerns as drug contaminants. Moreover, genetic modification for easy and unambiguous visual identification of seeds and plants are suggested, which would enable a simple differentiation of plants, seeds or fruits not intended for consumption (Commandeur et al. 2003; Ellstrand 2003). In addition, molecular confinement technologies are being introduced involving several complex changes in the plant genome. Molecular confinement aims at avoiding gene dispersal via pollen or rendering plants infertile (Daniell 2002). Other modifications proposed are knock-outs of plant-specific glycosylation and of plant protease which are decreasing the yield, e.g. in tobacco (Ma 2007).

Whether this translates into higher health and environmental risks will, however, depends on the particular case. With many PMIs there might be no intention of a biological effect in humans or animals. Nevertheless, hazardous properties could also be associated with this category. Avidin, for instance, which is presently produced as a fine chemical, is toxic to many insects and might cause Vitamin H deficiency in higher animals and humans. Aprotinin, to take another plant derived fine chemical, is considered a reproductive hazard. In contrast, enzymes like lipases or trpysin might pose less health risks in

18 The yield of 80% of TSP was achieved using a production system that is not intended for open field cultivation. It nevertheless shows what is technically feasible at present. For open field cultivation, yields of 10 to 35% might be more realistic – but might also be optimised as technology improves.

case of food contamination, because both types of enzymes are ubiquitous in nature (Freese 2002). Moreover, trpysin is considered safe and used in food production in the USA and elsewhere. Health risks might not necessarily be restricted to toxic or allergenic effects, though. For instance, a human hormone could have detrimental effects if contaminating the food chain. A vaccine, e.g. a virus protein, might lead to desensitization. If so, those affected would perhaps not develop a desired immune response when vaccinated (Kirk et al. 2005). Consequently, the hazards very much depend on the particular case.

Exposure, another key issue in risk assessment, will not only depend on the amount of protein produced but also on the area of land used for cultivation. Commercial production of large amounts of PMPs could take place on 10 to 1,000 hectares, which is in the range of larger US field trials with first generation GM crops. Beyond possible contamination accidents, exposure is, therefore, more likely restricted to workers processing or handling the crops. Environmental exposure will also be different due to the higher concentration of proteins per unit area. Environmental exposure and spread could, however, be diminished by molecular, physical and organisational confinement measures while worker's exposure could be reduced by appropriate protective measures. Unintended secondary effects (see further below) might be of less concern in the case of small cultivation areas, especially if confinement measures are effective.

6.4.2 Key problem: managing confinement

Regulatory and industry experts are thus framing the issue as a confinement problem. US and Canadian regulators have been working together with industry on a variety of physical and organisational confinement measures that can be applied to avoid outcrossing, spillage of seeds or biomass, and commingling with food or feed crops (see Table 12). Researchers are working on molecular confinement mechanisms that aim at avoiding gene dispersal via pollen and seed by

Table 12: Physical and procedural confinement measures proposed.

- Distinct visual markers
- Time shift in planting compared to food/feed crops nearby
- Cultivation in remote areas
- Fencing, restrictions to enter
- Extended isolation distances (e.g. 1600/800 m for normal pollinating maize), fallow zones, temporal shifts in planting (e.g. 21 days for maize), other plants as pollen barriers, detasseling (maize), covering of inflorescence
- Dedicated equipment, machinery and processing facilities
- Preliminary on-farm processing
- Post-release monitoring
- SOPs for
  - seeding, transplanting, side-maintenance, harvesting, seed cleaning
  - storage, drying and processing of biomass
  - disposal of biomass e.g. autoclaving, incineration etc.
  - handling and cleaning of machinery, equipment and containers
  - monitoring during growing seasons and post-harvest land use
  - dealing with non-compliance with terms and conditions for confinement
- SOPs for records and reporting of all activities dealing with the cultivation and transport to processing facility, documentation and logs for seeds and biomass
- SOPs for training of staff and workers to adequately handle the plant material
- Emergency response/contingency plans
- Strict control of compliance to measures imposed – either by regulators or by other independent institutions (third-party audits)
- Test for GMO detection in raw agricultural commodity

[a]) *Source: BIO (2005); Burtin (2006); CFIA (2003, 2004a, 2004b, 2004c, 2005); Spök* et al. *(2004) Abbreviations: SOP: Indicates that Standard Operating Procedures are developed/required.*

a variety of mechanisms (Daniell 2002). Most of the molecular confinement mechanisms being proposed (USDA 2003), however, are "leaky", i. e. not working 100%, and still far from being used for commercial production (Ellstrand 2003; Dunwell & Ford 2005). Standard Operating Procedures and other organisational or physical measures can fail due to human error. Physical measures have also obvious restrictions in terms of scale and applicability. Even a higher frequency and more thorough inspections of production sites which were announced by the USDA, might fail (UCS 2006a, b).[19] It has therefore been proposed that a combination of several different confinement measures has to be applied at the same time to establish a redundant system that would provide a sufficient level of safety. Even so, constant assessment and monitoring might be necessary to ensure that any breakdown in the mechanism is picked up and acted upon (Dunwell & Ford 2005).

What is considered by the biotech industry and regulatory experts as sufficient risk mitigation measures might, however, not be sufficient for the food industry or consumer and environmental groups, and perhaps also for the general public. The sensitivity of certain actors have to be seen against the backdrop of earlier contamination incidents, especially the case of StarLink (EPA 2000; Ellstrand 2003; Freese 2002; Spök et al. 2003) and ProdiGene (Cassidy & Powell 2002; Choi 2002a, 2002b; Jones 2003).

StarLink is a GM maize variant harbouring the bacterial protein Cry9C. This protein is specifically toxic to a variety of pests and thereby renders the maize resistant to certain insect pests. In 1998 the US Environmental Protection Agency (EPA) did not exclude the possibility of an allergic potential and granted a tolerance exemption for feed and industrial use only (i. e. not human food). The EPA required a buffer zone of 200 m between the GM and any conventional maize to avoid pollen contamination. StarLink maize and maize derived from the buffer zone were to be processed separately from food maize. Despite such safety measures Cry9C was detected in Taco Chips in September 2000 and subsequently also in maize flour. USDA eventually detected Cry9C in 9% to 22% of all maize samples. Given the huge variety of processed maize products, millions of people are assumed to have consumed contaminated maize products before those products were recalled and removed from supermarket shelves. Despite a considerable number of consumer reports about allegedly allergic symptoms, in none of these cases could actual allergic symptoms be attributed to the GM maize. Nevertheless, call-backs and compensations were reported to amount to billions of US$.

It was later revealed that in this case the contaminations occured via commingling after harvest. Commingling might happen, for instance, if storage facilities, equipment and machinery are used for both GM and conventional maize varieties without properly cleaning them in between. Farmers or wholesalers handling such material might have not been aware of the necessity to keep these types of maize separate. In fact, it turned out that some of the farmers and farm workers had not received appropriate information and training on both sowing and trading restrictions. In addition, there were indications of pollen flow to conventional maize varieties.

While the StarLink case was about a maize variety grown for feed use on large acreages, the ProdiGene incident was about a pharm maize variety grown on small areas. In 2002 USDA's Animal and Plant Inspection Service (APHIS) staff recorded two cases of violations against conditions for deliberate release of GM pharm crops, one in Iowa and one in Nebraska. In both

19 A more comprehensive overview on physical, procedural, and molecular confinement mechanisms proposed with its various advantages and disadvantages is provided in Annex 2: Containment strategies.

cases GM maize volunteers,[20] resulting from field trials of the US PM farming company ProdiGene, were detected in conventional soybean fields.

In the Iowa case, volunteers were detected in a late stage of development. Given the possibility of pollen flow to surrounding maize fields, more than 60 hectares of maize had to be incinerated.

In Nebraska, ProdiGene did not remove the volunteers despite the order to do so was issued by inspectors of the USDA-APHIS. Thus, the volunteer pharm maize was harvested together with the soybean plants. About 14,000 tons of soybeans were put in quarantine by APHIS. ProdiGene reportedly bought the entire batch of soybean. The US Food and Drug Administration (FDA) stated that the incident posed only minimal risks, if any at all. Nevertheless, economic damages in this case were considerable: fines and financial damage were reported to have amounted to some 3 million US$ and eventually led to the bankruptcy of ProdiGene. In this case total economic damage was small compared to StarLink but, according to several interviewees from PM farming companies, the incident nevertheless caused a severe setback for the PM farming industry.

From these cases the obvious lesson is that serious economic consequences might result from accidental commingling – even in case there are no or very little health or environmental risks. Furthermore, anxieties of civil society and actors in the food and feed sector might also be sparked by discussions to use the remainders of biomass after the pharmaceutical component has been separated, e.g. for feed purposes instead of expensive incineration, also referred to as "dual-use" (Freese 2002).

Consequently, a key challenge will not only be to design highly reliable and redundant confinement systems integrating physical, procedural, and molecular confinement strategies, but also to adjust confinement requirements to the particular PM farming application. As long as accidental and low-level presence of material from pharm crops in the food supply are considered as a huge risk confinement measures might be strict and, thereby, render open field production more costly for producers. This would in turn affect the range of products that can be produced in an economically feasible way.

6.4.3 Regulatory challenges posed to the EU

PM farming follows similar objectives like industrial production of pharmaceutical or other industrial substances: crops will be designed for maximum yield, accessibility and intactness of the target protein, and other technical requirements. With the possible exception of PMPs and PMIs for oral administration as crude extracts[21] PM farming crops are neither designed nor intended to be ingested by human or animals. Risk characteristics are likely to differ from first generation GM crops and risk mitigation requirements will become a focal issue. These specifics are likely to pose a number of challenges to policy makers and regulators in the EU detailed in the subsequent Sections (drawing on Sauter & Hüsing 2006; Spök & Klade 2005).

Risk assessment

For PM farming there will be a need to review and update current risk assessment approaches and guidelines established for first generation GM crops. Possible challenges for risk assessment approaches include the applicability of the concepts of substantial equivalence and

20 A crop that sprouts unexpectedly in a surprise location. Birds and animals often plant them in their droppings, or the seeds are carried by wind or humans to new locations. In the case of maize, kernel might remain in the soil, survive the winter and sprout in the next growing season. If the field is being used for some other cultivars, the maize might be a weed.

21 For instance, in case of certain feed additives and food supplements produced in food/feed crops extensive purification might not be needed.

familiarity, which both play important roles for structuring risk assessment of current GM crops. Familiarity, for instance, also refers to environmental and agricultural experiences gathered with the host crop in conventional agriculture (Barret & Abergel 2000). Familiarity might, however, be less important if the crops has been subjected to multiple and perhaps more substantial changes of genotype (see above) or if non-food/non-feed plants with which there is less experience are used, e.g. safflower in Canada. Likewise, substantial equivalence understood as compositional, morphological, and agronomic differences between the GM crop and its conventional counterpart might no longer be considered appropriate to guide risk assessment. Furthermore, with PMPs another step might be added to risk assessment: to thoroughly assess and to advise on the appropriate level of confinement and containment measures.

Managing accidental contamination

For PMPs the focus will clearly be on avoiding any trace contamination of the food and feed supply, while certain large-scale low risks PMIs might rather be considered as a coexistence issue. Perhaps the most important goal of regulation might therefore be to keep confinement measures of open field production of PMPs under continuous regulatory oversight, to adopt coexistence rules for plants producing PMIs and to set up provisions for accidental contamination. In the case of open field production of food crops with PMPs and PMIs, there might be a need for mandatory and harmonised coexistence rules at the EU level supplementing the present EU guidelines. Otherwise, PM farming companies could simply relocate up-stream production to the Member State with the least stringent rules (which is not possible in case of agricultural production of food and feed). These rules will likely need to include threshold limits in case of accidental contamination and for liability reasons. The present labelling threshold limit of 0.9% for GM events (authorised in the EU) in non-GM food products might only be envisaged for PMIs that do not have hazardous properties and that obtain an authorisation as GM food/feed under EU Regulation 1829/2003 (EPC 2003). Conversely, it is difficult to envisage a zero tolerance policy, as it is presently pursued by the USDA (USDA 2006; Howard & Donnelly 2004). Even thorough on-site risk mitigation measures and safety distances (for instance of one mile for maize producing PMPs (USDA 2006) are not considered to be a hundred percent effective by many commentators and, e.g., by Canadian regulators (CFIA 2005). Given the huge differences that can be assumed for the hazardous properties of PMPs, substance-specific threshold limits would be more likely. In analogy to the EU limit values for pesticide residues, Regulation 396/2005 (EPC 2005), harmonisation across the EU might be necessary, either for specific substances or for particular categories of PMPs, as differences in limits between Member States would hamper food and feed trade. Furthermore, this would not only be an issue of contaminating conventional or organic crops – it would also pertain to GM food/feed crops. Such a scenario would render food control a more complex business.

A related issue would be the question of liability, which is of course of paramount interest to the food and feed industry, as well as to farmers (Smyth et al. 2002). Who would be liable in case of accidental commingling with food or feed crops? Who would be responsible for the economic damages from low-level residues of pharm crops found in food crops although producers did fully comply with the rules? In such cases compensation might cover a broad range of direct and indirect costs, including (Wisner 2005):

- lost export earnings
- retrieval of contaminated grain
- reduced value of non-pharma grain or oilseeds
- recall of products from grocery shelves

- cleaning of grain elevators and processing plants
- testing expenses
- added transportation and handling costs
- lost storage and merchandising income
- long-term market loss resulting from increased foreign competition
- rejected supplies of meat, dairy products, and eggs
- animal or human illnesses.

An even more unfavourable scenario could emerge from possible contaminations of food or feed crop seed supplies. The recent cases of contaminations of conventional US rice varieties by GM rice lines (Pew Imitative on Food and Biotechnology 2006a) and the controversial cultivation of a GM rice producing a PMP nearby a research station where rice varieties are tested before introduction into the US rice breeding programmes (UCS 2006a) show that this is not an entirely hypothetical scenario. Clarification would also be needed whether and to what extent liability risks might be shifted to the contract farmer growing the pharm crops.

Conversely, with PMPs, manufacturers can be expected to avoid contamination of their drugs, e.g. with food and feed crops, pests, and pesticides to maintain the purity and safety standards of validated production processes. In certain areas concerns might, however, differ between food and drug producers. For instance, outcrossing via pollen transfer might be a particular concern for seed producers of pharm crops but less so for the commercial production stage – especially if the PMP will be purified from the green plant material. Furthermore, incentives for confinement might be much less for PMI producers.

With its framework on coexistence for GM and non-GM agriculture the EU appears to be in a better starting position to deal with these issues compared to the US. However, it has to be questioned whether the different coexistence and liability regimes in the EU Member State which have been established because of non-mandatory EU recommendations, are a sensible basis for PM farming. Furthermore, different to first generation GM farming contamination would be an issue for all food and feed farmers, irrespective of whether they grow organic, conventional or GM crops.

Even before the first PMP will be commercially cultivated in the EU: if this technology takes of in the USA, Canada or any other agricultural or food export country, regulators and food control will have to deal with questions of adventitious presence and threshold limits earlier than expected.

Beyond the cases of contaminations described above, Greenpeace lists about 100 documented incidents of adventitious presence conventional food/feed product or seeds of GM events which are not authorised in the importing country. Adventitious presence has therefore been acknowledged as a key issue for policy development, particularly in industrialised countries. In the EU, there are rules established for adventitious presence of GM events in conventional food/feed but rules for seeds are so far lacking (CEC 2007b). For adventitious presence of GM events not authorised in the importing country both the EU and the USA are still pursuing a zero-tolerance policy. This zero tolerance policy, the absence of thresholds and more broadly of a clear policy increases business risks for exporters of food/feed and seed from countries with significant commercial GM crops cultivation (ESA & EuropaBio 2007; Pew Imitative on Food and Biotechnology 2006b). Some EU Member States have therefore established national policies which differ from each other. The broader relevance of this issue for potentially impeding international trade is also reflected by the fact the Codex Alimentarius Commission is presently working on a guidance which includes food safety assessment procedures and an information exchange mechanism in case of low-

level presence (Codex Alimentarius Commission 2007, Appendix IV).

The possibility of low-level presence in conventional food/feed or seed of material from field trials as well as from GM crops not intended for food/feed purposes is, however, not considered in these discussions. This is nevertheless relevant, for several reasons: field trials for PM farming can continue under field trial permits for a decade and include substantial areas of cultivation before a PMP would arrive in the commercial stage. Thus, there is a potential for contamination. Under field trial conditions there is, however, no requirement to submit analytical methods to identify the GM crop. Food control might therefore have difficulties to identify such contaminations. Furthermore, the discussion about adventitious presence of GM material in conventional food/feed products is framing the issue as a business risks rather than a safety risk (Pew Imitative on Food and Biotechnology 2006b, ESA & EuropaBio 2007). In case of PM farming, however, at least for certain GM pharma and industrial crops health and environmental risks might be also relevant. While low-level presence of material from PM farming in food/feed or seeds is less likely to happen because of (stricter) confinement measures there is still the possibilities of human errors. Furthermore, if the tendency continues to conduct PM farming field trials (and perhaps also commercial production) in third countries such as Chile the question arises whether the regulations and enforcement would ensure the same level of confinement as in the USA, Canada or the EU. Therefore, food control of food/feed or seed importing countries might also need to be aware of PM farming field trial activities in food/feed or seed exporting countries.

Regulatory roadmap needed

There is no equivalent procedure in the EU to what is envisaged for commercial molecular farming in the US: The EU Directive 2001/18/EC (EPC 2001) foresees two different authorisation tracks: time- and area-limited field trials (Part B) and placing on the market of GM crops including import, transport, processing, handling, storage, and cultivation (Part C). Part B authorisation can be granted by the respective Member State only, although derived products must not be used for commercial purposes. Conversely, Part C authorisations would allow for commercialisation but have to be granted at EU level, involving all Member States in both risk assessment and decision making. Both procedures might not be entirely appropriate for PMPs:

It seems likely that most PMPs could be produced on areas that compare to large scale field trials and do not necessarily needed to be grown, transported, and processed in more than one Member State. In all likelihood such seeds and plants will also not be traded on the market. Given the US experience, companies might in fact be keen to operate under strict regulatory oversight during the commercial production stage (see e.g.: www.bio.org/healthcare/pmp/factsheet4.asp). Cultivation or processing of such plants might even be conducted in-house or by contractors under supervision of the manufacturer.

Part C authorisation procedures would be more proportionate for the increased rigour of their risk assessment and their demand for mandatory monitoring, but in the complex political environment of the EU there might be continued unpredictability around eventual authorisation decisions. National Part B procedures are more straightforward but might not be considered sufficient in terms of risk assessment and monitoring – and perhaps not as acceptable if there is a chance that possible contamination might effect food and feed products of other EU countries for commercialisation. Therefore, a separate authorisation track for PM farming might be considered. Given the sensitivity of the issue it is, however difficult to envisage such a procedure becoming established at any national

level without the involvement of the EU or other national authorities.

EU regulators might also reconsider the Part B track: in contrast to GM crops for food and feed use, pharm plants are cultivated for a long period of up to 14 years and are likely to be grown on larger areas in order to collect data and produce sufficient amounts of test substance necessary in the course of the authorisation as biopharmaceutical.

