

Pharming
A New Branch of Biotechnology
Margret Engelhard, Kristin Hagen, Felix Thiele (eds)



EUROPÄISCHE AKADEMIE

zur Erforschung von Folgen wissenschaftlich-technischer Entwicklungen
Bad Neuenahr-Ahrweiler GmbH

Direktor: Professor Dr. Dr. h. c. Carl Friedrich Gethmann

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Foreword

“Pharming” is a new branch of biotechnology where plants or animals are genetically engineered to produce pharmaceutical proteins. It is hoped that pharming may lead to new, better or cheaper drugs. However, questions remain with regard to the choice of plants or animals, environmental and pharmacological safety, the welfare of pharming animals, the legal regulation of pharming, societal concerns, and moral evaluation. To address these questions, the Europäische Akademie GmbH is conducting the interdisciplinary research project “Pharming. Genetically Modified Plants and Animals as Future Production Site of Pharmaceuticals?”. As part of the project, in order to highlight and discuss some specific aspects of pharming, a workshop was arranged in Berlin on 14th/15th September 2006.

Some of the results from the workshop are made available in this volume of the “Graue Reihe”. The collection of papers reflects the interdisciplinary scope of our approach. After a general introduction to pharming, the following topics are addressed: the prospects of pharming in plants, challenges faced by companies that wish to introduce pharming products to the marketplace, ethical aspects of pharming, and legal considerations with regard to the welfare of pharming animals.

We are grateful to the speakers who have provided written papers on the basis of their presentations at the workshop, and to the other workshop participants who contributed to the discussions. Further, the organisers gratefully acknowledge funding obtained from the German Federal Ministry of Education and Research’s (BMBF) programme “Innovations- und Technikanalyse”, and the editorial work by Katharina Mader and Friederike Wütscher at the Europäische Akademie.

Bad Neuenahr-Ahrweiler, November 2007

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Pharming – an Introduction

Margret Engelhard

Pharming¹ is a new branch of biotechnology that utilises transgenic plants or animals as living “factories” to produce pharmaceuticals for the use in humans or animals. Goats, for example, have been genetically modified with the human gene for the protein antithrombin, an anti-clotting factor. This protein, which is synthesised by the transformed animals in their milk, is ready, after a processing step, for pharmaceutical application. The term “pharming” is based on a merger of the words “farming” and “pharmaceuticals” which illustrates the combination between these two highly contrasted industries. The stakes on pharming are high in terms of benefit to human health and economic profits that might be gained. If pharming can be made a success, it could generate pharmaceutical industry and biotechnology firms billions of dollars in sales over the coming decade.

However, this new application of biotechnology also raises a number of questions regarding risks and ethical implications, e.g.: how can animal health and welfare be ensured, is such inference with and instrumentalisation of plants or animals acceptable and do plant-made pharmaceuticals pose risks to humans and the environment (particularly if they are produced in plants that also serve as food or feed crops)?

The production of biopharmaceuticals

The class of pharmaceuticals that are manufactured by pharming are biopharmaceuticals. They are pharmaceutical compounds – in most cases therapeutical proteins as for example hormones or monoclonal antibodies that are too complex to be produced by conventional chemical synthesis. Thus, they have to be isolated from biological material (e.g. from blood plasma). Since the isolation from e.g. blood plasma entails the risk of the transmission of pathogens and is in addition costly and sometimes limited in resources, strategies to produce biopharmaceuticals by the means of gene technology have been developed: Only twelve years after the discovery of the genetic code, which describes the connection between genes and the for-

¹ For several years the expression ‘pharming’ has also been used in information technology in a completely different way. There, pharming describes the undesired capture of information by a third party in a similar way as phishing.