Clarifying transboundary movements of crops used for PM farming

A related issue could emerge from the fact that EU-based companies tend to conduct their field trials outside of the EU, e.g. in Chile, USA and elsewhere. This is because of the more difficult regulatory environment and the less favourable public perception in the EU. Another reason is that a production in the EU and e.g. Chile would allow for more than one harvest per year. Such a practice could include both the export of seeds that are produced in the EU and the import of processed or unprocessed biomass. If downstream processing, formulation and marketing of the drug would still be conducted in the EU the vast majority of added value will be retained in EU. In the case of maize or in other cases of PMP production in seeds, it would be tempting to store and ship the PMP enriched kernels because of protein stability and the ease of handling. Companies wishing to take advantage of this might need to clarify whether it would constitute the import of a GMO into the EU requiring market authorisation under Part C of Directive 2001/18/EC (EPC 2001). If so, they might be forced to relocate processing activities as well.

Contained production

Most of what is said above pertains to open field cultivation; however, there are alternative production approaches using contained facilities, e.g. plant cell culture, duckweed, moss or root exudation (see Section 3.2). Contained production would drastically reduce the risks of food and feed contamination – while lacking some of the advantages of open field production. Furthermore, whereas confinement measures for open field production of PMPs are likely to be discussed and agreed at the EU level, commercial production under contained conditions is still under regulatory oversight of the particular Member State according to EU Directive 90/219/EEC (EPC 1990). Greenhouse productions would also be an alternative option, for greenhouses are normally considered contained facilities. Greenhouse space for contract cultivation is presently available up to some 30 hectares[22] which would be sufficient for producing significant quantities of several high-value proteins.

That said, some of these PMPs (e.g. allergens for diagnostics or medical therapy, vaccines, or hormones) might call for higher levels of containment than others. Member States might also have different opinions about what would constitute an appropriate level of containment for a particular substance. There might even be different ideas about the borderline between contained production and deliberate release. For instance, a commercial production using nethouses (saranhouse), as is envisaged with potatoes in Denmark (USDA 2006) might be considered by one Member State a rather unproblematic authorisation under the contained use Directive 90/219/EEC (EPC 1990), whereas others might classify the same practice as deliberate release that would require an application under Directive 2001/18/EC (EPC 2001) which can only be obtained after going through a much more cumbersome EU procedure. Such differences could translate into different levels of compliance costs and environmental and health protection and might therefore need review and perhaps harmonisation.

22 E. g. http://www.bevoagro.com/index.html.

6.5 Managing large-scale PM farming

Many impacts of open field production in PM farming would also depend on the expected scale of production; some speculations about the acreage needed might therefore be illuminating. The annual tonnage of a single biopharmaceuticals very rarely exceeds 1,000 kg/year. Hence the world production of each of this biopharmaceuticals could take place on an acreage of 1,000 hectare at maximum (e.g. estimated for the gastric lipase in maize) but will more likely be much lower, with many products requiring acreages in the range of larger greenhouses (see Table 1 and Figure 7, p. 42). Based on this calculation – as a rough estimate and for illustration only – all presently marketed biopharmaceuticals could be produced on about 50,000 hectares, roughly corresponding to the agricultural land presently dedicated to maize cultivation in Styria, which is a province of Austria. Even in cases of strong increases in demand, the areas needed will be quite small. For instance, the predicted insulin demand by 2012 of 16,000 kg could be met by safflower-derived insulin on 4,000 hectares. As one interviewee puts it "this is not agriculture this is gardening". As these PMPs would be high price products, extensive conferment measures and monitoring might be economically feasible.

A different picture would emerge from producing certain high-dose drugs that are presently being developed. E.g. for certain antibodies annual tonnages of 50,000 kg and up to 500,000 kg are anticipated. For instance, Slater (2006) presented a model calculation for an anti-HIV microbicide, applied in a vaginal cream and also distributed in the developing world. Assuming a yield of 0.5 g MAb/kg grain, about 11,000 hectares would be needed to produce 50 tons per year in maize. The actual acreage required might be well beyond this figure as the final product is envisaged to contain three different proteins. Another example might be PMPs dedicated as feed additives (e.g. antibody for piglets from Novoplant intended as feed additives). These types of biopharmaceuticals might to a much larger extend depend on low cost and large scale production.

While agricultural production of antibodies at this scale might still be far from reality, non-pharmaceutical applications might reach commercial stage much earlier and could drive large-scale agricultural production in PM farming. Here a range of products, including fatty acids, proteins, and vitamins, could be produced aiming at application as food supplements, food and feed additives. Unfortunately, no estimates are available on the annual tonnages and acreage required for these type of substances – they might well be in the range of 50,000 and more hectares for an individual product. Some of these substances might have pharmacological effects on humans or animals (nutraceuticals) and might therefore be perceived in a similarly problematic way as PMPs (e.g. the discussion on Ventria's lactoferrin and lysozyme). Others, especially those added to food, might be considered less problematic in case of accidental contamination regarding possible health and economic impacts.

Table 13: Estimate of productivity of different production platforms for pharmaceutical proteins.

Production platform	Productivity [kg/hectare/year]	Area needed for 1,000 kg [hectare]
Maize (kernel)	0.2-4	800-40
Rice/barley (seed)	2-12	80-12
Alfalfa (foliage)	4-6	40-8
Potato (foliage)	20-80	8-2

Source: Baez (2004), modified.

Economic impacts of these types of PMIs are likely to depend on a range of variables including scale, product properties, confinement measures,[23] coexistence and threshold regulations, liability rules, and the insurability.

It is very difficult to foresee how quickly – and if at all – PM farming for large scale production would be adopted. In order to deal with the 'co-existence' and segregation of an extended range of crops and agricultural production systems regulatory regimes and food/feed control are likely to become more complex. Not only GM crops would have to be separated from conventional and organic crops, GM crops producing PMIs would need separation from any food and feed crops and follow different threshold values regardless of whether they are GM or not. There might even be a need to separate certain kind of PMIs from each other.

With the possible exception of PMIs that are used as food supplements or food additives and without considering costs that need to be incurred to avoid accidental contamination and adventitious presence of PMPs and PMIs in food and feed, a widespread adoption of PMIs is likely to impose considerable costs on the agricultural system and the food and feed supply chain as well as on governments.

6.6 Adoption by big pharmaceutical and agrochemical companies

As a striking characteristic most companies active in PM farming are start-ups or, to a lesser extent, SMEs. Most of these companies are financed from public funds and venture capital; very few became publicly traded so far.

Few multinational companies seem to be active in this field. Besides Monsanto, Dow (both USA), Syngenta (Switzerland), Bayer, BASF (both Germany) no other multinational company acknowledged in-house R&D in the field. Two agrochemical multinational companies, Monsanto and Syngenta (Switzerland), had been active in PM farming but pulled out of it recently. Besides Bayer and BASF (both based in Germany), which only recently bought themselves into the business, only Dow Agro Science remains active in PM farming.

Monsanto conducted R&D focussing on maize as production platform mainly for antibodies. It had entered the business because of the combination of knowledge in producing biopharmaceuticals in its pharmaceutical branch (bovine growth hormone) and the knowledge of and long term experience with GM maize. In 2003 Monsanto decided to focus on its core business, large acre crops, and to discontinue R&D in PM farming. While no particular reasons were mentioned, the long timelines for commercialising a pharm product clearly played a role (company interviews).

Syngenta pursued R&D using tobacco as a platform for expressing antibodies and collaborated with companies such as SemBioSys. At the end of 2005 Syngenta announced to abandon it's PM farming activities. The decision was justified with a stronger strategic focus on the core seed business. Internally, PM farming was perceived as slow growing business that needs a lot of commitment and investments to succeed (company interview).

Particularly, interesting is the reluctance of large pharmaceutical companies to move into the PM farming area. Only two of four multinational pharmaceutical companies (Boehringer Ingelheim (Germany), Novartis (Switzerland), Novo Nordisk (Denmark/USA) UCB Celltech (UK)) that were contacted mentioned collaborations with

23 For instance, the establishment of an identity preservation system allowing that a particular PM farming crop can be easily distinguished from normal food and feed crops.

research institutions to explore the potential use of PM farming.

All four companies are closely observing PM farming but so far are hesitating to move into the area. This hesitation is explained by technical and regulatory reasons and by the lack of public acceptance, all which add to the uncertainties already exist in the manufacturing of biopharmaceuticals and that lead to higher total business risks and lower expected economic returns. Problems mentioned by interviewees include:

- Unresolved problems in downstream processing with respect to scale and characteristics of by-products (see also Section 6.1.2).
- Differences in glycosylation pattern compared to mammalian cell lines and the need to humanize glycosylation while at the same time new systems are being established that allow glycosylation of proteins expressed in yeast (e.g. by GlycoFi in Pichia sp.).
- Lack of speed: the time it takes to have a stable product line is longer compared to mammalian cell lines.
- Regulatory uncertainty: companies consider market authorisation of PMPs and PMVs as more costly and time consuming compared to well established production systems - partly because of the novelties of the process. Therefore, they do not want to be the first to take a product through the entire authorisation process.
- Possibility of outcrossing and environmental contamination in case of open field cultivation.
- Lack of public acceptance of GM crops, risk of activism and a backlash of consumers and the media as well as field devastation by activists in the EU.
- Difficult policy climate and regulatory system for GM crops in the EU.

Because of these concerns and because the upstream production process can be better defined and controlled contained PM farming production systems are perceived to be more interesting. On the other hand this would require more infrastructure investments and diminish any cost advantages.

In sum, savings in production costs and some safety benefits do not seem to be a key point for pharmaceutical companies as there is little pressure to lower the cost of drugs. Facing a number of technological and regulatory uncertainties pharmaceutical companies are rather taking a wait-and-see approach.

The reluctance of large pharmaceutical companies to embrace PMPs has created serious problems for small PM farming companies. Given the tremendous costs and the long time required for taking a biopharmaceutical throughout the regulatory procedure pharm crops developers are actively seeking collaborations with large companies which have enough money and experience with the regulatory procedure as well as in marketing of pharmaceuticals. PM farming companies have continued to grow and their own proprietary PMPs are now approaching advanced stages of clinical trials. Because the financial requirements, especially for Phase 3 clinical trials, are exceeding what would be available as venture capital, the pressure increases to raise new funds. As these new funds are not forthcoming some companies have already closed down or changed their business strategy. (company interviews). Yet, this financing gap is not entirely specific for the PM farming sector and has been described for other biotech areas, too (Jonsson 2007). Interestingly, PM farming companies subscribing to major food crops and open field production were thereby opting out suggesting disapproval from potential partners and financiers (one case was confirmed in the interviews). Nevertheless,

key actors in the field of PM farming consider it pivotal for the further development of their sector to get these companies interested and involved (e.g. Arntzen 2007; Dean 2007). Public research groups which are developing PMVs or PMPs for non-profit purposes are facing similar constraints and are therefore calling for public funds. This could ensure further advancement of the technology by taking selected products through the regulatory procedure. Funding would then also have to consider the substantial costs for the regulatory procedure, as there are no fees waivers for public sector non-profit research – at least in case of the EMEA (interview researcher).

6.7 Summary

Regulators and policymakers in the field of PM farming are facing a number of technical, economic, safety, regulatory, and business strategic challenges which need to be tackled or overcome if this technology shall go ahead. Most of the challenges are associated with the use of food crops and/or open field production. Differences are evident between PMPs and PMIs for non-pharma applications.

PM farming is being developed for commercial production. In order to strengthen its competitiveness vis-à-vis mammalian cell lines and microbial systems, PM farming needs to further increase yield and improve in-planta engineering and humanizing of the plant-specific glycosylation which is potentially immunogenic to humans. A stronger focus on the downstream purification process will be important to overcome the problems of scale and to remove plant-specific compounds and contaminants (e.g. phenolic compounds, pigments, plant proteases). Innovations and improvements in the established production technologies and the advent of first products from new technological platforms, such as insect cells and animal pharming, are however steadily raising the bar for a successful market entry of pharm crops.

Drug regulators in the USA and the EU consider PMPs and PMVs to pose novel problems for market authorisation. Especially the less controlled environment of agricultural production seems to represent a paradigm change. Key challenges include quality assurance for upstream production, choice of adequate agricultural practices including monitoring and control measures, and an appropriate seed banking system. More controlled production environments are deemed less difficult (e.g. greenhouse and bioreactor production with Moss, Lemna, algae).

In case of open field production the developers of PMPs have to consider environmental and health impacts in the context of the established agricultural biotechnology frameworks. High concentrations in plant tissue of proteins intended to be pharmacologically active in humans or higher animals could be a source of novel health and environmental risks: human exposure might occur from accidental contamination by pharm crops of the food/feed supply (inadvertent admixture, pollen flow, etc). Economic and liability risks include compensation for recalls and reduced value of food/feed products and damage to domestic and export markets for agricultural food/feed products. The key risk mitigation challenge, therefore, is to design and police a system of physical, organisational and molecular confinement measures.

The specific characteristics of PM farming compared to first generation GM crops pose challenges to the established regulatory regimes of agricultural biotechnology. Key risk assessment concepts established for first generation GM crops such as substantial equivalence and familiarity appear to be of limited use for assessing pharm crops; confinement might become a new focus of the risk assessment. In order to manage accidental contamination of the food/feed supply EU-wide harmonised thresholds and liability rules have to be considered. In case of food/feed imports from countries with significant PM farming activities thresholds might need to be established and

controlled very soon. A separate authorisation track might be considered under Directive 2001/18/EC (EPC 2001) for GM crops that will not be traded and that will be cultivated by contract farming on limited acreage and under constant regulatory oversight only. Other regulatory challenges include clarifications for transboundary movements, reconsideration of field trials and EU harmonisation of containment criteria.

In case of a wider adoption of the technology extra costs are likely to arise not only from contamination accidents but will also have to be incurred for routine food/feed control and for controlling confinement measures. A simultaneous production of various types of PMIs might render coexistence regimes and segregation measures including thresholds much more complex and costly. Based on experience with presently used biopharmaceuticals, the production of PMPs would very rarely exceed 1,000 hectares per product and may in fact in many cases not exceed acreages for larger greenhouses. The high value would justify strict, redundant and costly confinement and monitoring regimes. Novel types of antibodies and PMIs, in contrast, would require much larger acreage and would perhaps not allow for the same level of confinement without becoming inefficient from a commercial point of view.

A particular challenge to developers of pharm crops is the reluctance of large pharmaceutical industry to move into PM farming and to partner on technology and/or product development. Large pharmaceutical companies are still discouraged by technological problems (glycosylation, downstream processing, and lack of speed) and additional uncertainties (market authorisation, GM crop regulations, stakeholder campaigning, and the policy climate for agricultural biotechnology in the EU). This has created serious problems and even bankruptcy for a number of start-up and SME type companies, which could no longer pursue costly clinical trails solely on public funds or venture capital. Public research groups developing PMVs for non-commercial purposes are facing similar problems.

7 Public and Stakeholder Perception

7.1 Introduction

Agricultural biotechnology for food products is a highly controversial issue in many countries. Especially in Europe public acceptance of GM food is very low. According to the most recent Eurobarometer survey, 58% of Europeans think that production of GM food should not be encouraged, because it is considered to be not useful, morally unacceptable and a risk to society (Gaskell et al. 2006). Canadians consider GM food slightly more acceptable than Europeans, but on average Europeans and Canadians have similar views on GM food. In contrast, USA citizen see GM food as being more useful for society, less risky, more morally acceptable, and they also express more confidence in its regulation. In general, there is greater support for GM food in the USA than in Canada, and even more so than in Europe.[24]

Public scepticism is frequently attributed to the lack of perceived benefits, and to possible or unknown environmental and health risks of GM crops. Kuznesof & Ritson (1996) suggest that the acceptability of GM products increases with perceived benefits, and quality improvements of the product (particularly taste and naturalness). Several studies (e. g. Einsiedel & Medlock 2005; Frewer et al. 1997; 2004; Hossain et al. 2003; Knight et al. 2005; Urala & Lahteenmaki 2004; Verbeke 2005) showed that perceived benefits have the most important influence on consumer purchase decisions and public acceptance of use of genetic engineering. Especially first generation GM crops, such as herbicide tolerant or insect resistant crops, primarily aim to improve agronomic properties to lower production costs. Lower costs are, however, perceived by the public to benefit agricultural biotechnology companies only, and neither the consumers nor the farmers (c. f. Einsiedel & Medlock 2005; Canadian Citizens' Panel 2007).

Inspired by the conclusion that "benefit matters" biotech proponents expected that pointing out the benefits of GM crops and GM food will raise public acceptance. In the case of health biotechnology, benefits may be more evident to the general public and public perception studies have indeed shown that the public is more supportive for the application of biotechnology for medical purposes (Gaskell et al. 2001; Nielsen et al. 2002; Gaskell et al. 2006).

Against this backdrop, it has been speculated that PM farming will be more positively perceived compared to first generation GM crops because this kind of GM crops produce pharmaceuticals, vaccines, bio-materials, and they promise more tangible health and environmental benefits (e.g. Krueger 2001).

In order to go beyond speculation this Chapter brings together and discusses empirical findings relevant to PM farming from public perception studies as well as stakeholder views from interviews. The first part summarizes the results of recent studies on public perception of PM farming (Section 7.2). While there are numerous studies on first generation GM crops and food, only a few address the use of GM crops for producing pharmaceuticals or other substances of industrial interest. This is especially true for the EU.

The second part (Section 7.3) describes stakeholder perception of PM farming in the USA, Canada and the EU by drawing on a literature and document review as well as on interviews. In the EU, stakeholder groups, especially environmental

24 Other high quantity major food/crop producing countries – like Australia, Japan or China – have not been investigated within the scope of this report.

and consumer NGOs but also organic and small farmers, have been campaigning against first generation GM crops and food since many years and have exerted considerable influence on EU biotechnology policy. In the USA and Canada these groups were less active on first generation GM crops but, after being reinforced by the food industry, became more influential in the context of PM farming. On the other hand, patient groups started to express views in favour of PM farming.[25]

7.2 The "general public"

The public perception studies that were reviewed for this report used a range of different methods including phone surveys, public venue interviews, questionnaires, face-to-face interviews, group discussions, workshops, public consultations, focus groups, citizens' panels and an online-consultation, and were conducted in different regions in Canada, the USA, UK, and Denmark. Any comparisons between studies or countries have therefore to be taken with great care. So far, there is no Europe- or US-wide public perception survey on PM farming. The most recent Eurobarometer (Gaskell et al. 2006) included only one very general question on PMPs from greenhouse production in the context of confidence into the regulation and regulators. A brief summary of each study is included in Annex 4: Stakeholder views on PM farming.

7.2.1 Contextual issues

Based on the presumption that citizens are evaluating GM applications in a specific context, the following section addresses the contextual issues that might have an impact on acceptance.

7.1.1.1 Does application matter?

First, there seems to be a hierarchy of applications and purposes. Frewer et al. (1997, 2004) and others (e.g. Hossain et al. 2003; Urala & Lahteenmaki 2004; Verbeke 2005) suggest a link between acceptance and perceived benefits, which depends on the individual application.

As several authors indicate, attitudes towards PM farming are developed on a case-by-case basis by considering the particular application. The purpose of the product produced by PM farming is a major factor for acceptance (Einsiedel & Medlock 2005). Therefore, *what is the application for?*, followed by *who is going to benefit?* seem to be main aspects for acceptance or rejection of a particular application (c. f. Einsiedel & Medlock 2005; Willbourn 2005). As shown in studies conducted in North America and the EU applications with health implications are perceived to provide a significant benefit and receive higher levels of support than all other types of application (Einsiedel & Medlock 2005; Willbourn 2005; Knight 2006). When comparing different medical applications differences in acceptance are reported relating to the severity of the illness and possible alternatives in treatment (Willbourn 2005). Hence, if a new pharmaceutical substance could be produced by PM farming only, provided that the disease is severe and of societal relevance, acceptance is high, even if there might be concerns about risks (Willbourn 2005; Einsiedel & Medlock 2005).

Two other important factors for the acceptance of PM farming are the number of people potentially benefiting by a particular application and who they are. The more people are expected to benefit from an application, the more likely there is acceptance. Potential benefits for unprivileged groups, like people in developing countries, for instance, tend to be considered to be very positive (Huot 2003; The Danish Board of Technology 2006).

Alternatives are always part of the considerations: if – for a given application

25 This Section focuses on countries with significant commercial activities, the USA, Canada and the EU. Countries that have little commercial activities, such as Australia and South Korea have not been investigated. According to exploratory interviews there seem to be very little awareness of PM farming in these countries.

– alternative approaches exist, there is less acceptance of PM farming. For instance, a deliberative public engagement activity on the application of biotechnology for non-food use in the UK showed that the acceptance for GM plants producing antibodies to treat dental plaque is very low. Although this is a medical application and many people are affected by dental caries, the participants dismissed this application as a "waste of money" (Willbourn 2005). It was argued that an alternative strategy of promoting proper dental hygiene and better dietary habits would be far cheaper, pose less risk and produce at least the same – if not even better – results. Similar results came from a Canadian Citizens' Panel[26], where the panellists concluded that the development of PMPs needs to be considered in the context of the overall public health strategy, including alternatives such as the promotion of healthy life styles. If no alternatives are available, the application is likely to gain more public acceptance than if the same results could be achieved by already existing conventional alternatives. Beyond medical applications this seems to be also true for PMIs[27] (Fischoff & Fischoff 2001; Huot 2003; Willbourn 2003; Einsiedel & Medlock 2005).

Lower production costs through PM farming are considered to benefit industry only (c. f. Einsiedel & Medlock 2005; Canadian Citizens' Panel 2007; stakeholder interview). In contrast, potential benefits for farmers or the development of rural areas seems to be of more relevance. As a Canadian study (Huot 2003) and a citzens' panel (see fn. 27) showed, an advantage of PM farming is assumed, if it constitutes a new source of income for the hard-pressed farm sector either by creating new employment opportunities or by adding higher value to products. While it is generally questioned whether PM farming offers an economic benefit to consumers, the claim by promoters of PM farming that it can create new business opportunities and new jobs is more readily accepted (The Danish Board of technology 2006; Canadian Citizens' Panel 2007).

In focus group discussions on PM farming conducted in Canada most participants found it difficult to decide whether the benefits of molecular farming outweighed the risks and vice versa (Huot 2003). Almost all participants agreed, however, that the highest benefits associated with PM farming will be its application in medicine: the possible discovery of novel cures for disease, the availability of cheaper drugs, the development of better drugs, improved societal health care, and better access to drugs for developing countries.

Not only medical application, but also industrial applications are ranked for their purpose: If the application is related to the production of more environmentally sound products, acceptance is clearly higher compared to an application that only produces substances at lower cost (Einsiedel & Medlock 2005; expert interview). Again potential alternatives play a role: for example the UK focus group members mentioned in the context of energy crops that to use other alternative sources, like wind, would also reduce fossil fuel consumption and green house gas emissions (Willbourn 2005).

In general it can be concluded, that medical applications of PM farming are preferred over industrial applications. Important aspects are available alternatives, the severity of the treated disease, and who would benefit. In case of PMIs, environmentally sound products are preferred over those solely promising economic benefit, again weighing the benefits against alternatives (Nevitt et al. 2003; Einsiedel & Medlock 2005; Knight 2006; stakeholder interview).

26 Report: Pharming the Future – A Citizens' Perspective on Plant Molecular Farming, March 2007, available at: http://www.fw.ucalgary.ca/pharmingthefuture/resources/Pharming%20the%20Future%202.pdf

27 Alternatives mentioned in the context of PMIs: GM crops for bioplastics: reducing waste by reducing the use of packaging materials, recycling of ordinary plastics or use more of natural products instead, energy crops: using less energy overall, using other renewable resources such as wind and solar, instead of using genetic modification to improve the energy yield from short rotation coppice or conventional breeding, GM pharm plants: to focus on prevention of diseases.

7.1.1.2 Perception of risks

Public perception and the acceptability of a specific PM farming application is – more (Einsiedel & Medlock 2005) or less (Willbourn 2005) – based on balancing benefits and risks.

Concerns are mostly focussing on one or more of the following issues: potential contamination of the food chain, health risks and environmental safety issues including long-term effects, economic issues and the adequacy of regulation. Among these, the accidental contamination of the food supply through PM farming was the dominant issue raised in Canadian citizen panels, focus groups, public consultations, and on stakeholder interviews (Einsiedel & Medlock 2005; Einsiedel et al. 2005; Canadian Citizens' Panel 2007). Concerns include cross-pollination and the transfer of plant material by human action, either inadvertently or by malicious intent (e.g. bioterrorism) (Einsiedel & Medlock 2005).

Concerns about long-term side effects on the environment were also frequently expressed, raising the question whether enough time had been or would be allowed to effectively study such effects. Canadian consumers (Huot 2003) and UK focus group participants (Willbourn 2005) felt that still not enough research is carried out and that the long-term risks of GM are still unknown and potentially irremediable. Canadian citizens pointed out that there the lack of long-term studies of human health effects from GM crops in general (Canadian Citizens' Panel 2007).

As shown by Einsiedel & Medlock, citizens are also concerned about the abilities of regulators to adequately manage the technology, particularly about the adequacy of monitoring longer-term impacts. Moreover, concerns about proper balancing of commercial versus public interests by regulatory systems were expressed (Einsiedel & Medlock 2005). It is argued that commercial interests would ultimately supersede the public interest in terms of safety. For example, the participants of focus group discussions showed little faith in companies.[28] They felt that even if the rules and regulations are stringent, companies and growers would not necessarily follow these rules carefully.

Balancing risks and benefits

The risks are often weighted against benefits for the individual and for the society as a whole, such as greater availability of drugs, lower prices, or reduced mortality for patients, the reduction of waste, and the use of renewable resources for the environment. In case of greater benefits, and benefits for a large number of people, and with no or more unfavourable alternative options, risks are more likely to be accepted (Einsiedel & Medlock 2005). Overwhelming benefits can make up for clear risks (Willbourn 2005). As already mentioned in the context of application, if benefits for developing countries are assumed – especially in terms of improving public health – acceptance is very high, even if the perceived risk is high (Fischoff & Fischoff 2001; Willbourn 2005; Einsiedel & Medlock 2005). On the other hand, if there is no substantial benefit, people tend to err on the side of caution, even if the risk is perceived not to be very high (Willbourn 2005); Maliga & Graham (2004) state, that unless the consumer sees and appreciates direct benefits of GM crops, then any perceived risk, no matter how small or misplaced, will outweigh the benefits.

7.1.1.3 The role of the production platform

Another hierarchy seems to exist on the production organism used, also referred to as the "vehicle". Einsiedel & Medlock (2005) and Knight (2006) showed that the vehicle (e.g. micro-organisms, plants or animals) is highly relevant for the acceptance of a specific application. Based on a US phone survey, Knight (2006) even argued that this appears to be more important than both the function for health or food purposes, and the type of application. In general

28 The focus groups were conducted in Canada in 2004 (see Annex 3: Public Perception Studies on PM farming).

GM micro-organisms generate least concern. The use of plants receive higher support than animal applications, which is mainly related to ethical and moral concerns and animal welfare aspects (Einsiedel 2005; The Danish Board of Technology 2006). For instance, a survey of public views on molecular farming among US Americans carried out by the Pew Initiative showed that 81% agree that designing GM crops to produce affordable drugs is a good idea, but only 49% agree that genetically engineering with animals to produce drugs is acceptable (Einsiedel 2005).

In case of PM farming production platforms concerns about contamination of the food supply are considered. Studies conducted in Canada, UK and Denmark indicated that there is higher public acceptance of PM farming carried out with minor or non-food crops than for major food crops (Einsiedel & Medlock 2005; Willbourn 2005; The Danish Board of Technology 2006). Comparing the acceptance of plants for non-food use and minor food crops, a recent consultation in Canada (expert interview) suggests that both types of crops might be equally acceptable. However, others regarded the sole use of non-food crops as the most important precondition to accept PM farming (The Danish Board of Technology 2006).

7.1.1.4 Containment

According to Willbourn (2005) and other studies (e.g. Einsiedel & Medlock 2005; Knight 2006; The Danish Board of Technology 2006; Milne 2007) citizens consider containment measures to be of high priority, especially in the context of GM crops producing pharmaceutical substances. Measures should be taken to prevent the GM material from getting into the food chain (e.g. Willbourn 2005; Canadian Citizens' Panel 2007), thus preventing consumers from inadvertent exposure to a biologically active compound that could prove dangerous, especially for infants, people who suffer from illness or elderly people. Concerns are also expressed that plant material containing pharmaceutical or industrial substances might contaminate ground water and soil (Canadian Citizens' Panel 2007).

UK citizens discussed[29] how to prevent such risks, and they concluded that a range of different containment measures should be used (Willbourn 2005): biological containment, such as sterile plants to prevent gene transfer, physical containment, such as growing the plants on isolated plots far away from any related species and closed environments, such as greenhouses, which were deemed the safest method for containment of crops in PM farming.

In general it can be concluded that strictly contained PM farming would receive the highest acceptance (Einsiedel & Medlock 2005; Huot 2003; The Danish Board of Technology 2006; Willbourn 2005; Milne 2007). While it is occasionally argued that full containment is considered impossible, and contamination is very likely to happen accidentally (e.g. through human error or natural disasters (Huot 2003; Canadian Citizens' Panel 2007) or by malicious intent (Einsiedel & Medlock 2005), greenhouses and tightly controlled laboratories are deemed acceptable by a Canadian consumer panel for PM farming if strict regulations are in place to ensure public and environmental safety (Huot 2003).

7.1.2 Differences in public perception of PM farming and first generation GM crops

The resistance to GM food is often attributed to the public perception that it does not offer consumer benefits (e.g. Knight et al. 2005). In fact, a positive correlation between perceived benefits and acceptance is described in several studies (e.g. Frewer et al. 1997; Hossain et al. 2003; Urala & Lahteenmaki 2004; Verbeke 2005).

29 The discussions were held in the context of the "GM nation" initiative, a national debate on GM issues held in 2003.

The second and third generation of GM crops might be test cases for the "applications matters" hypothesis, since they could bring consumer benefits. In the case of GM functional foods (second generation of GM crops) benefits are mainly conceptualized in terms of health benefits and, according to this hypothesis, should receive higher support compared to first generation GM crops (Knight 2006).

Similarly, it could be hypothesized that third generation applications – particularly for medical purposes – would receive higher support as well. For instance according to Maliga & Graham (2004) molecular pharming promises more readily identifiable benefits for consumers in the form of inexpensive safer medication, more wholesome food and environmentally sustainable industrial feedstock. However, as direct comparisons are rarely included in the public perception studies and only a few studies have so far included PM farming there is still a lack of empirical evidence backing this conjecture.

7.1.2.1 Summary

Notwithstanding the scarcity of empirical data on public perception of PM farming a few observations can be made.

The studies available so far concluded a higher support for non-food applications of GM crops compared to GM food crops (Frewer et al. 1997, 2004; Einsiedel & Medlock 2005; Hoban et al. 1992; Hoban 1998; Kirk & McIntosh 2003; Knight 2006; Willbourn 2005; The Danish Board of Technology 2006; Voss et al. 2006; expert interview).

The literature on public perception indicates that with GM crops in fact application matters. For instance, medical applications of PM farming are preferred over industrial applications. Important aspects are available alternatives, the severity of the targeted disease, and who would benefit. In case of PMIs, environmentally sound products are preferred over those promising only economic benefits, again weighing the benefits against alternatives (Nevitt et al. 2003; Einsiedel & Medlock 2005; Knight 2006; stakeholder interview).

Important risk issues being considered include the potential of contamination of the food chain, safety issues, long-term impacts, economic issues and proper regulation.

Acceptance of risks seems to depend on the characteristics of the benefits, because citizens are weighing up benefits and risks on a case-by-case basis, considering the aspects mentioned above. Therefore it is difficult to generalise. Some applications might be appreciated under certain conditions, others might be rejected. In general it can be concluded that risks are more likely to be accepted in cases of substantial benefit.

PM farming production in food crops is perceived to be more risky compared to non-food crops, and open field production is deemed riskier than production under contained conditions. This is mainly related to concerns about inadvertent human exposure following contamination of the food chain by gene-transfer and commingling.

Consequently, strictly contained PM farming would receive the highest acceptance (Einsiedel & Medlock 2005; Huot 2003; The Danish Board of Technology 2006; Willbourn 2005; Milne 2007). While it is occasionally argued that full containment is considered impossible, and contamination is very likely to happen anyway, either accidentally or by malicious intent (Einsiedel & Medlock 2005), greenhouses and tightly controlled laboratories will be deemed acceptable for PM farming if strict regulations are in place to ensure public and environmental safety.

7.2 Stakeholders' views on PM farming

Stakeholder awareness and activities in the field of PM farming differ a lot between North

America and Europe. In North America various public interest groups (especially environmental and consumer groups), farmers associations, the food industry, the biotechnology industry associations and to a less extent advocacy groups, in particular patients associations, have organised and/or actively participated in stakeholder debates and public hearings since early 2000. Most groups have meanwhile publicly positioned themselves on PM farming in press releases, position papers, statements as well as comments on field trials and draft guidance documents (Mellon & Rissler 2004; Andow et al. 2004; UCS 2006a; Freese et al. 2004; Freese 2002, 2006, 2007; Huot 2003). The Canadian Government proactively started stakeholder consultations even before the first PM farming field trial was approved.

In Europe, in contrast, there seems to be little awareness of and activity on the issue of PM farming. Debates have been triggered by and focussing on PM farming field trials, and are therefore essentially limited to France and –more recently –Germany. Even in these Member States debates rarely reached the national level. Civil society seems to be preoccupied with the first generation of GM crops. As a rare exception a hearing was hosted by the German Parliament in 2006, where different stakeholder groups together with Members of Parliament discussed the findings of a technology assessment study on plant molecular farming conducted by the Office of Technology Assessment at the German Parliament (Sauter & Hüsing 2006).

7.2.1 Stakeholder groups active

Presumably the most powerful actor in the US debate is the US food industry (Freese 2006; stakeholder interviews). In the EU the food industry has no officially agreed position on PM farming but started internal discussions in 2005, following pressure from some member companies that are active on both sides of the Atlantic. A working group established at the Confederation of the Food and Drink Industries of the EU (CIAA) discussed the topic and eventually reached internal agreement in 2006. In contrast to the US, the EU food industry has not held or participated in any stakeholder discussions in the EU.

North American public interest groups have been active on PM farming since the end of the 1990ies and have issued numerous reports and statements critical to industry and regulatory activities (e.g Andow et al. 2004; Center for Food Safety 2007a, 2007b, 2007c; Consumers Union 2002; Freese et al. 2004; Freese & Caplan 2006; Freese 2002, 2006, 2007; Huot 2003; Jaffe 2004, 2006; Mellon & Rissler 2004; UCS 2003, 2006; Wisner 2005). Overall the views of these groups seem to be very similar (see also Annex 4: Stakeholder views on PM farming). In the EU, these groups have been very active and influential at both national and the EU level on first generation GM crops. In contrast, activities on PM farming are, so far, limited to regionally and nationally operating environmental groups and largely focussing on PM farming field trials in France and Germany. Consumer groups do not seem to be active at all.

Farmer's associations take up different positions (stakeholder interviews): alternative and organic farming groups in North America and in Europe reject the use of GM crops in general because of coexistence problems, and because of the general threat they pose for alternative agriculture. While being still active in the context of first generation GM crops, there is little activity on PM farming in particular. The most vocal French group for alternative farming, the Confederation Paysanne, strongly opposes GM crops in agriculture and is also active against PM farming.

Conventional farmer's groups in Europe are quite often reluctant to take up a clear stance on GM crops, and they do not appear to have a position on PM farming. Awareness seems to be limited to groups in France, the only country with a history in PM farming field trials in the EU. Some European groups, such as the German

"InnoPlanta" network,[30] proactively promote agricultural biotechnology innovations, including PM farming.

In North America conventional farmer associations appear to be divided: Some groups appreciate biotechnology innovation in agriculture, and publicly support such developments, for instance the US National Corn Growers Association (National Corn Growers Association 2001). Others, such as the US Rice Growers Associations publicly oppose open field cultivation of PMPs (Freese 2006). Campaigns against PM farming are frequently supported by state based groups such as Kansas Rural Center, Mississippi Rice Council, Arkansas Rice Growers Associations, Missouri Rice Research and Merchandising Council.

Patients' organisations represent a new actor in the debate on agricultural biotechnology (Spök 2006) which potentially have a strong interest in PM farming. Interestingly, these groups have so far rarely shown up in public consultations or issued any statements, with the Cystic Fibrosis Foundation[31] (IAPO 2005), and the French Cystic Fibrosis Association "Vaincre la Mucoviscidose"[32] both based in France being an exception. These groups publicly supported PMPs by protesting against the destruction of PM farming field trials by anti-GM activists which were conducted for developing a maize-derived gastric lipase for cystic fibroses treatment. In the US, the Arthritis Foundation also has publicly supported the development of PMP technology, while nevertheless urging due caution (IAPO 2005).

The North American biotechnology industry while advocating cost, capacity and safety advantages of PM farming proceeds with great care. As a response to a number of contamination incidents (in particular StarLink (2000) and ProdiGene (2002); for details see Section 6.4) and to growing concerns within other stakeholder groups as well as from food and feed biotechnology companies the US biotechnology industry association BIO has started to develop confinement procedures (including standard operating procedures and identity preservation systems). BIO stresses that PM farming – as opposed to other GM crops – should continue to be under regulatory oversight of the USDA. These activities were subsequently broadened to recently launched stewardship policy to "enhance regulatory compliance and product quality for consumers" (BIO 2002a; 2002b; 2005; 2006; 2007; Dry 2002). The EU biotechnology industry association EuropaBio, in contrast has not been active in the field of PM farming, so far. Although an internal working group dedicated to this issue was established in 2005 there is apparently little pressure and has been no outcome, so far (stakeholder interviews).

Several concerns raised are very similar to those associated with first generation crops. While their interests and focus might differ public interest groups, certain farmer groups and the food industry, nevertheless, have similar views on four main and interrelated issues specific to PM farming: i) the risk of using food/feed crops in open field production, ii) environmental risks from open field production, iii) risks for human health, and iv) economic risks. The views are particularly similar on the use of food/feed crops and open field production as well as related economic risks while human health and environmental risks are emphasised more by public interest groups.

The following section briefly summaries the main points raised. Given the lack of awareness and activities in the EU it mainly portrays the views of US and Canadian stakeholder groups.

30 InnoPlanta is an association of agricultural producers, plant breeders, companies, scientific institutions, and universities that inter alia promotes plant biotechnology for raw materials for the cosmetics, pharmaceutical industries, and plant-derived ethanol as energy source.

31 Cystic Fibrosis Foundation (2003): Comments re: FDA/USDA Guidance for Industry. Letter to the FDA. 10 January, http://www.bio.org/healthcare/pmp/fdaregsAARDA.asp.