mation of proteins and four years after the first artificial introduction of a gene in an organism that thereby became “transgenic” or “recombinant”, in 1977 the first human gene was introduced into a microorganism in order to produce recombinant human proteins. Similar to the indigenous genes the incorporated human gene is utilised as a matrix for protein synthesis: the biochemical machinery of the cell is translating the nucleic acid sequence of the gene into the amino acid sequence of the protein. The proteins themselves are the driving engines for the physiological functioning of the cells and for the biochemical processes of living cells. This experiment is often referred to as the advent of biotechnology. Five years later “humulin”, the first recombinant biopharmaceutical, was approved and received marketing authorization in the U.S. Humulin is human insulin that is produced by the bacterium *Escherichia coli*. Before its development pharmaceutical insulin was extracted directly from pancreatic tissue of slaughterhouse cows and pigs to treat diabetes mellitus patients. Since the development of this first recombinant biopharmaceutical, many others have followed including some of the most important blockbusters as for example a drug against rheumatism called “Enbrel” (by Amgen/Wyeth) with 4,4 billions U.S. \$ sales in 2006, or the cancer drugs Rituxan/Mabthera (by Biogen/Genentech/Roche) with 3,9 billions U.S. \$ sales in 2006 and Herceptin (by Genentech/Roch) with 3,1 billions U.S. \$ sales in 2006 (Lawrence, 2007). Currently recombinant proteins are produced with the help of the fermenter grown recombinant bacterium called *Escherichia coli*, the bakes yeasts (*Saccheromyces cerevisiae*) or CHO (Chinese hamster ovary) cell cultures. However, this current method to produce biopharmaceuticals is costly and inefficient, since complex production facilities are needed. In addition, the demand for the production of biopharmaceuticals is rapidly increasing and has caused a shortage in production capacity leading to some patient waiting lists for these products. It is estimated that the market for recombinant biopharmaceuticals is rising by 10–15% annually (Ernst&Young, 2003). The rise in demand is caused by two developments: firstly, an increasing number of people suffer from illnesses that could be treated with biopharmaceuticals. For example, the number of people that develop diabetes is likely to double by 2030 according to estimates by the World Health Organization (WHO). Although only a minority of these patients will actually require daily injections, the current world market for insulin is valued at in excess of U.S. \$ 4,5 billions (Knäblein, 2005). That makes insulin together with recombinant erythropoietin (EPO) – which has currently a market value of U.S. \$ 6,5 billions (Knäblein, 2005) – two of the mainstay products

of the biotechnology branch of the pharmaceutical industry. Secondly, there has been a rise in the number of newly developed drugs that are biopharmaceuticals, e.g. drugs on the base of antibodies.

In pharming a new production platform is introduced: instead of utilizing lower organisms to produce recombinant biopharmaceuticals, pharming makes use of transgenic plants and animals. It is hoped that the use of higher organisms as production platform for biopharmaceuticals should overcome the logjam described above. In pharming the enlargement of production capacities (e.g. growing more transgenic crops or breeding more transgenic animals) may be quicker, cheaper, and more flexible compared to current production processes that are dependent on industrial facilities. In addition, on the level of the estimated prize per gram raw protein and equipment maintenance costs, as compared to the costs of keeping the transgenic animals, pharming is expected to be far cheaper than the use of traditional cell culture. By overcoming technical or financial limitations, pharming may also enable the development of new therapeutic compounds.

Plants and animals as production platforms for recombinant pharmaceutical proteins

Pharming technology has been applied to goats, cattle, pigs, sheep, rabbits and chickens and to a number of plants with corn, rice, soybean and tobacco as most prominent examples. Sheep and cattle – for example – have been transformed for the expression of human factor VIII and IX which is needed for the treatment of haemophilia or with fibrinogen that is assigned for the treatment of wound healing. Transgenic chicken, cows and goats are utilised for the production of monoclonal antibodies. Mostly, the recombinant protein is expressed in the milk of the transgenic mammals but it could also be directed to the blood, urine or to the eggs (of transgenic chicken). In the case of phytopharming recombinant proteins – as for example EPO – are usually expressed in the seeds or leaves of the recombinant plant. Currently, an increasing number of field and clinical trials are running and just recently the first protein that is produced by pharming has gained market approval: In August 2006, the European Commission granted market authorization to ATryn®. The U.S. based biotech company GTC Biotherapeutics of Farmingham Massachusetts produces ATryn® in the milk of female goats carrying a transgene for human

antithrombin. Antithrombin is an important anticoagulant in human serum and is applied for the prophylaxis of venous thromboembolism in surgery of patients with congenital antithrombin deficiency. Antithrombin products that were available before are derived from human plasma. The complex structure of antithrombin precludes its efficient production in traditional bioreactors. Thus recombinant human antithrombin can only be produced in higher organisms as expression platform.