32 Vaincre la Mucoviscidose (2003): Rapport annuel 2003.

However, the views of EU groups seem to be very similar to their North American counterparts. The Section is structured along the points raised A table summarising the main points of each stakeholder group is included in Annex 4: Stakeholder views on PM farming.

7.2.2 PM farming using food/feed crops

The most frequently raised concern related to PM farming is the use of food/feed crops in open field production, which is linked to inadvertent contamination of the food chain. Admixture might pose health risks and economic risks (especially in the form of market losses or liability claims) for domestic food and feed producers and farmers. Stakeholder groups concerned about insufficient safety evaluation of pharmaceutical producing crops, are calling for a zero contamination threshold[33] (e.g. Consumers Union 2002; UCS 2003, 2006a, 2006b). Confinement strategies such as spatial separation, temporal separation, dedicated machinery and infrastructure, biological confinement measures, etc. are not perceived as sufficient by GM critical groups (e.g. Andow et al. 2003). It is also questioned whether current regulations could avoid adventitious presence.

Is it possible to protect food supply from industrial or pharm crops?

Pollen dispersal and admixture during seed production, harvest, storage, transport or handling are considered as major routes for the contamination of the food supply. Combinations of different confinement measures – even allowing for redundancy, tightly controlled supervision, traceability, and accountability are recommended (Andow et al. 2004). Still, absolute confinement is deemed impossible (Freese 2006). Therefore, non-food/feed plants and/or contained production such as greenhouses, and mines are proposed (stakeholder interviews, Consumers Union 2002; Huot 2003; Mayer 2003; Freese et al. 2004; Andow et al. 2004; UCS 2006b; Greenpeace[34]). Consumers and environmental groups call for more preference to the development of completely contained production systems based on plant or animal cell culture, bacteria, fungi, and algae (stakeholder interviews, UCS 2006b).

The US biotechnology industry – despite the strong pressure from certain societal groups is still supporting the use of food/feed crops for PM farming. Activities have focussed on the development of extensive stewardship programmes including confinement procedures (BIO 2002b, 2005, 2007).

7.2.3 Risks for human health

Unintended exposure to material from pharm plants might occur via admixture but also via pollen, dust debris from leaves, stems and flowers, and from polluted surface and groundwater. It is considered to be particularly problematic in case of pharmaceutical substances which might exert toxic, allergic or hormonal effects (e. g. Mayer 2003; UCS 2003; Freese et al. 2004; Umweltinstitut München 2006; Cystic Fibrosis Foundation 2003; Freese 2007). Possible risks for vulnerable groups such as infants, sick persons, elderly people, and long-term effects for farm workers are of particular concern (Huot 2003; Mayer 2003).

Besides concerns about unintended exposure, efficacy and safety of the products are also called into question, e.g. in case of the recombinant lactoferrin and lysozyme produced from rice (Freese 2007).

33 This means that PM farming should be conducted in a way that the likelihood of contamination would be so low as to be nearly zero.

34 E. g. press release Ottawa Citizen 29.4.2007 available at http://www.gmwatch.org/archive2.asp?arcid=7809

7.2.4 Environmental risks from open field production

Open field production in PM farming is of concern because of potential effects on non-target organisms and the environment, including the soil fauna and flora. In this area a tremendous lack of knowledge is identified, especially by environmental groups (e.g. Mayer 2003; UCS 2003; Jaffe 2004; Ober & Mertens 2007). Although a better knowledge base would be essential for sound environmental assessments, there is too little research going on (Ober & Mertens 2007).

Even in case of strictly confined fields, pollinators and herbivorous insects will frequent these fields just like microbes and animals present in the soil (UCS 2003). With genes expressing pharmacologically active substances introgression into wild types via pollen is considered a particular problem (Mayer 2003; UCS 2003; Jaffe 2004). The GM crop itself may also become a weed being toxic in the ecosystem.

This does not imply a call from all critical groups for a ban on all open field production. Some groups, however, content that environmental impacts will dependent very much on the particular characteristics of both the crop and the novel protein involved (stakeholder interviews; Huot 2003; Jaffe 2003; 2006; Mayer 2003; IAPO 2005; Ober & Mertens 2007). If a strict regulatory system would be in place non-food crops will be considered acceptable also by some groups (e.g. UCS 2006b).

7.2.5 Economic aspects

Farmers, millers, processors, and retailers in the food and feed industry have expressed concerns about possible adverse economic effects on their products and markets in case of accidental contamination of the food/feed supply chain (NAMA 2002, 2003a, 2003b; UCS 2006b). Such concerns relate for example to the potential contamination of neighbouring fields with genetic material from GM industrial or pharm crops, which might damage the quality and value of food/feed crops that are grown there. Especially alternative and organic farming groups but also some conventional farmer groups, such as the US Rice Growers Association,[35] publicly oppose field cultivation of PMP. The liability and insurance issue to cover damages from PMIs and PMPs contamination is still unresolved since GM crops are among the riskiest of all possible insurance exposures (Freese & Caplan 2006). Critics argue that if insurance companies are increasingly reluctant to insure even "garden-variety" GM crops, then their disinclination to cover companies whose operations threaten to put drugs and industrial chemicals in the food supply may be still greater (ibid).

According to some critics benefits would not necessarily be harnessed by farmers or by consumers, as pretended by proponents of GM farming (stakeholder interviews, Greenpeace[36], Huot 2003; Mayer 2003; IAPO 2005; Freese 2006; Wisner 2005). The required acreage for PM farming (at least for PMPs and PMVs) is very small compared to commodity crops and only a small number of growers could potentially benefit. Moreover market forces will drive farmers' compensation down and it is not clear if the farmers investments will pay off (Huot 2003). Besides uncertain gains growers of food and feed version of pharma and industrial crops could be put at risk because of the potential for contamination of conventional products (Wisner 2005).

Is the regulatory context appropriate?

Regulatory measures proposed are often seen as insufficient to guarantee food safety and protection of the environment. Many stakeholder groups criticise a lack of clear standards for PM farming by which the industry and growers would be expected to operate (Andow et al. 2004;

35 They stopped field trials in corn in Colorado in 2003, and rice in California in 2004, and in Missouri in 2005.

36 E. g. press release Ottawa Citizen 29.4.2007 available at http://www.gmwatch.org/archive2.asp?arcid=7809.

Mayer 2003; Freese 2004; UCS 2006a, 2006b). The Canadian Option Consommateurs (Huot 2003) point to deficits in PM farming guidelines for confinement, the review of applications and monitoring of field trials, and the lack of public information. Transparent regulation is considered to be another important factor to gain more acceptance for PM farming by GM critical groups. An independent scientific committee should advise the regulators on appropriate containment measures (UCS 2003) and review field trail applications (Huot 2003). Such an advisory committee should also include representatives from academia, the food and bio-farming industries, consumer and environmental organisations, and organic and conventional commodity crop grower groups.

According to Union of Concerned Scientists (UCS) only substantial modifications to the current mixed grain production system of the major food crops and the regulatory context would avoid contamination of the food and feed chain (UCS 2006b), e. g. to eliminate as many steps as possible in seed development, seed production, crop production and handling, storage, and delivery operations. A virtually zero contamination system might only be achieved by a collaboration between industry, academia and regulatory bodies. An appropriate management and oversight system would be necessary, which involves reproducibility in the production process, predetermined performance standards, documentation and auditing, and associated biological confinement, and – again – third-party monitoring. UCS doubts, that authorities could establish, monitor, and ensure regulatory oversight and control of such a complex system.

The US food industry[37] has been less vocal but nevertheless influential. The Grocery Manufacturers of America (GMA) have exerted considerable pressure on the USDA and FDA to tighten their regulatory framework for PM farming, demanding strict confinement measures and to support the use of non-food crops to protect the food supply from any contamination by PM farming (GMA 2002, 2003a). Proposed changes by the USDA in 2003 were considered insufficient and the pressure towards non food crops was increased. "There should be a presumption against the use of food/feed crops for pharmaceuticals unless the company developing the drug product clearly demonstrates that it is not feasible to use non-food crops." (GMA 2003b). In 2007 GMA/FPA[38] reiterated their disapproval of food or feed crops due to concerns about negative impacts on food safety, on domestic and international markets for food crops, and on the integrity of the wider food despite tightening of the regulatory framework by USDA and FDA. If food crops , however, are used for PM farming, a food safety evaluation by the FDA prior to issuing a permit should be required (GMA 2007). Accordingly, food or feed crops should not be used unless "reliable management measures are implemented".

The Canadian competent authority CIAA would like to see the risks of adventitious presence in the food/feed chain to be addressed by the regulatory framework. The CIAA anticipates the need to develop a regulatory framework as these crops are not aiming at food or feed use and would consequently not be evaluated under the GM food and feed regulation. The CIAA aims at improving transparency and communication between the PM farming, the food and feed industry, and the regulators. Therefore it calls for an intensive dialogue between all relevant stakeholders. Beyond the issues mentioned above the nature of the risk assessment for PM farming and the measures to protect the food/feed chain would be most important (stakeholder interview).

37 In contrast to the US the EU food industry has not hold or participated in any stakeholder discussions in the EU.

38 In 2007 the Grocery Manufacturers Association (GMA) and the Food Products Association (FPA) merged to become GMA/FPA.

7.2.6 Summary

North American stakeholder groups have been active on PM farming since early 2000. In the USA a coalition of public interest groups (environmental, consumer, food safety, and other), some conventional farmer's associations, the food industry, and regional groups are campaigning against PM farming. PM farming developers are supported by some farmer's organisations as well as patients groups.

Concerns raised by opponents focus on accidental contamination of the food/feed supply, resulting health risks for consumers and economic risks for food/feed producers and the inadequacy of the regulatory system. The use of food/feed crops in open field production is therefore the key point in the debate. While opponents have been very active, patients groups have not been very vocal so far.

In the EU there is still little awareness among stakeholders with activities essentially limited to France and recently started in Germany. Public interest groups and in France, some farmer's associations, and patients groups became active when confronted with PM farming field trials. So far, there is little or no visible activity from organisations active at EU level including major environmental and consumer organisations, farmer's organisations and the food industry. Internally some organisations have started to discuss the issue. Concerns and objections are essentially similar to those raised by their counterparts in the USA and Canada.

8 Impacts on innovation and company strategies

The challenges described above appear to impact both companies business strategies and the focus of innovation. Important changes identified include a shift away from major food crops and/or open field production to greenhouse and more contained systems, a stronger focus of technological innovation on downstream processing, and a broadening of the product portfolio and targeting of lower profile PMPs. Also apparent are increased interests in biosimilars and orphan drugs.

8.1 Shift to non-food crops and contained production

Comparing R&D activities at present and a couple of years ago reveals a remarkable shift from food crops and open field cultivation to non-food crops or minor food crops and greenhouse or other contained systems. As illustrated in Table 3 (p. 23) the number of field trials with major food crops went down since 2003, in particular field trials in maize which was (and still is by some) considered to be the most valuable production platform for PM farming before. Most companies that focussed on food crops and/or open field cultivation meanwhile shut down business, for instance Large Scale Biology and ProdiGene. Meristem shifted from maize as their major production platform to tobacco (with the exception of its flagship product gastric lipase). Monsanto (maize) and Syngenta (safflower) decided to discontinue their PM farming business.

Very few companies are still aiming at open field production using major food crops, for instance Ventria (rice). SemBioSys is proceeding its development with safflower, which is a minor food crop, cultivated on a small acreage in California only. Recent company acquisitions also suggest that there is an increased interest in contained systems: The US company Biolex acquired France-based LemnaGene (duckweed), Bayer acquired the German company Icon Genetics (transient expression in tobacco in greenhouses). This shift essentially is a reaction to the range of problems faced: the campaigning of the US coalition of food industry, farmer's associations and public interest groups against food crops and open field cultivation in PM farming, the liability threats in case of contamination of the food/feed supply, the emerging complex regulatory regime from USDA and FDA. Perhaps also important it became evident that biopharmaceutical product authorisation would face less problems if the production environment will be better controlled compared to an open field system. Furthermore, model calculations for a PMV resulted in greenhouse production costs being in the same range or even cheaper than open field production (ProVacs 2006). Although it would be difficult to generalise this points to the fact that the range of PM farming products that might be feasibly produced in greenhouses might be broader than initially considered thought. Furthermore, at least in the EU even the biotechnology industry seems to be more prone to contained systems (company interview).

This analysis is not true for all areas of PMPs and definitely not for PMIs. The recently established company Novoplant (Germany), for instance, is developing antibodies against pig diseases that are intended to be used as feed additives. And BASF is aiming to produce their food supplements and additives in rape and other food crops. A couple of other PM farming companies are also targeting feed additives or food supplements (see Section 8.2). The economics of producing a food supplement or feed additive might drive developers into food and feed crops which would allow applying a product with little or even no purification and processing. Open field cultivation would be important for the scale

and overall production costs. Targeting products other than high-price PMPs would therefore maintain economic pressures to go for food/feed crops and open field production.

8.2 Targeting non-pharma and lower profile PMPs

Until early 2000 many small PM farming companies were aiming to develop new blockbusters, novel types of biopharmaceuticals or targeting novel indications to put their technology platform to market stage. This type of business strategy would be successful if either the proprietary technology platform or the flagship products become attractive for collaboration with or even be acquired by a large biotechnology or pharmaceutical company. A more SME type of business strategy aims at bringing own products to market stage. So far these strategies seem to pay off for a very few companies only. Given the challenges to reach market stage described above and the reluctance of large pharmaceutical companies to adopt the technology PM farming developers are facing serious financial problems to continue with advanced stage clinical trials.

Non-pharma products and nutraceuticals

Therefore, small companies in the field of PMPs started to broaden their product range in order to put their technology to commercial stage and create short-term cash flow. While still pursuing their technology and PMP development they are also targeting food supplements, as well as feed and food additives. This strategy is not entirely new (ProdiGene commercialised some of their PMPs as research chemicals for diagnostics or other technical purposes; see Table 7), developers are, however, paying much more attention to this option.

Ventria (USA), Cobento (Denmark), SemBioSys (Canada), and Maltagen (both Germany) are targeting the markets for food supplements, food additives or feed additives (company interviews). ProdiGene (more precisely Stine Seeds which acquired IPRs held by ProdiGene) and recently Meristem (France) are marketing products as research and technical grade chemicals.

Requirements for and time frame to market authorisations for these type of products are much lower compared to biopharmaceuticals and vaccines and even non-existing in some countries.

The economic potential of PM farming for these kind of products is difficult to estimate. According to interviewees PM farming is unlikely to successfully compete with microbial fermentation to produce purified food and feed enzymes at relatively large scales. This is also true for food supplements. Proteinic food supplements are in many cases enzymes (capturing a 5% share or about 40 million US$ of the total food enzyme production[39]). More likely high-value niche products as those described in Sections 4.5 and 5.11 will be targeted.

Veterinary vaccines and antibodies

Other developers are targeting antibodies and vaccines for preventing diseases in livestock, e.g. Novoplant (Germany), Dow AgroSciences (USA). Biolex (USA) recently announced a collaboration with one of the biggest vaccine producer, Myriel, on developing animal vaccines (Biolex 2007)) anticipating lower regulatory barriers for market entry.

The production of PMPs for veterinary use has sparked an increasing number of academic and commercial R&D activities. A recent review by Floss et al. (2007) lists 67 scientific studies on vaccines and antibodies for veterinary use. Box 1 provides economic figures characterising the animal health market.

39 Based on figures provided in BCC Research (2004)and Zika et al. (2007).

Box 1: Market size of animal health products

In 2004 the world animal health market was worth US$$ 13.7 billion with the EU and North America capturing a similar proportion of 34% and 34% resp. The total animal health market represents about 2.5% of the world human pharmaceutical market.

The world market is divided between products for livestock and pet care products, with the latter having an approximately 40% share. Pressure on production costs is higher in the segment of livestock products. Medicinal feed additives are capturing 13%, biologicals 23% of the total market. The global share of animal vaccines has been estimated at 2.6 billion € (about 20% of total animal health products), with an EU share of 50%. 8 of the top 16 veterinary pharmaceutical companies are located in the EU.

Modern biotechnology is used in the development and production of vaccines and antibiotics. Recombinant animal vaccines have been more quickly adopted compared to human vaccines: 75% of the animal vaccines approved by EMEA between 1996 and 2006 are recombinant products while the proportion of recombinant human vaccines is estimated to be 20%.

It costs up to 50 million € to bring a new animal health product to the market.

Sources: Company interviews; IFAH (2005); Zika et al. (2007).

Vaccines in general do not need to be purified to the same extent as pharmaceuticals although the requirements differ between the USA and the EU. As animal diseases are a major concern to livestock there is also a strong demand for corresponding vaccines. This can be explained by the fact that producers are running economic risks if they do not vaccinate. Recent scares from zoonosis such as bird flu increased interest in veterinary vaccines further.

PMVs for veterinary use are considered by some to be more promising business goals compared to PMPs for human use (Streatfield 2005b; company interview).

- Simplified regulatory procedure compared to human vaccines, which also translates into shorter times to market (3 to 5 years compared to 5 to 10 years).

- Regulatory authorities might be more open to new production platforms compared to human vaccines.

- The lower costs and shorter timeframes of vaccine development lower the risk of taking vaccine candidates through later stages of the regulatory procedure, which makes them attractive for small companies.

- Major animal health companies are showing interest in PMV for animals, e.g. Dow Agro Sciences, Boehringer Ingelheim, and Myriel.

Furthermore, there might be some additional drivers that focus R&D on PMVs for veterinary use (company interview):

- The increasing reluctance in many countries –and the ban in the EU from 2006 onwards– to use antibiotics for the prevention of diseases, and the raise of organic farming which does not allow for antibiotics as feed additives at all.

- Global pandemic threats especially if disease can be transmitted by farm animals such as avian flue, will change the attitude towards vaccination and get companies

and governments interested in vaccine development.

In fact, the first PMP to win regulatory approval from the USDA was a tobacco cell culture-derived vaccine against the Newcastle Disease Virus, in early 2006 (Dow 2006).[40] According to self portrayal, Dow has established plant-cell culture as a cost effective alternative production platform and Dow is determined to apply for market authorisation in the EU as well. Other companies with veterinary vaccines or antibodies in the pipeline include Dow, Boehringer Ingelheim (via collaboration), and SemiBioSys.

In the development of vaccines oral administration is considered an ultimate goal as it would greatly facilitate vaccination and thereby save labour costs. For this reason, oral vaccines are especially preferred in case of poultry and fish. For veterinary vaccines the original concept of edible vaccines as administering unprocessed plant kernels or only slightly processed plant tissue (fruits, leaves) to the animals is still maintained by some developers. Certainly, the inherent problems of edible vaccines for animal use are the same as for human use: how to administer appropriate and controlled doses if protein concentration differs between plants and kernels. On the other hand edible vaccines might be more realistic for animals as the diet of animal is much better controlled. More importantly, orally administered PMVs can still be cost effective even if they are not fully efficacious. According to Streatfield (2005a) "partial protection leading to decreased levels of mortality and morbidity and an increase rate of weight gain across herds should be a sufficient economic driver to stimulate uptake of this technology."

Whether at all – and to what extent – oral vaccination might work is entirely dependent on the particular disease, type of protein, formulation, etc. In cases it does work purification costs are significantly reduced. Despite the fact that veterinary vaccines are already considered to be cheap in production, compared to human vaccines, this would bring back cost savings as an additional driver for the development of PMVs: the concept of edible PMVs for veterinary purposes and stronger economic pressure (compared to human vaccines) to lower the costs for vaccines might be a strong incentive to go ahead with feed crops such as maize and peas.

Technical challenges include improvements for oral immunisation and shortening the time to market. The latter aspect in particular poses limitation to the application of PMV to diseases with new viral strains frequently occurring (Streatfield 2005a).

An interesting concept might also be the use of orally administered antibodies for prevention and treatment of gastro-intestinal) disorders in production animals. Novoplant (Germany) is developing an antibody against E.coli directed against a surface antigen of enterotoxigenic E. coli to prevent E. coli infections in post-weaning piglets. The antibody is expressed in field peas which would be added to animal diets without significant processing. This technology targets indications where vaccination and the use of therapeutic antibiotics is difficult or impossible, e.g. in broiler and post-weaning piglets.

Biosimilars

Targeting biosimilar drugs (follow-on biologics) are another option to reduce costs and time in the regulatory procedure. Biosimilars are generic equivalents of biopharmaceuticals which are no longer protected by patents. Of particular interests are biopharmaceuticals with high turnover and big margins and a low proportion of production costs.

40 This particular case, however, only served as a proof of principle and was never intended to be commercialised (company interview).

Two of the most advanced PMPs for human application are biosimilars: PMPs, glucocerebrosidase, and insulin are about to enter Phase 3 clinical trials. Other developers targeting biosimilars are Medicago and Large Scale Biology Corporation, now Kentucky BioProcessing (both developing aprotinin). Potentially interesting candidates are epoetin alpha, insulin, interferon alpha, and monoclonal antibodies (Spök & Klade 2005).

As most biopharmaceuticals are more complex molecules produced from microbes or cell culture, the establishment of a generic status is much more difficult. Minor changes in the production process can lead to structural and functional changes of the active substance or of by-products which might have a bearing on efficacy and safety. The EU established the world-wide first regulatory pathway to authorise biosimilars, Directive 2004/27/EC (EPC 2004), while the discussion is still ongoing in the USA and at the FDA. In 2006 the first two biosimilars were authorised in the EU. Given the pending regulation in the USA and the still ongoing discussions in the EU (e.g. Aldridge et al. 2007), the details of the regulatory requirements for biosimilars are still not sorted out. Nevertheless, aiming at a biopharmaceutical with a well established indication and history of successful treatment reduces market risks, especially if compared to new indications or new type of biopharmaceuticals. The possible market size might be huge as close to 20 billion US$ in biotech product sales will go out of patent and therefore be vulnerable to biogeneric competition over the next 8-10 years (Herrera 2004). It would, however, depend on the regulatory barriers to market entry and on technology acceptance whether PMPs will be able to capture a significant share of the biosimilar market.

Orphan drugs

Another possible strategy to reduce costs for market authorisation is to target orphan drugs. An orphan drug status is designed to encourage the development of drugs for rare diseases – some of which are serious and life-threatening – but would be prohibitively expensive/un-profitable to develop under normal circumstances. Many industrialised countries established incentives to invest into the development of therapeutics and vaccines for diseases that have lower prevalence and are therefore less interesting for the commercial product development. In the EU incentives for investors include exclusive marketing for 10 years, financial support for R&D and the authorisation procedure, free support and advice during compilation of dossiers as well as fee waivers. Examples of PMPs are the gastric lipase of Meristem Therapeutics for treating cystic fibroses (EMEA orphan drug status in 2003), the glucocerebrosidase (Protalix) treating Gaucher Disease and the ß-galactosidase A against Fabry disease of Large Scale Biology Corp (FDA orphan drug status from the FDA in 2003) (Spök & Klade 2005).

Besides fee waivers and exclusive market rights another advantage of developing orphan drugs could be the small number of patients, e.g. in case of Fabry Disease there are only about 1,200 patients in the EU. Thus, the normally large and expensive clinical trials of Phase 3 can be conducted on very small groups of patience only. A similar case is the glucocerebrosidase (EU: 27,500 patients). After completion of Phase 1 the FDA decided to waive Phase 2 trials (perhaps partly because another glucocerebrosidase is already authorised and commercially available (marketed as Genzyme produced from mammalian cell culture).[41] Moreover, Phase 3 trials will be limited to 30 patients (Almon 2007).

8.3 Focussing downstream

Earlier optimistic accounts of PM farming developers seem to have ignored the importance

41 FDA has not yet introduced a policy for biosimilars. However, requirements for clinical trails might already be influenced in such cases.

of downstream processing capturing up to 80% of total production costs (see Section 5.2). Furthermore, downstream purification of proteins from green tissue seems to be more challenging than initially expected (see Section 6.1.2).

Developers are therefore aiming not only to establish their own tailor-made downstream processing but also to innovate the purification process by providing novel technical solutions that would offer speed and cost advantages. Hence, technological platforms which offer purification advantages as part of the technology design seem to be of particular interest.

For instance, SemBioSys (USA) is targeting its proteins into oilbodies of safflower seeds, which can be easily extracted and offers savings in downstream purification. According to company calculations the technology would allow for a total reduction (up- and downstream processing) of capital costs up to 70% and of costs of goods by about 40% compared to mammalian cell lines (company interview; SemBioSys 2007).

Another example is the system used by Greenovation (Germany). Maximum yields presently reached in a moss bioreactor are about 30 mg/l/day which seems to be quite low compared to other PM farming systems and mammalian cell culture. Target proteins, however, can be secreted into the medium which only contains very few other moss proteins at low concentrations. Starting with such fairly pure crude protein extracts allows for a simplified downstream purification procedure which is anticipated to result in overall cost savings of 50% (company interview).

8.4 Summary

The challenges for PM farming described above appear to impact company strategies and the innovation process.

First, within a few years, there has been a striking shift in R&D activities for producing PMPs from major food crops and open field production to non-food crops and/or more contained systems. Greenhouses and more contained systems such as moss, Lemna, algae, and plant-cell culture are attracting more attention. Only one US company is still developing its product, rice, while the only EU company active in maize hast shifted all its product to tobacco and greenhouse production. On the other hand the increased interest in non-pharma products and the production of PMIs in general seem to renew the interest for open field production, especially for economic reasons.

Second, the focus of PM farming developers has been shifting from blockbuster type drugs, novel type drugs, and novel indications to more secure targets. Developers are broadening their product portfolio to include non-pharma products, nutraceuticals (to be used as food supplements, feed additives, and fine chemicals), and lower profile PMPs such as veterinary vaccines and antibodies, biosimilars (i. e. pharmaceutical generics), and orphan drugs. Targeting the former type of products reduces time and costs to market and can put the technology to work for a commercial product. The latter category of products is attractive because of lower costs for the clinical trials and the regulatory procedure.

Third, improvements and innovations in downstream processing have become more important. Therefore, some companies which not only offering a proprietary plant production platform but also innovative and cost-saving downstream processing solutions seem to have a competitive advantage, for instance the oilbody based system in safflower and the secreted proteins in moss bioreactors.

9 Overall conclusions

This Chapter summarises key aspects discussed in the preceding part of the report and draws general conclusions for points to consider in further policy development.

9.1 Techno-economic potential of PM farming

The analyses in the preceding Chapters suggest possible techno-economic and safety advantages of PM farming over presently used methods for production of biopharmaceuticals. It also suggest that the full economic potential of PMPs will rather unfold with particular novel type drugs needed in high amounts, for instance certain antibodies, as well as biopharmaceuticals and vaccines administered via non-parenteral routes, especially oral administration. For the type of biopharmaceuticals presently on the market PM farming application might be limited to specific niche products. In the long run the picture might change, however. Speed advantages to full-scale production could, for instance, create a demand for PMVs, and cost pressure from public health systems or global competition might favour PMPs.

The analysis, however ,points to a range of associated uncertainties that must be clarified and a number of challenges that must be tackled before the potential of PM farming will become clear. Challenges of a techno-economic nature are significant but might be solved as the technology is being further developed, e.g. downstream processing and humanization of plant-made carbohydrate structures, or improving drug delivery via non-parenteral routes. Regulatory and policy challenges might be more difficult if open field cultivation and/or food/feed crops are envisaged. As a matter of fact the timeline is very difficult to anticipate.

The application of PM farming to produce food supplements, food and feed additives has only recently emerged and its potential is still unclear. Unlike PMPs, this substances are intended for regular/long-term consumption in food/feed and will not necessarily require high levels of purity if produced in food/feed crops. Unlike PMPs, and with the possible exception of certain high-value food supplements, the economic pressure towards open field production using food/feed crops might be very high.

9.2 Relative position in PM farming of the EU

A range of indicators show a dominant position of the USA in advanced stage commercial R&D for PMP development. For earlier stage R&D, the differences between the EU and the USA are much less striking and in case of publicly funded R&D there seems to be little difference. EU researchers and entrepreneurs have apparently started at a later stage, compared to their North American colleagues to exploit the technology for commercial purposes, but European R&D has evolved in a dynamic way over the recent years.

With respect to PMIs that are targeting food/feed application, there is generally much less activity and fewer products developed compared to PMPs. Similar to PMPs the USA has a dominant position in PMIs.

9.3 Links to EU policy arenas

PM farming is linked to several EU policy arenas. The Lisbon European council set the overall policy goals for the EU's socio economic development (EC 2002). The Sustainable Development Strategy (SDS) complemented and

strengthened the environmental dimension of the Lisbon Strategy (EC 2001). Biotechnology has been generally concluded to contribute to the aims of the Lisbon Agenda. (Zika et al. 2007).

Following advice from its Technology Platforms (e.g. Plants for the Future 2004, 2005, 2007) the European Commission is presently implementing the Lisbon and SDS agenda by setting a particular focus on the exploitation of crops for non-food purposes, including PM farming in the course of its 7th Framework Programme (e.g. CEC 2007a). Thereby PM farming is linked to the policy arenas of renewables, greening of industry or generally to sustainable development. This frequently includes, for instance, the substitution of traditional chemical processes by more environmentally sound biotechnological processes. This is perhaps less relevant for the production of proteins that are used as PMPs and PMIs, as these substances are already produced by the help of industrial biotechnology. If envisaging large scale production of non-proteinic PMIs, to substitute a chemical production, a different picture might emerge improving both efficiency and competitiveness as well as sustainability.[42]

The potential environmental advantages arising from such improvements might, however, conflict with environmental and health risks associated with open field production of GM crops. In case of using food crops for PM farming there might be even economic risks involved. In that sense PM farming would find itself located at the crossroads of two debates: the risk debate on agricultural biotechnology and the sustainability debate. Some ten years ago a similar but less controversial, 'crossroad' issue, the production of enzymes from genetically modified microorganisms triggered a major conflict in the German Green Party (reviewed in Spök et al 1992) and led to a difficult debate about how to value factual environmental benefits vs. hypothetical risks. In contrast to enzymes, which are produced by GM microbes in contained systems the PM farming issue would be certainly of much higher profile.

PM farming is also linked to agricultural problems and the reform of the Common Agricultural Policy (CAP) in the EU. In the USA some rural states where cropland is abundant and jobs are rare anticipate that PM farming will generate economic benefits to rural economies. In the EU, which is struggling with heavily subsidised agricultural production, industrial crops are considered as an interesting option to diversify European agriculture. In that context PM farming has been explicitly welcomed by some commentators (e.g. APA 2005). Individual farmers who – in some Member States – are receiving compensations for not cultivating parts of their land might be tempted to explore other agricultural products, especially if these products would promise a higher added value. As this analysis suggests, a higher added value from pharm crops might, however, be restricted to a few contract farmers. GM crops for PMIs that would be grown on a larger scale might in fact provide an interesting alternative though, if the problems of coexistence, confinement and adventitious presence in food/feed products can be solved.

9.4 A possible scenario for PM farming commercialisation

In the first phase commercial and public sector R&D activities in PM farming centred in North America. The first generation of PM farming frequently aimed at open field production using major food crops and proceeded for a while in an innovation friendly environment with little public resistance. Venture capital was readily available for attracting academics to business making.

The first incidents of inadvertent admixture of conventional food crops with GM crops,

42 Hypothetical case for PMIs used in food and feed. A more conclusive example might be bioplastics from GM plants.

including in one case PM farming, were followed by huge economic damages from compensation payments. This eventually led a coalition of public interest groups, certain farmers associations, and the food industry to campaign for stricter rules and against open field production in PM farming. Since then, numerous reports, statements, and public consultations made clear that this kind of PM farming is eventually linked to a number of complex regulatory and economic problems. Subsequent cases of inadvertent admixture with first generation GM crops – partly from field trials – have been fuelling the debate ever since. US and Canadian regulatory authorities have tried to alleviate the problem by proposing strict regulations. Canadian regulators also discouraged the use of major food crops in the open field without prohibiting their use, though. The contamination incidents and the subsequent pressure from a powerful stakeholder coalition caused a dramatic backlash to the US PM farming sector. Nevertheless, continuous attempts of PM farming promoters to maintain optimistic scenarios and high expectations, for instance, let The "global growth consulting company" Frost & Sullivan in their 2004 report anticipate the PM farming industry to flourish into a 800 million US$ business by 2009 (Webster 2005). Yet, this seems a very unlikely scenario.

In contrast to North America, PM farming has hardly been recognised as an issue by EU stakeholder groups and has not yet made it to their official EU agendas. This difference between the EU and the USA can partly be attributed to the fact that for a long time field trials with pharm crops were essentially limited to France. European PM farming developers have pursued R&D either in contained facilities or conduced their field trials and biomass production – partly or completely – outside the EU. PM farming was therefore hardly 'visible' at all. The EU food industry has never experienced a StarLink-type crisis and EU public interest groups are still preoccupied with first generation GM crops.

Meanwhile, developers on both sides of the Atlantic have become increasingly aware that besides the resistance encountered in the USA open field production of PMPs also brings about uncertainties for market authorisation of PMPs. This adds a big question mark to the estimated huge savings in production costs that were a key driver of this technology's initial development. The prevailing uncertainties and little demand have so far discouraged large multinationals, especially the pharmaceutical industry, to invest into this technology. This has aggravated the problem of late-stage financing gaps in PM farming companies. PM farming developers find it increasingly difficult to proceed into the very costly late stage clinical trials. This has led to a still ongoing market consolidation which dramatically reduced the number of companies aiming at PM farming production in the open field using major food crops. PM farming developers reluctantly acknowledge that innovation in the biopharmaceutical industry needs the acceptance of the regulators and one or more successful examples and therefore may take a longer time to materialize. For example, in the case of insect cells, which have been developed as an alternative production platform to mammalian cell lines it took 24 years from the first scientific publication to have the first commercial product on the market.

This context provides advantage to companies targeting lower-profile biopharmaceuticals and vaccines, the development of which would be less capital intensive and face fewer business risks. In order to generate short-term cash-flow, some PM farming companies started to diversify into non-pharma products.

This brief review sets the scene for the next steps of PM farming development. Open field production of PMPs using major food crops is *the* key concern coming up from stakeholder and public perception studies. Open field production also seems to be a key obstacle for clearing the regulatory pathway and subsequently getting adopted by large multinationals. For these

reasons it appears that a majority of PM farming developers are shelfing the idea of food crops and/or open field production for the moment – at least for PMPs and high-value PMIs.

Given this context, the first commercial PMPs will rather be less spectacular products, biosimilars, orphan drugs, and nutraceuticals, that will be manufactured from non-food crops and/or in greenhouses or in even more contained systems. PM farming might also occupy a niche for proteins difficult to express in other systems. As long as production remains in containment it may not even come to the attention of stakeholder groups. The use of non-food or minor-food crops in the open field, while alleviating some concerns though, will likely capture the attention of stakeholder groups and spark debate. In the latter case, as suggested by public perception studies, perception and eventual acceptance will depend on the particulars of the risk-benefit equation and the trust into the regulatory regime.

While PMPs, PMVs for human use and some high-price PMIs could be produced in greenhouses or by other contained PM farming platforms and still pay off, the production of lower-price veterinary PMPs and PMVs as well as PMIs only becomes profitable if open field cultivation using food/feed crops is possible. In the latter case, the enticing idea is to save on both upstream and downstream process because high-level purity is neither needed nor a safety or quality issue.

A renewed interest for open field production could also come from a demand for much larger tonnages of certain biopharmaceuticals and vaccines. For instance, oral vaccines, antibodies administered to the skin, as well as inhaled insulin would require higher dosages because of a lower frequency in uptake. In case of substantial advancements in oral administration of biopharmaceuticals or oral immunisation PM farming could be an enabling technology.

Whether and when the pharmaceutical industry might revisit the idea of producing lower-volume biopharmaceuticals by PM farming, or even switch production from presently established systems to PM farming depends on various aspects. The first successful PMPs or PMVs from greenhouse or contained production might encourage such revaluations, as would pressure on drug prices from public health systems and global competition. For certain human vaccines against pandemic diseases the speed advantages of PM farming might also be of interest.

As developments timelines for PMIs are much shorter compared to PMPs it so appears that in the near future visible PM farming activities on European fields will rather be crops producing PMIs. Some of these substances will also target the food/feed chain. Some PM farming crops might be developed for two purposes at the same time, for processing into functional food or alternatively, for purification of particular substances that can then be marketed separately, e.g. in case of omega-3 and omega-6 fatty acids.

With these substances the framing might be important for stakeholder and the wider public perception whether such crops would be framed as functional food crops providing health benefits or as industrial production facilities for substances. Food supplements or feed additives with pharmacological properties might raise similar concerns as PMPs, thought, as indicated by the US debate on Ventria's lactoferrin and lysozyme rice.

Against the backdrop of the US debate on PM farming and the reluctance of EU publics and stakeholder groups to adopt agricultural biotechnology, developers still aiming at open field production in food/feed crops might consider to move production outside of the EU, e.g. to the USA and Canada if eventually the regulatory pathway there becomes clear, or to other countries such as Chile. This might be appealing to some because it seems to avoid yet

another complex EU policy problem. Eventually however, this could have unfavourable impacts: following relocation not only field production but also downstream processing operations might be moved too and might therefore not contribute to the EU's economic goals. Although in case of high-value PMPs produced in kernels it might be economically feasible to move upstream production while maintaining downstream processing in the EU.

The relocation of open field production to third countries could be even more troublesome for another reason, though. Assuming a lower level of regulatory oversight and enforcement in the host countries, food and feed exports to the EU would 'import' the problem of potential contamination and thresholds for PM farming. The possibility of adventitious low-levels presence of material from PM farming in food/feed products also applies in case of significant PM farming activities in other industrialised countries which are food/feed exporters into the EU. Long-term field trials and increasing acreages over time which are both necessary in PMP development might also pose contamination risks.

Despite a longer timeline for commercialisation in the EU of PM farming than expected an analysis three years ago (Spök & Klade 2005) the scenario described above and the associated prospects and concerns will inevitably lead to a broader discussion. Given the sensitivity of agricultural biotechnology in the EU it might therefore be wise to proactively approach these challenges.

9.5 Issues for further consideration by policy makers

As mentioned at the beginning of the Chapter there is still prevailing uncertainty about the techno-economic potential of PM farming, which is also mirrored by the reluctance of the pharmaceutical industry to adopt the technology. It is, therefore, very difficult at present stage, to include a sound quantitative analysis, e.g. anticipate potential market sizes, employment figures, effects on prices, land use/surface requirements etc. These aspects and the nature and extent of the costs and benefits for society as a whole will definitely dependent on the future development of PM farming. Given the complexities described in this report, this future development can have many different faces, depending e.g. on policy decisions on the use of food/feed crops and open-field cultivation as well as the regulatory burden to industry, developments in human and animal health care etc. At present, however, commercial development of PM faming is still in an early and perhaps in a critical stage as the most relevant markets targeted did not yet accept the technology and policy frameworks for PM faming are mostly absent or pending.