Societal implications of pharming

Besides the great hopes pharming evokes, it raises a number of ethical, legal and social questions that need to be discussed in parallel to its scientific and industrial development. Moral arguments in support of pharming can be based on the expected benefits to patients or its predicted economical potential. Moral arguments against pharming may arise from concerns regarding the use of plants and animals and from ecological concerns. Obviously the health and well-being of transgenic animals in zoopharming is an important issue. Are there any health and welfare problems specific for pharming animals? Further questions are on what basis the right to interfere with and alter higher organisms does exist and to what degree of their instrumentalisation they have to be evaluated.

Moral arguments against pharming may also be based on human safety and ecological concerns: Biopharmaceuticals are usually highly bioreactive compounds and thus, in most cases, toxic. Biological risks can therefore be identified in the areas of pharmaceutical safety, ecology and food safety.

Pharming makes use of conventional domestic plants and animals, and it will be crucial how – and to what extent – pharming crops and animals can be kept separate from food- and feed-organisms at all stages of the production chains. The plausibility of a scenario of food-chain contamination is demonstrated in the first documented pharming-accident in 2002 in the U.S. There, 13,000 t of vaccine contaminated soy beans had been discovered. Also recent cases in Europe of contaminations of rice, with a genetic modified rice strain (LL RICE 601) that was never approved for commercial use, demonstrates impressively that neither confinement strategies nor import regulations have been efficient so far. In addition it remains to be investigated whether confinement strategies are suitable for restricting consequences of pharming for nearby flora, fauna and soil microbiology. In this context, we need to take

into account the problem of risk assessment with a large degree of uncertainty: biotechnology in general and pharming in particular are relatively young developments, and there are, in many cases, no scientific findings on potential implications available (nor expected in the near future).

For the evaluation of pharming societal values need to be integrated. The future development and regulation of pharming is likely to be influenced by public perceptions of and attitudes towards it. Expectations, beliefs, fears and moral attitudes need to be evaluated and taken into account. Societal dimensions of phytopharming and zoopharming probably differ and need to be compared: for instance, it could be the case that zoopharming is preferable to phytopharming from an economical point of view, but not socially acceptable, and that zoopharming products therefore may not capture the market.

Finally, the legal regulation of production, release, processing and marketing of pharming-products is diverse and lies within the responsibility of a number of institutions. Phytopharming, for example, represents for a first time a merge of green and red biotechnology with the consequence that different authorities are responsible. For instance, the deliberate release of genetically modified organisms (GMOs) is regulated by the EU directive 2001/18/EC (and by gene technology law, and implementation control on the national levels), whereas the European Medicines Agency (EMA) is responsible for the evaluation and supervision of medicines for human and veterinary use. There may also be a need for preventive regulation by the European Food Safety Authority (EFSA) due to the risk of contaminations in the food and feed chain discussed above. For the responsible further development of pharming potentials and risks of pharming and the possible need of legal regulation and policy action have to be discussed. Furthermore it should be analysed which steps industry and government regulators are taking to minimise the risks connected with pharming and whether these actions are sufficient.

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Pharma-Planta: Recombinant Pharmaceuticals from Plants for Human Health

Stefan Schillberg and Richard M. Twyman

Introduction

Mankind has used plants as a source of raw materials and medicines for thousands of years. From the earliest stages of civilization, plant extracts have been used to obtain useful materials and drugs to ease suffering and cure disease. Since the late 1970s, many valuable therapeutic and diagnostic proteins have been discovered through molecular biology research and molecular medicine, but widespread use of these molecules has been hampered by production bottlenecks such as low yields, poor and inconsistent product quality and a shortage of production capacity. In the late 1980s, the application of recombinant DNA and protein technology in plants allowed the exploration of plant-based expression systems for the production of safer and cheaper protein medicines (Table 1).