Overall though, the potential benefits of PM farming suggest to carefully proceed with and actively explore PM farming and its possible impacts on human health, society and the environment.

From the analyses in this report a number of issues can be identified that should be further considered by policy makers at the European Commission and the national level. Given the extensive discussions in the preceding Chapters and the limited scope of the Report, these issues are listed as bullet points without repeating points from previous Chapters. These issues are interlinked but can be listed under three headings:

Participatory development of a policy framework

- **Awareness raising**: awareness is a precondition for a informed debate. As there is little awareness among stakeholder and the general public: proactive awareness raising might be considered by policymakers, stakeholder groups and the PM farming developers

- **Meet your constituency**: research into public perception of PM farming and public consultations could help to identify key issues and develop socially robust strategies
- **Open debate**: EU level discussions on PM farming are presently being held behind closed doors. The proactive launch of an open debate would be helpful to avoid distrust and suspicion from stakeholder.
- **Informing the debate:** encouraging research into possible environmental and health impacts of PM farming, as well as economic impacts.
- **Policy framework**: as can be learned from Canada and the USA, developing an overall policy framework which would clarify key aspects (open field production, food crops, liability rules, threshold limits in food/feed, need to adopt the GM crop regulatory regime (Directive 2001/18/EC, coexistence etc.) and include stakeholder consultations does take time and should therefore be started soon. The policy framework should in particular allow handling of large-scale cultivation for bulk PMIs as well as small-scale cultivation of high-value products.
- Watch the neighbours: comparative policy studies could fed into the process experiences and strategies developed in other jurisdictions
- **International level:** PM farming related regulations, minimal standards should be discussed and agreed on international level, e.g. Cartagena Protocol, Codex Alimentarius Commission to avoid a bargaining in terms of health, environmental and economic risks

Improving knowledge base/exploring and securing technological options

- **Non-food plants:** research to improve the knowledge base on the suitability of non-food crops in general as well as on the biology, agronomy and ecology of potential non-food candidate plants. The superior knowledge base on major food crops has frequently been raised as an argument why these crops should be preferred for PM farming. The only way to counter this argument is to seriously evaluate a broader range of non-food crops and to improve the knowledge base on these crops.
- **Contained production systems:** research could clarify in more detail the economics and technical advantages and limitations of contained systems including greenhouses. Research could also help to explorer and advance a broader range of contained production systems to bring them closer to commercial application.
- **Confinement systems, assessment methods**: research could explore and further improve molecular and organisational confinement systems for open field production as well as approaches and methods to routinely assesses and monitor confinement measures.

Possible gaps in funding schemes

- **Financing gap for PM farming companies**: the continuing reluctance of large pharmaceutical and biotechnology companies to invest into the area pose serious problems to start-up and SME type companies in the PM farming sector. Strategies to alleviate this problem should be considered, e.g. clearing the regulatory pathway by taking one product through the entire regulatory procedure.
- **Public sector research in PM farming**: fee waivers and other kind of support should be considered for enabling public sector PMPs through phase 1 and 2 clinical trials.

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Table 14: PM farming developers and selected public research organisations.

Company/Institution	Land	Description	Plant host(s)	Products/Indication	Status product development	Webpage
Agrenvec S.L.	Spain	Founded in 2001 as a spin-off from INIA (Agriculture and Food Research National Institute). Focuses on the production of recombinant proteins and peptides in a variety of host plants using viral vectors based on turnip mosaic virus	Brassica (viral expression)	N.sp.	N.sp.	http://www.agrenvec.es/eng/index.php
Agrisoma Biosciences Inc	Canada	Founded in 2001 as a spin-off from its parent company, Chromos Molecular Systems Inc., Agrisoma was established based on technology employing an artificial chromosome-based gene delivery and expression platform in plants developed by Chromos since 1996. Production of industrial and therapeutic protein.	Brassica (viral expression)	N.sp.	N.sp.	http://www.agrisoma.com/home_frames.htm
Azbio	USA	Arizona State University, BioDesign Institute, Centre for Infectious Diseases and Vaccinology. Focus on therapeutic compounds and vaccines in the leaves, fruits, grains, or storage tissue, they have been able to produce immunogenic proteins that can act as oral vaccines when ingested.	Tomato, others	Oral-administration vaccines	Phase 2 clinical trials with plant-derived vaccines against hepatitis B, enterotoxigenic E. coli, and Norwalk virus.	http://www.asu.edu/
BASF	Germany	Active in developing GM crops for open field of food supplements, food and feed additives. Acquired Crop Design in 2006; established SunGene (Germany) as a joint venture with the Institute of Plant Genetics and Crop Plant Research.	Rape (Brassica napus), soybean, other	Omega 3 and omega 6 fatty acids in rape; carotinoids, amino acids, vitamins	N.sp.	http://www.corporate.basf.com/en/produkte/biotech/plantscience/pflanzenalsfabrik
Bayer	Germany	Active since 2003, acquired Icon Genetics (Germany) in 2005. Focussing on transient expression in tobacco (containment). Licence agreement with greenovation (Germany).	Tobacco (transient expression)	Antibodies, vaccines including products for veterinary application	N.sp.	http://www.bayercropscience.com
Biolex Inc.	USA	Formed in 1999, acquired Epicyte Pharmaceutical in May 2004 and LemnaGene in 2005. Focuses on the production of pharmaceutical proteins in Lemna minor (the LEX system). Operating a GMP manufacturing facility.	Lemna sp.	Locteron™ (interferon alfa) for the treatment of hepatitis C; BLX-155, thrombolytic	Phase 1 completed for Locteron™ and BLX-883 (alfa interferons)	http://www.biolex.com/

Company/Institution	Land	Description	Plant host(s)	Products/Indication	Status product development	Webpage
Ceres, Inc.	USA	Identification of possible break-through plant and plant-based products of interest to a wide variety of industries. Application of metabolic pathway engineering of medicinal plant and related species. Technology provider for protein expression in plants.	Arabidopsis	N.sp.	N.sp.	http://www.ceres-inc.com/
Chlorogen	USA	Formed in 2002. Focuses primarily on the development of generic and proprietary human therapeutic products in tobacco using chloroplast expression.	Tobacco	Human therapeutics proteins, antibodies, vaccines, biological reagents; ovarian cancer, pancreatic cancer	N.sp.	http://www.chlorogen.com/
Chromatin Inc.	USA	N.a.	Centromeres and mini-chromosome platforms for soybean, Brassica species, corn and tomato	N.sp.	N.sp.	http://www.chromatininc.com/index.php
CIGB	Cuba	N.i.	Tobacco	Antibodies, vaccines	CB Hep1, hepatatis B vaccine is the first product for human use to obtain national authorisation	http://www.cigb.edu.cu
Cobento Biotech	Denmark	Founded in 2001 by as a spin-off from the University of Aarhus and the Aarhus University Hospital; focuses on Arabidopsis and greenhouse production and aims at moving production into potato in the open field.	Arabidopsis thaliana	Human intrinsic factor transcobalamin Protein(food supplement for vitamine B12 deficiency)	Authrisation for commercial production in in greenhouse; authorisation for commerical application as food supplement in Poland	http://www.cobento.dk/
Controlled Pharming Ventures	USA	Offers a scalable, controlled environment that accelerates the development and production of value added agricultural goods on a year-round basis.	Maize tomato, tobacco, rice, barley, alfalfa and others	Contract research and manufacturing services	N.sp.	http://www.controlledpharming.com/

Company/Institution	Land	Description	Plant host(s)	Products/Indication	Status product development	Webpage
Crop Design	Belgium	Founded in 1998 as a spin-off from the Flanders Interuniversity Institute for Biotechnology. Focuses on protein expression technology in rice grains. In 2006, CropDesign was acquired by BASF Plant Science and is since then integrated in the international research network of BASF Plant Science	N.sp.	N.sp.	N.sp.	http://www.cropdesign.com/general.php
Dow AgroSciences LLC	USA	Wholly owned subsidiary of Dow Chemical Co., formerly the joint venture Dow Elanco. Has a portfolio of plant-derived antibodies and vaccines, in partnership with Epicyte and Centrocor	Plant-cells	Antibodies and vaccines: infectious diseases; auto-immune disorders; food safety and therapeutic antibodies. Targets include West-Nile Virus, Avian flue virus, and diabetes in ducks.	First PMV to obtain an USDA authorisation (for preventing Newcastle disease in chickens).	http://www.dowagro.com/homepage/index.htm
ERA Plantech,	Spain	Founded in 2001. Focuses on plant-derived proteins accumulating in the endoplasmic reticulum	N.sp.	develops and deploys the Zera® technology as a standard productivity tool for the manufacture of protein-based products for pharmaceutical, industrial, energy and health/nutrition applications.	N.sp.	http://www.erabiotech.com
Evogene Ltd,	Israel	Founded in 2002 as spin-off of Compugen. Has various technologies on offer including a molecular farming platform based on tomato trichomes for the secretion of recombinant proteins.	N.sp.	N.sp.	N.sp.	http://www.evogene.com/index.asp
Farmacule BioIndustries Ltd	Australia	Founded in 2001 as a spin-off from Queensland University of Technology. Focuses on precision gene expression in transgenic plants using the INPACT regulated expression technology .	Tobacco, banana, sugarcane	Bioplastics, vaccines, high value proteins, industrial proteins	N.sp.	http://www.farmacule.com/
Fibrogen Inc,	USA	Founded in 1995. Concentrates principally on the development of novel therapeutics for the treatment of fibrosis. Actively exploring the use of plants for the production of recombinant human collagen and related proteins.	N.sp.	N.sp.	N.sp.	http://www.fibrogen.com/
GenoMine Inc.	Korea	Founded in 2001. Focus is primarily genomic and proteomic technologies in plants, but also plant-derived vaccines. Currently developing a human papillomavirus vaccine expressed in plants.	Soybean sprouts, magnolias,	N.sp.	N.sp.	http://www.genomine.co.kr/

Company/Institution	Land	Description	Plant host(s)	Products/Indication	Status product development	Webpage
Greenovation Biotech GmbH	Germany	Founded in 1999. Focuses on the production of pharmaceutical proteins in the moss bioreactor system Physcomitrella patens	Moss	Monoclonal antibodies and other complex proteins	Early stage of development	http://www.greenovation.com/
Hayashibara Co. Ltd	Japan	At the forefront of Japanese biotechnology and marketing recombinant interferon since 1988. Now diversifying into plant-derived edible vaccines.	N.sp.	Food ingredients, pharmaceutical ingredients, functional dyes, cosmetic ingredients, health food ingredients, reagents	N.sp.	http://www.hayashibara.co.jp/english/
Icon Genetics	Germany	Incorporated in 1999 as a provider of new plant engineering technologies which address precision, speed, yield, expression control and safety of transgene management in plants. Develop new generation production platforms and product prototypes for pharmaceutical, agricultural, animal health and chemical biotech markets.	Tobacco, Nicotiana benthamiana, spinach, red beets	Viral and bacterial infections, cancer, enzyme replacement therapy, industrial enzymes, food additives. 9 product candidates including microbial and viral vaccines, antibodies, follow-on biologicals and specialty proteins	Acquired by Bayer in 2005, fully integrated in 2006.	http://www.icongenetics.com/html/home.htm
IME Frauenhofer	Germany	The Fraunhofer Institute for Molecular Biology and Applied Ecology IME conducts research in the field of applied life sciences from a molecular level to entire ecosystems. They offer research and development services for medicine, agriculture and environmental protection.	Tobacco, corn, rice, wheat, tomato, plant suspension cells	Antibodies, vaccines (injectables and oral administration), enzymes for oncology and infectious disease	N.sp.	http://www.ime.fraunhofer.de/fhg/ime/
Integrated BioPharma	USA	Owns many subsidiaries, including NuCycle Therapy, Inc., which is currently collaborating with the US Navy in the development of a plant-based anthrax vaccine.	Brassica juncea	Nutritional products, vitamins food, cosmetic products, vitamins, amino acids, herbal extracts, OTC pharmaceuticals, excipients, dietary supplements,	N.sp.	http://www.ibiopharma.com/
Instituto de Virologia	Argentina		Alfalfa	Vaccine for foot and mouth disease virus, swine-transmissible gastroenteritis coronavirus, bovine rotavirus		http://www.inta.gov.ar/
Kentucky Tobacco Research and Development Center	USA	Contract bioprocessing company to extract purified proteins and other value added products from plants and other organic materials. In 2007KBP announced a collaboration with Arizona State University's Biodesign Institute and Mapp Biopharmaceutical on development and production of monoclonal antibodies for use in microbicides and mucosal vaccines.	Tabacco.	N.sp.	N.sp.	http://www.uky.edu/KTRDC/

Company/Institution	Land	Description	Plant host(s)	Products/Indication	Status product development	Webpage
Kumho Life & Environmental Science Lab	Korea	N.a.	Hevea treeas (protein secreted in rubber)	N.a.	N.a.	http://www.kumho.co.kr/
Linnaeus Plant Sciences Inc	Canada	Engineers specialized plants to provide oils that can be used to replace entire families of petroleum-based industrial feedstocks.	Lesquerella fendleri, Arabidopsis thaliana	Vegetable-based motor oil, high recinoleic acid crop plants, other speciality oils	N.sp.	http://www.linnaeus.net/
Maltagen Forschung GmbH	Germany	Formed in 1994. Focuses on the production of recombinant proteins in barley grains.	Barley	Lactoferrin, lysozyme, human serum albumin, hepatitis vaccine, edible vaccines, and recently thaumatin	N.sp.	http://www.maltagen.de/
Maxygen, Inc.	USA	Founded in 1997. Focuses on the production of recombinant proteins. The lead product candidates address substantial market opportunities in infectious disease, haemostasis and cancer.	N.sp.	treatment of neutropenia, hepatitis C virus infection, uncontrolled bleeding in trauma, intracerebral hemorrhage (ICH), diopathic pulmonary fibrosis (IPF)	N.sp.	http://www.maxygen.com/
Mapp Biopharmaceutical Inc.	USA	Founded in 2003 to develop novel pharmaceuticals for the prevention and treatment of infectious diseases.	Tobacco, potato, maize, spinach, lettuce	Monoclonal antibodies against herpes simplex virus, HIV-1, mucosal vaccine	N.sp.	http://www.mappbio.com/
Medicago, Inc	Canada	Formed in 1999. Medicago has currently four products under early stage development. Preclinicals are planned to start in 2006 for two products.	Alfalfa (cell culture, transiently transformed plants and transgenics in greenhouse) .	Vaccines, monoclonal antibodies, vaccines and biogenerics (aprotinin)	Preclinical study launched in 2007 for a influenza hemagglutinin (vaccine)	http://www2.medicago.com/en/
Meristem Therapeutics	France	Formed in 1997 to implement the plant genetics programme 'molecular pharming' initiated by the Limagrain group. Focuses on the development of large-scale processes for the production of therapeutic proteins mainly in tobacco (greenhouse) and maize.	Corn, tabacco	Gastric lipase - MERISPASE®; albumin; human collagen; human lactoferrin; human IgA (x4); dust mite allergens; murine IgM (monomeric); human plasma proteins	Gastric lipase in Phase 2 clinical trials	http://www.meristem-therapeutics.com/sommaire_en.php3
Metabolix	USA	Founded in 1992 and focuses now on commercializing PHA natural plastics through the conversion of agricultural products such as sugars and oils using microbial biofactories. Is also developing the ability to produce natural plastics directly in non-food crop plants as viable, sustainable alternatives to general purpose plastics such as polystyrene, polyethylene, PET, and polypropylene, and to a variety of currently important industrial chemicals.	Switchgrass, tobacco, and alfalfa	Bioplastics	N.sp.	http://www.metabolix.com/

Company/Institution	Land	Description	Plant host(s)	Products/Indication	Status product development	Webpage
NeoRX Corp	USA	Formed in 1984. In May 2006 it changed name into Poniard Inc. Engages in the development and commercialization of cancer therapy products and focusing on the development of picoplatin, for the treatment of small cell lung, colorectal and hormone-refractory prostate cancers. The company is collaborating with The Scripps Research Institute on the discovery of novel, small-molecule, multi-targeted protein kinase inhibitors Collaborator in the development of Avicidin® (see above)	N.sp.	small cell lung, colorectal and hormone-refractory prostate cancers	Unclear if still pursuing R&D on PM farming.	http://www.poniard.com/
Nexgen Biotechnologies Inc.	Korea	Formed in 1999. Has Canadian subsidiary Guardian Biotechnologies, Inc. Focuses on producing highly valuable proteins for medicine, agriculture, and industry and expands to the fields of molecular farming of useful proteins for cosmetics and industrial process, edible vaccines, phytoremediation for the cleaning of contaminated environments, and the development of transgenic plants.	Tobacco, Korean melon, cucumber, Ethiopian mustard, canola, root vegetables	Pharmaceuticals, Diagnosis KIT (Hantaan & Puumala Virus Multi Rapid KIT, Graves' Disease ELISA & Rapid KIT), antigens (HIV, HBV, HCV, HPV, Dangue Virus, Malaria Virus), cosmeceuticals (EGF, EGF: Albuman, Amima)	N.sp.	http://www.guardianbio.com/2004/main.htm
Novoplant GmbH	Germany	Formed in 1998 as a spin-off of the Institute of Plant Genetics and Crop Plant Research (IPK) in Gatersleben. Focuses on orally administered antibodies for animal health for the veterinary medicine industry	Tubers, rape seed, flax seed, peas	Antibody against E.coli infections in post-weaning piglets.		http://www.novoplant.com/
ORF Genetics	Iceland	Formed in 2002. Focuses on the production of pharmaceutical proteins in barley, which does not grow naturally in Iceland offering a natural containment system, and lettuce.	Barley, lettuce	Growth factors, proteases, antibodies, vaccines, : granulocyte colony stimulating factor, and interleukin-3.	N.sp.	http://www.orfgenetics.com/
Phycotransgenics	USA	Formed in 1999 as seed financed start-up. Focuses on the production of recombinant proteins in the algae Chlamydomonas reinhardtii.	Green algae	Animal health (vaccines) and animal nutrition (Chlamydomonas reinhardtii)	N.sp. (perhaps early stage)	http://phycotransgenics.com/standard/index.html_
Phytomedics Inc	USA	Formed in 1996. Focuses on the production of recombinant proteins from tobacco roots by secretion. Example products include alkaline phosphatase.	Tobacco	Type II diabetes (PMI-5011); Natural alternative to Aspirin (PMI-5001) nutraceuticals/dietary supplements, cosmeceuticals, functional/medicinal foods, and plant-produced biologics	N.sp.	http://www.phytomedics.com/

Company/Institution	Land	Description	Plant host(s)	Products/Indication	Status product development	Webpage
Phyton Biotech	USA	Founded in 1990 in New York and acquired 1993 the Phyton GmbH in Ahrensburg Germany. In 2003, Phyton Biotech was acquired by DFB Pharmaceuticals, a private Texas-based pharmaceutical company. It is the world leader in the application of plant cell culture technology for the commercial production of high value pharmaceuticals.	Plant cells	N.sp.	N.sp.	http://www.phytonbiotech.com/index.htm
Phytoprotein Biotech Ltd,	Singapore	Is involved in the development and manufacture of recombinant antigens and vaccines using the "next generation" plant cell expression systems. Focuses on producing immunogenic recombinant proteins that are used in diagnostic tests and vaccines (animal and human).	N.a.	N.a.	N.a.	N.a.
Plantechno SRL	Italy	Created in 1995. Is specialising in plant-based biotechnology projects with commercial and consumer interest. Holds several patents on technology to express human therapeutic and nutraceutical proteins in plants, as well as expression of genes to reduce the allergenic potential of certain foods and is also committed to the development of platform technologies which improve the efficiency and utility of plant transformation.	Rice, wheat, tomato, maize, poplar, agaricus, barley, soy	Enzymes, phytoremediation, pharmaceutical and nutraceutical proteins to improve treatment of genetic diseases, cholesterol diseases,	N.sp.	http://www.plantechno.com/
PlantGenix	USA	Formed in 1999. Works on membrane transport technology to improve storage and accumulation of recombinant proteins				http://www.plantgenix.com/ url, die gekauft werden kann
Planet Biotechnology Inc.	USA		Tobacco	Antibodies (secretory IgA), and immunoadhesins primarily of topical, oral, nasal administration; eg dental caries, rhinovirus infection, drug-induced alopecia	Phase 1 trails completed witht DoxoRx™; Phase 1 trails with CaroRxTM; the latter also approved as a medical device in the EU	http://www.planetbiotechnology.com/index.html

Company/Institution	Land	Description	Plant host(s)	Products/Indication	Status product development	Webpage
Planta-Pharma Project European Community	Europe	The Pharma-Planta Project started in 2004 and is a consortium of 39 principal scientists from academic and industrial institutions in Europe and South Africa. It is funded for 5 years, by the European Commission and focuses on developing efficient and safe strategies for the production of clinical-grade protein pharmaceuticals in plants, and to define procedures and methods for the production of these proteins in compliance with all appropriate regulations.	Tobacco, maize	Antibodies against HIV (topical application), rabies	Phase 1 trials envisaged in late 2008	http://www.pharma-planta.org/index.htm
PlantBio Products	South Africa	PlantBio Trust is a National Innovation Centre for Plant Biotechnology, initiated by the Department of Science and Technology as part of the National Biotechnology Strategy for South Africa and was started in 2004. Focuses on the development of biotech initiatives with commercial impact and on the building of capacity in South Africa to create human skills required to develop competitive biotech projects.	maize, cotton, soybean	Bioplastics	N.sp.	http://www.plantbio.org.za/default.asp
Plantigen Inc.	Canada	Formed in 1999 by the London Health Sciences Centre in Canada. Focuses on the expression of pharmaceuticals in tobacco plants. Example products include glutamic acid decarboxylase and interleukins	Tobacco	GAD and cytokines, Inflammatory Bowel disease, IL-10 (interleukin 10), IL-4 (interleukin 4), others	N.sp.	http://www.plantigen.com/
Planton GmbH	Germany	Founded in 2000. Focuses in the development and the production of a novel class of antiinfectiva – antimicrobial peptides. Example products include antimicrobial peptides	N.sp.	N.sp.	N.sp.	http://www.planton.de/en/index.html
Plant Research International	Netherlands	Platform technologies applicable in all plant hosts (tobacco, potato, tomato, rice, others)	N.a.	Antibodies as a model: vaccines for oral application and targeted delivery, antisera against plant viruses and plant pathogenic bacteria	N.a.	http://www.pri.wur.nl/uk/

Company/Institution	Land	Description	Plant host(s)	Products/Indication	Status product development	Webpage
Prairie Plant Systems, Inc	Canada	Was established in 1988 as a privately held plant biotechnology company which concentrated on the development of micropropagation protocols for the Saskatoon berry tree. Expanded and relocated into the L.F. Kristjanson Biotechnology Complex in Innovation Place, Saskatoon in 1989. Research efforts continued and, by 1999 it had 29 different varieties of plants in culture including Saskatoon's, apples, plums, raspberries, cherries, cut leaf birches, miniature roses and several medicinal plant species.	Medical marijuana, Saskatoon's apples, plums, raspberries, cherries, cut leaf birches, miniature roses	Biosecure underground growth chamber system, production of prairie hardy fruit trees (f.ex. Saskatoon Berry Tree…)	N.sp.	http://www.prairieplant.com/
Protalix Biotherapeutics	Israel	Protalix has achieved successful expression of biologically active proteins including antibodies and other complex enzymes.	Plant cell culture	Human Glucocerebrosidase (prGCD), for the treatment of Gaucher Disease; fully humanized IgG1 used in anti-cancer therapy;	Received FDA approval for Phase 3 clinical trial of prGCD; marketing expected in early 2008	http://www.protalix.com/
Quantum Tubers Corp	USA	Specialises in potato technology. Currently producing the first crop of potato-based oral vaccines.	N.sp.	potato minitubers	N.sp.	http://www.quantumtubers.com/
SemBioSys Genetics Inc.	Canada	Founded in 1994 as a spinout from the University of Calgary. Focuses on the expression of pharmaceuticals and technical proteins in oilseeds (safflower) using proprietary oleosin fusion technology.	Safflower	Recombinant therapeutic proteins, insulin, apolipoprotein A-I, therapeutic oils, animal vaccines, topical ingredient systems, industrial enzymes and protein purification systems. Diabetes, cardiovascular disease, dietary & nutritional health, animal healt	Entering Phase 3 for insulin; advanced stage for carp somatotropin	http://www.sembiosys.ca/
Scipps Research Institute	USA	Formed in 1955 and is a non-profit research institute. Focuses on the basic research of immunology, molecular and cellular biology, chemistry, neurosciences, autoimmune diseases, cardiovascular diseases, virology and synthetic vaccine development.	Algae	Antibodies, vaccines	N.sp.	http://www.scripps.edu/e_index.html

Company/Institution	Land	Description	Plant host(s)	Products/Indication	Status product development	Webpage
SunGene	Germany	Founded in 1998 as a joint venture of BASF Plant Science, the Institute of Plant Genetics and Crop Plant Research (IPK). Focuses on the metabolic engineering of biosynthetic pathways in order to increase the content of valuable compounds in plants, such as vitamins, carotenoids and proteins.	Rapeseed, potato, tagetes, arabidopsis, tobacco, tomato	N.sp.	N.sp.	http://www.sungene.de/
Sunol Molecular Corporation	USA	Founded in 1996. Operates as a biopharmaceutical company and focuses on the discovery, development, and commercialization of novel antibody-based therapeutics. Produces antibodies for the treatment or prevention of cardiovascular diseases, inflammation, cancer, and infectious diseases.	Lettuce, arabidopsis	Antibodies	N.sp.	http://www.sunolmolecular.com/ Not available
Toxin Alert, Inc.	Canada	Founded in 1998. Focuses on food diagnostic products and the use of antibodies as diagnostic reagents. Now developing production capabilities in plants	N.sp.	Toxin Guard™ an US-patented food freshness and safety test	N.sp.	http://www.toxinalert.com/
UniCrop Ltd	Finland	Founded in 1998. Focuses on recombinant pharmaceuticals produced in sprouting plants in bioreactors	Camelina sprouts	Model proteins: monoclonal antibodies, immunoglobulin fusion protein; human serum albumin, enzymes	N.sp.	http://www.unicrop.fi/
Ventria Bioscience	USA	Founded in 1993 as Applied Phytologics Inc. Focuses on pharmaceutical production in transgenic rice grains.	Rice, barley	Lactoferrin, lysozyme as food supplement and against topical infections purposes		http://www.ventria.com/

Companies no longer active (in PM farming).

Company/Institution	Land	Description	Plant host(s)	Products/Indication	Status product development	Webpage
AltaGen Bioscience Inc	USA	Formed in 2002 as a merger between Phytagenics and Sierra Biosource, acquired in June 2004 by Serologicals Corp. Focused on the production of pharmaceutical proteins from transgenic plants and plant cultures, greenhouse containment, and hydroponics.	N.sp.	N.sp.	N.a.	N.a.
Axis Genetics PLC	UK	Formed in the mid 1980s after a management buyout. Focused on the production of vaccines in transgenic potatoes and in plants infected with recombinant cowpea mosaic virus. Liquidated in 1999 after failing to secure adequate funding.	N.sp	N.sp	N.a.	N.a.
CropTech Development Corp.	USA	Formed in 1992, focussing on tobacco-based production, including > 20 products in a facility opened in 2001. MeGA PharM (mechanical gene activation) system allows post harvest expression. Liquidated in 2003 after failing to secure adequate funding.	N.a.	N.a.	N.a.	N.a.
Epicyte Pharmaceutical Co		Founded in 1996, acquired in May 2004 by Biolex, Inc. Focused on plant-derived antibodies. Leading products (now under development by Biolex, Inc.) include HX8 against herpes simplex virus, R19 against respiratory syncytial virus, antibodies for contraception and antibodies against HIV and Clostridium difficile.	N.i.	N.i.	N.i.	N.a.
Large Scale Biology Corp.	USA	Formed in 1987, formerly Biosource Technologies, Inc., and built the world's first bioprocessing facility for plant-derived proteins. Focuses on the production of proteins in transgenic plants and plants infected with plant viruses (GENEWARE® platform).	Nicotinina species (transient expression)	Therapeutics enzymes and enzyme inhibitors; human and animal health vaccines; antibody fragments; cardiovascular therapy, metabolic disorders and oncology	N.sp.	http://www.lsbc.com/
LemnaGene LLC	France	Formed in 2002. Forged a licensing agreement with Bayer CropScience and Yeda Research in 2003, enabling the completion of first round of financing. Focuses on the large-scale production of recombinant proteins in Lemna; acquired by BioLex in July 2005.	Lemna	Anti-infectious peptides; enzymes; antibodies, probiotics, proteins, vaccines for human and animals	N.sp.	http://www.lemnagene.com/

Company/Institution	Land	Description	Plant host(s)	Products/Indication	Status product development	Webpage
MPB-Cologne GmbH	Germany	Formed in the 1999 as a spin-out from the Max Planck Institute, with a focus on the production of recombinant protein in potato tubers and rape seeds in the field and on plant disease resistance engineering. Liquidated in 2002 due to lack of funding	potato, rape	N.a.	N.a.	N.a.
Monsanto Protein Technology	USA	Division of Monsanto concerned specifically with biopharmaceuticals with a focus on the development of large-scale processes for the production of therapeutic proteins in maize. Collaborated with NeoRX Corp. to produce the Avicidin anti-EpCAM antibody. Monsato announced in 2003 to exit the Monsato Protein Technologies.	maize	N.a.	N.a	http://www.monsanto.com/monsanto/layout/default.asp
Prodigene Inc.	USA	Formed in 1996, and was the first company to commercialise proteins from transgenic plans (1998). Focuses on the expression of pharmaceuticals and technical proteins in maize. Example products: avidin, β-glucuronidase, trypsin, antibodies and vaccines. Confronted with a fine by USDA APHIS for violation of regulations and subsequent compensation payments the company went bankrupt. The IP was then purchased by Stine Seeds and production of fine chemicals seems to continue ever since.	Maize	Enzymes, others	N.a.	N.a.
Syngenta International AG	Switzerland	Formed in 2000 through the merger of Novartis agribusiness and Zeneca agrochemicals. Among many plant biotechnology products, Syngenta is involved in the development of at least six biopharma products with partners including SemBioSys Genetics, Inc. The company decided to abandon the business in late 2005.	Safflower	Biopharmaceuticals for a range of indications, including antibodies, enzymes and other protein therapeutics	N.a.	http://www.syngenta.com/de/index.aspx

Source: Sauter and Hüsing 2006; Spök 2007; Twyman et al. 2005; http://www.cpmp2005.org/Plants.asp, updated and extended.

** outdated information from company webpage; N.a.: information not available, n.i.: not investigated, n.sp.: not specified.*

Annex 2: Containment strategies

Table 15: Overview on confinement strategies.

Technique	Advantages	Disadvantages	Status
Physical separation	Growing transgenic plants expressing valuable industrial compounds are easier to monitor in physically contained areas Removal of external factors of growth into a completely controlled environment	High costs incurred from growing plants indoors or under ground Regulation of large scale underground facilities unclear	Under development for field crops Contained growth of non-GM algae is established
Natural genetic containment	Choice of an organism not used in the human food chain for bio-pharming applications could prevent the compound entering the human food chain Expression of transgene product in the leaves may negate need for flowering	Selection of a new organism may set a project back in time and increase costs Cultivation, harvesting and processing may not be established for new organisms	Expression of bio-pharming products in non-conventional crop species under development (see section 4)
Plastid transformation	Prevents escape via out-crossing Well developed High levels of transgene expression Well suited to bio-pharming	Does not prevent escape via wild-to-crop pollination Not all plants have 100% maternal inheritance Many desirable traits cannot be produced by proteins in the chloroplast	Successful technique in tobacco Demonstrated in potato, tomato, petunia, cotton, carrot, soybean Field trials of tobacco in the US expressing pharmaceutical proteins
Conditional lethality	Control of lethality may be timed to prevent flowering or the development of reproductive organs	Incomplete expression may occur if the application of the chemical inducer is insufficient or fails to penetrate plant tissues	Not yet demonstrated in the field
Inducible promoters	Gene only activated when necessary	Confines the trait but not the transgene Not applicable to traits required throughout the life of the plant Incomplete expression may occur if the application of the chemical inducer is insufficient or fails to penetrate plant tissues	Not yet demonstrated in transgenic crops

Technique	Advantages	Disadvantages	Status
Engineered male sterility	Prevents out-crossing to wild and to non-GM crop plants Well developed in a wide range of crop plants	Seed crops require additional pollen source Potential for volunteer seed dispersal Male sterility often leaky Recombination of chromosomes during meiosis could separate transgene from sterility system	Barnase based male sterility demonstrated in tobacco, rice, maize, alfalfa, oilseed rape, tomato, wheat, citrus and birch 121 field trials in the US of maize, oilseed rape and Brassica oleracea crops with barnase based male sterility 19 field trials in Europe of crops with barnase based male sterility There are 2 lines or oilseed rape, 2 of maize and 1 of chicory commercially available with barnase based male sterility Male sterile oilseed rape is widely grown in Canada and is pending release in the EU under directive 2001/18.
The 'terminator' concept and seed lethality	Prevents transgene escape via out-crossing and volunteer seed dispersal	Recombination of chromosomes during meiosis could separate transgene from sterility system Not suitable for crops where seed is saved Negative public perception	'terminator' technologies withdrawn from commercial development and not been demonstrated in the field
Apomixis	Prevents transgene escape via out-crossing and volunteer seed dispersal	Genes controlling apomixis not yet identified but likely to involve a complex gene construct Likely to be leaky GM apomicts likely to be invasive Does not prevent seed dispersal	Genes controlling apomixis not yet identified Not yet demonstrated in transgenic crops
Cleistogamy	Prevents transgene escape via out-crossing and volunteer seed dispersal	Genes controlling floral development not yet identified Likely to be leaky Seed escape may still lead to volunteers Not suitable for all crops Does not prevent seed dispersal	Very little development as a containment strategy Genes controlling cleistogamy not yet identified Not yet demonstrated in transgenic crops

Technique	Advantages	Disadvantages	Status
Transgene mitigation	Prevents introgression of transgenes into wild or weedy populations Addresses crossing of GM crop in both directions	Does not prevent gene flow from GM crops to non-GM crops May be harmful to natural populations of wild relatives Allows formation of transgenic F_1 hybrids Depends on weed competition to succeed Recombination of chromosomes during meiosis could separate transgene from mitigation system	Demonstrated experimentally in tobacco and oilseed rape Requires further development
Recoverable block of function	Transgene and containment system are inseparable during chromosome recombination Can be engineered to control pollen or seed sterility	Incomplete expression may occur if the application of the chemical inducer is insufficient or fails to penetrate plant tissues	Demonstrated experimentally in tobacco
Inteins	Prevents escape of a complete, functioning transgene	Allows escape of non-native but non-functioning DNA May 'contaminate' 'non-GM' crops Function of the recombinase requires optimal conditions that may not be obtainable in the field	Demonstrated experimentally in tobacco and Arabidopsis
Auxotrophy	Prevents survival of transgenic plant outside controlled environment	Does not prevent formation of F1 hybrids Recombination of chromosomes during meiosis could separate transgene from mitigation system High costs on a large scale	Not well developed as a containment mechanism Demonstrated experimentally in Nicotiana plumbaginifolia and Arabidopsis
Transgene excision	May be engineered to produce non-transgenic seed/fruit from transgenic plants	Requires complete expression of the recombinase Recombinase excision site will remain as non-native DNA Deletion products may remain intact within the cell and may be passed on to the next generation Not applicable to traits expressed in seeds	Requires further development

Source: Dunwell and Ford 2005.

Annex 3: Public Perception Studies on PM farming

The following section gives a short description of the reviewed surveys and studies on public perception of plant molecular farming, summarising the studies main findings.

USA

The first study of public attitudes to PMPs from transgenic tobacco was carried out by Nevitt et al. (2003) from October 2001 to September 2002. 672 stakeholders from the agricultural sector, industry, academia, NGOs and activist groups, and U.S. government regulatory officials answered questions related to perception of risks and benefits for a pharmaceutical produced in transgenic tobacco. Data were obtained using face-to-face interviews; telephone interviews; and email, small group discussions, and observation at a conference on PMPs. The focus of this study was on the knowledge of transgenic tobacco to produce pharmaceuticals, the participants' views on market potential, field practices, environmental and ethical issues, social benefit and regulatory issues. Although this study showed support for pharmaceuticals produced in tobacco, the two survey questions (out of 19 in total) that related to acceptance of a PMP were focused on medicines available from a store and subject to price comparisons with alternative, non-GMO products. Thus, it is difficult to draw any specific conclusions from the results of this study for the potential acceptance of PMPs in general. Moreover, many medicines –for instance vaccines - are not available from retailers or pharmacists, they are generally not price-sensitive in nature, and rarely have multiple brands available for patient choice.

Kirk & Mc Intosh published a study in 2005, which was based on a survey carried out in Arizona, on the acceptance of PMVs focussing on the product level. The survey was conducted using random telephone interviews, public venue interviews and classroom questionnaires. 706 people were asked to answer three multiple choice questions, which aimed (I) to evaluate the preference among the general population for non-injectable vaccines, (II) to indicate public perception of the use of biotechnology in producing vaccines, and (III) to survey the acceptance for the use of a vaccine produced in GM plants. The results demonstrated a strong potential support for PMVs: The preference for oral vaccines in general and for vaccines produced in GM plants was very high: 68% of the respondents declared to be "very" or "somewhat likely to accept", whereas only about 19% were "somewhat" or "very unlikely to accept" PMVs. Another outcome of the study was that the public perception of risks and benefits of vaccines is significantly different from those of food commodities. According to Kirk & McIntosh (2005) public perception differentiates between the application of biotechnology for food and for medical purpose: "[…] the risks and benefits of vaccines are significantly different than those of food commodities, and inferring either acceptance or rejection of PMVs based on these trends would be inaccurate."(p. 229) The article, however, does not comparatively analyse public perception of GM food and PM farming nor does it draw any explicit links to such studies.