Over the last decade, plants have emerged as a convenient, safe and economical alternative to mainstream expression systems which are based on the large-scale culture of microbes or animal cells. The production of plant-made pharmaceuticals and technical proteins is known as Molecular Farming (Molecular PharmingTM). The objective is to harness the power of agriculture to cultivate and harvest plants or plant cells producing recombinant therapeutics, diagnostics, industrial enzymes and green chemicals. Molecular Farming has the potential to provide virtually unlimited quantities of recombinant antibodies, vaccines, blood substitutes, growth factors, cytokines, chemokines and enzymes for use as diagnostic and therapeutic tools in health care, the life sciences and the chemical industry. Plants are now gaining widespread acceptance as a general platform for the large-scale production of recombinant proteins. The principle has been demonstrated by the success of a diverse repertoire of products, with therapeutic proteins showing the greatest potential for added value and technical enzymes the first to be commercialized (Twyman et al. 2005). Pharma-Planta is a project funded by the European Union within the Sixth Framework Program which is using molecular farming to produce candidate products for clinical evaluation in Phase I human trials (Ma et al. 2005). Now in its fourth

Table 1: Key events in the history of Molecular Farming

Year	Highlight	Reference
1986	First plant-derived recombinant therapeutic protein – human growth hormone in tobacco and sunflower ¹	Barta et al.
1989	First plant-derived recombinant antibody – full-size IgG in tobacco	Hiatt et al.
1990	First native human protein produced in plants – human serum albumin in tobacco and potato	Sijmons et al.
1992	First plant-derived vaccine candidate – hepatitis B virus surface antigen in tobacco	Mason et al.
1992	First plant-derived industrial enzyme – α -amylase in tobacco	Pen et al.
1995	Secretory IgA produced in tobacco	Ma et al.
1996	First plant-derived protein polymer – artificial elastin in tobacco	Zhang et al.
1997	First clinical trial using recombinant bacterial antigen delivered in a transgenic potato	Tacket et al.
1997	Commercial production of avidin in maize	Hood et al.
1999	First glycan analysis of plant-produced recombinant glycoprotein	Cabanes-Macheteau et al.
2000	Human growth hormone produced in tobacco chloroplasts	Staub et al.
2000	Triple helix assembly and processing of human collagen produced in tobacco	Ruggiero et al.
2001	Highest recombinant protein accumulation achieved in plants so far – 46.1% total soluble protein for <i>Bacillus thuringiensis</i> Cry2Aa2 protein	De Cosa et al.
2001	First multi-component vaccine candidate expressed in potato – cholera toxin B and A2 subunits, rotavirus enterotoxin and enterotoxigenic <i>Escherichia coli</i> fimbrial antigen fusions for protection against several enteric diseases	Yu and Langridge
2001	Glycan modification of a foreign protein produced in a plant host using a human glycosyltransferase	Bakker et al.
2003	Expression and assembly of a functional antibody in algae	Mayfield et al.
2006	Rapid high-yield expression of full-size IgG antibodies in plants	Giritch et al.
2006	Dow AgroSciences receives the world's first regulatory approval for a plant-made vaccine for animals	

¹ Human growth hormone was expressed as fusion with the *Agrobacterium tumefaciens* nopaline synthase enzyme, but only transcript was detectable.

year, the project has focused not only on the technical aspects of production, but also on regulatory compliance, risk assessment, environmental safety, process development and intellectual property. Uniquely, the consortium of scientists running the project has agreed to make the technology, materials and intellectual property arising from the project available at no cost for humanitarian use in developing countries.