A phone survey of 432 adults from Arkansas, Louisiana, New Mexico, Oklahoma, and Texas conducted in 2004 (Knight 2006) was also examining the relevance of application of GM plants and animals for gaining public support. The questions comprise the use of animals and plants not only for 3rd generation application of biotechnology but also for 1st and 2nd. The 4 animal applications were: GM animals, which produce human organs (3rd); which are resistant

to diseases, such as Mad Cow (1st); which produce more tasty and tender meat (2nd); and with increased production, like milk (1st). The 4 plant applications were: plants to produce industrial products, such as plastics (3rd); non-food plants, like cotton (1st); plants to produce pharmaceutical drugs, like vaccines (3rd); and fruits and vegetables (1st). The main focus of the study was to explore whether the determinants of support for each application vary by knowledge, trust, benefits, and sociodemographic variables.

The survey also revealed that the organism used (animal or plant) outweighs the function and the type of application (in relation to objections to biotechnology applications in general similar findings were shown in Frewer et al.1995): GM plants received higher support than GM animals. The study also concluded that acceptance varies by application: higher support is granted to non-food applications compared to GM food (c.f. Hoban et al. 1992 and Hoban 1998 in the context of the 1st generation biotechnology).

Canada

A public consultation investigating views on food versus non-food crops, medical versus industrial applications, and containment approaches was conducted in four Canadian regions using a modified focus group approach (Einsiedel & Medlock, 2005). Five specific applications (trypsin for industrial use, interleukin from GM tabacco as treatment for Crohn´s disease, vaccine from GM potatoes against Norwalk virus, gastric lipase as treatment for cystic fibrosis, GM corn to produce bioplastics) were used. There are any kind of concerns in regard to the results indicates that public assessments were taken on a case-by-case basis: They were based on balancing benefits and risks as well as considerations of environmental impacts and regulatory oversight. The acceptance of the 48 attendees for PM farming tend to depend on the purpose of the application on a case-by-case basis (application was identified to be the most important factor). Non-food crops were preferred to the use of food-crops, and PM farming products grown outdoors were perceived as riskier than those grown indoors. If the plant host is able to go to seed or flower, it was seen as riskier. Medical applications were in favour of industrial use, because a possible economic benefit is not expected to benefit consumers. The study revealed that industrial applications of PM farming for more environmentally sound products gains more public acceptance than the production of substances at lower cost. The results of the focus group discussions also showed that potential benefits for the developing countries tended to be considered as very positive and highly accepted. The main concerns raised by the participants were linked to environmental issues due to cross-pollination [43] and the contamination of food crops including potential long-term side effects, especially impacts on human health and the environment. Full containment was considered by the participants as impossible and contamination was estimated likely to happen accidentally or by malicious intent. Moreover the participants were concerned about the ability of the regulators to adequately monitor these technologies and that the interest of those growing, farming or researching these applications might not being consonant with the public interest. This also relates to the fact that potential economic benefit was not a key issue for acceptance.

In February 2003 the consumer association Option Consommateurs commissioned a series of focus groups on PM farming in order to investigate Canadian consumers' level of awareness about this issue and their opinions towards this issue (Huot 2003). In particular levels of knowledge, fears and concerns, assessment of benefits and risks, and potential commercial use of molecular farming were discussed. The discussions took

43 This might be particular for Canada, since many participants made direct references to the Monsanto versus Schmeiser case.

place in Montreal and Toronto. The results of the study showed that most participants could not conclusively decide whether the benefits or the risks were greater for PMP. They felt that they lack of in-depth knowledge, and they are not confident that sufficient research on possible impacts of PM farming has been conducted. In their sense there is still too much uncertainty about possible impacts of PM farming, and therefore weighing the benefits and risks of molecular farming was simply too difficult to judge for them at this point in time. Thus, they were very reluctant to accept the commercialization of PMP. Tightly controlled laboratories and greenhouses for PM farming are deemed acceptable if strict regulations are in place to ensure public and environmental safety. Open field farming would not be accepted without further research on environmental risks. In principle the participants were in favour of the possibility that PM farming could lower the production costs of drugs, perhaps discover new cures for diseases, to offer greater access to drugs for third world nations. In addition, many thought that plants might produce more "natural" medicines with less side effects. On the other hand participants also expressed considerable concerns. Almost all participants cited environmental safety as their primary concern, mainly related to the contamination of soil and water supplies. Secondly, most participants expressed concern about possible short and long-term effects in humans.

Very recently, in early 2007, about 400 people from across Canada took part in an online consultation on PM farming. The consultation covered - amongst other topics - awareness and general views on PM farming, specific applications, crop platforms, environmental considerations, and risk management approaches. The consultation showed that the vast majority of the participants (72% in the beginning, 80% in the end of the consultation[44] considered PM farming to be a "positive development" (half of them even considered PM farming to be a "very positive development") with the caveat that strict conditions were required to safeguard protection of the food supply and ensure minimal environmental risk (Einsiedel & Klinkhammer, 2007). Concerning specific applications and the use of major or minor food and non-food crops the consultation did only show slightly more acceptance for medical than for industrial applications [remark: both industrial applications were linked to environmental sustainability, which has a higher acceptance than other industrial uses anyway – as we know from other surveys]. On the other hand in regard to the crop platform there were differences: The production of a pharmaceutical and of a substance for industrial use was more "fully acceptable" in a minor or non-food crop than in a major food crop. Surprisingly, about the similar numbers of participants considered PM farming as being conditionally acceptable in corn (a major food crop) and in safflower (a minor food crop). This study again shows that judgments of acceptability being made on a case-by-case basis, with preferences dependent on the product being produced and the plant employed. The areas identified as being of greatest concern were related to risk management measures and to the regulatory capacity to do long-term monitoring.

Europe

Most of the EU surveys on public acceptance for agricultural biotechnology are dealing primarily with the 1st generation GM crops and food, sometimes including a few questions related to PM farming. This is also true for the Eurobarometer surveys on biotechnology (Gaskell

44 The explanation for the higher acceptance in the end of the consultation ("those initially uncertain appear to have made up their minds in the positive direction") might be only partially right, because there were indicated 14% saying they were unsure in the beginning.

et al. 2006), which are based on a representative sample of 25,000 respondents from all EU Member States. The most recent survey on biotechnology, conducted in 2005, included some questions on industrial applications of biotechnology to bio-fuels, bio-plastics and plant molecular pharming. The results related to these fields of application differ considerably from those for GM food. Whereas a majority of Europeans thinks that GM food should not be encouraged since it is not deemed useful, as morally unacceptable and as a risk for society, industrial applications of biotechnology in bio-fuels, bio-plastics[45] and plant molecular pharming are widely supported. About 60% of respondents - except Austria, where the participants disapproved in all applications – approved molecular pharming if it would be tightly regulated and over 70% of respondents supported incentives to develop bio-fuels and bio-plastics.

Willbourn (2005) conducted a study based on workshops in the course of the UK"GM-Nation" initiative, which mainly aimed at being a "deliberative public engagement exercise" on the application of biotechnology to non-food agriculture and the related social, political, ethical, economic, environmental, health and safety criteria were discussed along eight case studies. Another objective was to explore the attitudes towards non-food agricultural biotechnology and whether there is a difference to GM-food. The project was designed as a four workshop series starting with benchmarking of current knowledge and attitudes on three non-food case studies, energy crops, a pharmaceutical application and plants for the production of packing materials. The second workshop was a stakeholder meeting, the third consisted of participants´ independent research, discussions, reflection and deliberation on the issues, and the forth workshop was dedicated to explore the conclusions. The main findings, which were gained from this deliberative public engagement exercise, were that the majority were clearly very concerned about the use of GM in non-food agriculture, only some were willing to consider its use under controlled conditions if there were serious medical benefits. Improved economics or efficiency of a technical process, in contrast, was not considered a sufficient benefit. Because of its potential for future agriculture the majority of the participants believed that non-food agriculture should be progressed but without GM crops. Non GM feedstock was in general favoured over the application of genetically modification. If the application was evaluated to be basically beneficial, field growing was less acceptable compared to contained conditions, and the use of non-food crops was preferred to the use of food crops. In regard to the field of applications the analysis states an interesting fact: mentioning that within past studies it had been noted that the public claimed to be more supportive for the use of GM technology in medical applications. Willbourn (2005) concluded that the use of genetic modification in non-food agriculture is also controversial and even if it were to gain acceptance, stringent safety measures similar to those requested for food applications are likely to be required by the public. Interestingly, participants did not conduct a sophisticated or finely balanced risk-benefit analysis. If the benefit seemed to be of high value (e.g. cure for cancer or HIV) many participants considered it to be worth running the risk of cultivating a GM crop – although ideally under strictly controlled conditions. The study stresses that the public perception is always linked to possible alternatives to the PM farming applications. For example it was deemed as "waste of money" to develop PM farming for the production of antibodies against dental caries, whereas treatments for severe diseases with PM farming was seen to be viable. PM farming for industrial use was on one hand seen as favourable application, as it was the case for the production of bioethanol. On the other hand possible alternatives were preferred to PM farming, for instance efficient re-cycling

45 The questions were emphasizing on products linked to environmental sustainability.

or using less packing material in general instead of developing bioplastics. Overall, GM crops for bioethanol or bioplastics were largely rejected.

In 2006 16 citizens were participating in a citizens' jury organized by the Danish Board of Technology to discuss new GM plants. The citizens responded in general positively to use GM plants to produce pharmaceuticals and industrial raw materials under certain conditions. As the most important conditions non-food crops should be used, appropriate measures to monitor and control the growth, refinement, and use of these plants should be in place and the environmental impacts must be assessed. Cultivation of these plants should not pollute more than existing modes of production, particularly concerning fertilizer or pesticide usage. Future risk assessments should include the impact on ground water and soil. Given the GM crops do not harm the environment the jury considered both, the application of GM-plants to produce medical substances and industrial plants as useful developments, because of their potential to improve public health, environment, business opportunities and financial advantages. The participants expressed their confidence in existing regulation and did not identify any major problems with the present GM plants for food and feed use. Accordingly, the jury expected also the control of GM plants for new purposes to be sufficient. The most distinct conclusion the citizens´ came up with was the necessity of informing the public about advantages, disadvantages and conditions with these new plants as part of an "open and nuanced debate".

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Annex 4: Stakeholder views on PM farming

Table 16: Main points in stakeholder views on PM farming summarised for each group.

Stakeholder group	Views (a)	Groups active
Environmental & other public interest groups North America: actively campaigning since the early 2000 EU: very little activity limited to France and Germany; groups are still mainly preoccupied with the first generation GM crops	■ Use of food/feed crops is opposed due to risks of inadvertent contamination of the food/feed chain. ■ Concerns about possible health risks (e.g. immunogenic effects like allergies, inflammations, food sensitivities etc.) ,resulting from e.g. unintended consumption, exposure to pollen dust debris, or polluted water. Similar concerns are related to the end product. ■ Open field production is disapproved because of environmental risks: - Effects on non-target organisms - Soil and water pollution - Introgression of the GM crops into wildtype plants ■ PM farming is accepted under strictly contained production, like greenhouses, caves. Even more preference is given to completely contained production systems based on plant or animal cell culture, microbial fermentation and algae. ■ Critics on economic aspects: - Most benefits would be harnessed by companies, only a very small portion of the benefits is expected to go to farmers - Only a small number of farmers could benefit. - Market forces may drive down farmer compensation. - Untenable liability for farmers (and others) - Alternative (technological) options for disease control would be available in several cases ■ US groups are campaigning for tightening regulations and changes in research policy: - Current mixed grain production of major food crops cannot avoid contamination even in case of a very strict regulatory regime. Thus it is proposed to eliminate of as many steps as possible in seed production, crop production, handling, storage, delivery operations. - Demand of a management and oversight system, which involves reproducibility in the production process, predetermined performance standards, documentation and auditing, third party monitoring, biological confinement. - Criticism of lack of transparency and opportunities for public participation, data are not publicly available. - Criticism of too little funding for biosafety field studies and risk assessment.	Center for Food Safety, USA Center for Science in the Public Interest, USA Environment California, USA Friends of the Earth, USA GeneWatch, UK Greenpeace Canada Greenpeace, France Greenpeace, International Institute for Science in Society, UK The German Society for Nature Protection (NABU), Germany The Munich Environmental Institute, Germany Union of Concerned Scientists, USA US Public Interest Research Group

Stakeholder group	Views (a)	Groups active
Consumer groups See comment above	■ Concerns about contamination of the food/feed chain: - Recommending that PM farming should not be carried out by farmers but by trained biotech company staff - Opposing the use of food crops. - Demanding PMP to be kept under strict confinement. ■ Health concerns: - Long term effects on farmers´ health. - Potential risks for consumers. ■ Environmental risks: - Effects on non-target organisms, including soil fauna and flora ■ Criticism on weak regulation: - With respect to confinement. - The review of market applications including drug safety evaluation with respect to synergistic or cross reactive, and long term effects. - Monitoring of fields trials. ■ Criticism on economic aspects: - Benefits not necessarily harnessed by consumers. - Questioning economic benefits for farmers considering high investments of money and time. - Liability problems in case of contamination - Farmers´ loss of independency. - Threat for the food industry.	Consumers Union, USA Option Consommateurs, Canada
Patient groups Little activity in North America and the EU:	■ Especially groups affected by diseases with few therapeutic options are supportive expecting: - New possibilities for treatment - Therapeutically effective medicine. - Uncontaminated proteins. ■ Economic benefits from lower costs and increased availability of drugs.	Arthritis Foundation; USA International Association of Patients Organisations Vaincre la Mucoviscidose, France
	■ Concerns about environmental risks depending on the crop and the type of novel proteins ■ Concerns about possible adverse health effects: - Of the biopharmaceutical product - Via unintended intake of plant products containing the biopharmaceutical - Demand for careful evaluation of potential benefits and risks. ■ Ethical concerns related to intellectual property issues ■ Economic concerns that lower production costs may not necessarily translate into lower costs for the patients or health care provider ■ Concerns about the efficiency of PMP	International Association of Patients Organisations

Stakeholder group	Views (a)	Groups active
Alternative farmers Little activity in North America and the EU	■ Mainly preoccupied with GM crops in general, not specifically focussing on PM farming ■ Critics on economic aspects: - Concerns that coexistence would be impossible - Threatening markets for alternative agriculture (this concern is related to GM crops in general)	Confederation Paysanne, France Ecological Farming Association, USA Farmer to Farmer, USA PCC – Natural Markets, USA
Conventional farmers EU groups are reluctant to adopt a clear position related to GM plants in general; North American farmer groups are divided	■ Economic and food safety concerns - Risk of market loss and safety risks following commingling of food and feed crops with pharma/ industrial crops - Doubts that PM farming would be accepted by a broader public - Lack of information on possible health effects of molecular farming for growers, processors and consumers.	Arkansas Rice Growers Association USA Mississippi Rice Council, USA Rice Growers Association USA Rice Producers of California Riceland Foods USA U.S. Rice Producers Association USA Rice Federation
	■ Appreciating PM farming in agriculture as a new way of adding value to agricultural products.	InnoPlanta, Germany National Corn Growers Association, USA
Food industry Actively campaigning in North America; no official position but internal discussion in the EU	■ Risk of contamination of the food/feed supply: - Use of non-food/feed crops, food or feed crops should not be used unless reliable management measures are implemented. ■ Economic risks: - Negative impacts on domestic and international markets for food crops. ■ Regulation issues: - Demand for tightening the regulatory framework. - Demand for strict confinement measures. - Need to develop a regulatory framework as PM farming crops are not aiming at food and feed use and consequently not being evaluated under the GM food and feed regulation. - Wish for greater transparency and more communication between the PM farming sector, the food and feed industry and regulators	Confederation of the Food and Drink Industries, EU Grocery Manufacturers of America, USA

Stakeholder group	Views (a)	Groups active
Biotechnology industry associations Very active in the USA Very little activity in EU (b)	■ Emphasises advantages of PM farming in terms of lower capital investments, scale-up flexibility, faster access to new drugs, safer products; highlight shortage in production capacity based on mammalian cell culture and microbial fermentation ■ Support strong and continuous regulatory oversight of PM farming by USDA APHIS (different to first generation of GM crops); confinement and handling plans as well as standard operating procedure should be under regulatory oversight by USDA APHIS ■ Focus on developing and monitoring of confinement systems, e.g. the Containment Analysis and Critical Control Point (CACCP) ■ Voluntary agreement to limit PM farming except under conditions of substantial spatial isolation from major areas of food/feed crop production	BIO, USA EuropaBio, EU

a) Most articulate positions and arguments come from North American groups. Only few EU stakeholder groups are active in the field of PM farming.

b) Most EU-based PM farming companies are not directly members of EuropaBio.

Annex 5: List of Interviews

Interviews were conducted with senior level representatives from the companies, organisations, and regulators listed below[46]:

Companies

- BASF, Germany
- Bayer, Germany
- Boehringer Ingelheim, Germany
- Cobento Biotech, Denmark
- Dow Agro Science, USA
- Fraunhofer IME, Germany
- GE Healthcare Life Sciences, Sweden
- Greenovation, Germany
- Meristem Therapeutics, France
- Monsanto, USA
- Novartis, Switzerland
- Novo Nordisk A/S, Denmark
- Novozymes Biologics, USA
- Philip Morris International, Switzerland
- Sembiosys, USA
- Syngenta, Switzerland
- UCB Celltech, UK

Industry Associations

- EuropaBio, Brussels
- European Biopharmaceutical Enterprises (EBE), Brussels
- Society for Moleculture, Canada

Competent Authorities

- CFIA, Canada
- DG-SANCO, EU
- EFSA, EU
- EMEA, EU
- FDA, USA
- Health Canada
- USDA APHIS, USA
- Ministry of Agriculture, France

Stakeholder

- Confederation of the Food an Drink Industries of the EU (CIAA), Brussels
- Fédération nationale des syndicats d'exploitants agricoles (FNSEA), France
- Confederation Paysanne, France
- Innoplanta, Germany
- GeneWatch, Great Britain
- European NGO Network on Genetic Engineering - GENET, Germany
- Union of Concerned Scientists, USA
- The German Society for Nature Protection (NABU), Germany
- The Munich Environmental Institute, Germany

46 Including semi-structured full fledged interviews and mini interviews on a subset of questions.

In addition, three expert interviews with senior level public perception researchers from Georg-August-Universität Göttingen, Germany, University of Calgary, Canada, and Monash University, Australia who had investigated into PM farming were conducted.

Not responding or refusing to provide information or conduct an interview

- Ajinomoto, Switzerland
- Association of the British Pharmaceutical Industry (ABPI), UK
- BEDE, France
- BEUC Bureau Européen des Unions des Consommateurs, Belgium
- Bevo Farms, Canada
- Biotechnology Industry Organization (BIO), USA
- Cystic fibrosis Foundation, France
- Environmental Network, Canada
- Farmacule BioIndustries, Australia
- Food and Consumer Products Manufacturers, Canada
- Global 2000, Austria
- IAPO – International Association of Patient Organizations, Great Britain
- L'association Inf'OGM, France
- Leukemia & Lymphoma Society, Canada
- Medicago, Canada
- Nexgen, Korea
- Option Consommateurs, Canada
- Pharming Group N.V., The Netherlands
- UniCrop, Finland
- Ventria, USA
- Zymogenetics, USA

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Abstract

The main objective of this study was to identify advantages, prospects, and drivers of and challenges from plant molecular farming (PM farming) with a particular focus on the EU. The report considers techno-economic, regulatory and wider policy aspects including stakeholder and public perception. It covers PM farming for producing biopharmaceuticals and vaccines, subsequently referred to as plant-made pharmaceuticals (PMPs) and plant-made vaccines (PMVs), and for plant-made industrials (PMIs) intended to be used for food and feed purposes (food supplements, food and feed additives). The study is based on literature reviews, document analysis and interviews.

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