The Molecular Farming platform

Many pharmaceutical proteins and industrial enzymes have been produced by genetically engineered microbes and cultured mammalian cells, but these systems have two major problems. First, recombinant proteins made in microbes are often structurally distinct from their native human counterparts, because microbial cells lack the ability to synthesize all the correct components. Second, although mammalian cells synthesize authentic human proteins, they are very expensive to grow and they may harbour viruses. This causes a severe lack of production capacity throughout the world, and expensive processing and purification methods are required to ensure the final product is free of disease-causing agents. In contrast to the above, plants are able to produce authentic recombinant proteins, agricultural production is inexpensive and unlimited in scale, and many plants are considered safe based on the fact that we eat them every day without ill effects.

It should be made clear that plants are not suitable for the production of all therapeutic proteins. Some proteins cannot be synthesized properly in plant tissues, while others can be synthesized but the costs are too high. Generally, the costs of production by Molecular Farming in plants are lower than other production systems, but the cost of recovering functional products may be too high in some cases to make production economically feasible.

From the point of view of industry, the key advantage of molecular farming in plants is the capacity for virtually limitless scale-up with minimal associated costs. This will allow transgenic plants to be cultivated over large areas and the potential for profit will increase with scale, limited only by the amount of plant biomass that can be harvested. High-intensity agriculture can produce surprisingly large amounts of biomass. For example, intensive cultivation of tobacco plants can yield 170 tonnes per hectare, 100 tonnes of which is leaves. Assuming that the levels of production seen

at the laboratory scale can be maintained in the field, a single hectare of tobacco could yield 50 kg of a secretory IgA per harvest (Ma et al. 1995). Production costs of only U.S. \$ 40 per gram have been estimated and with optimization of downstream processing methods this could be reduced to U.S. \$ 20. This compares favourably with animal culture systems which are more expensive by two orders of magnitude.

Plant transformation technology

Techniques have been developed for the expression of proteins in stably transformed plants (where the gene is incorporated into the plant genome), and in transiently transformed plant tissues. Transient gene expression is rapid compared to stable transformation and gives results in days. However, transient gene expression is limited in scale and is generally used to test the constructs used for protein expression before stable transformation is performed.

Expression in stably transformed plants

Stable plant transformation is defined as the genomic integration of a transgene. Both the nuclear (Horsch et al. 1985) and plastid (Maliga 2003; Staub et al. 2000) genomes can be transformed using a variety of methods. The principal transformation technologies currently used in plant biotechnology are *Agrobacterium*-mediated gene transfer to dicots, such as tobacco and pea (Horsch et al. 1985), or biolistic delivery of genes to monocots, such as wheat, rice and corn (Christou 1995). Ease of transformation has been a critical bottleneck in plant biotechnology and still influences the choice of crops used in Molecular Farming. The basis of stable transformation is well understood but is uniformly time consuming. Three to nine months are needed in our hands, depending on the plant variety, to generate stably transformed plants that can be used to test the function and characteristics of the expressed protein.

Transient expression systems

Transient expression can be used to test the function of an expression construct before progressing to large-scale production in stable transgenic lines, but it is also possible to rely completely on transient expression for protein production. A useful method is agroinfiltration, in which recombinant *Agrobacterium tumefaciens* are infiltrated

into plant tissue (Kapila et al. 1997). The T-DNA is transferred to the nucleus in a large number of plant cells resulting in the production of milligram amounts of recombinant protein within a few days (Vaquero et al. 1999). Viral vectors have also attracted interest because viral infections are rapid and systemic, and infected cells yield large amounts of virus and viral gene products (Gleba et al. 2004, 2005). Since plant viruses do not integrate into the genome, there is no stable transformation and the transgene is not passed through the germ line. However, plant viruses often have a wide host range, are easily transmissible by mechanical inoculation and can spread from plant to plant, making it possible to infect large numbers of plants rapidly. For example, plant viral vectors have been used to express scFvs and full-size antibodies.

Host systems and production systems

A large number of species are now amenable to Molecular Farming including model plants (tobacco, *Arabidopsis*), cereal crops (rice, wheat, maize), legumes (pea, soybean, alfalfa), fruit crops (tomato, banana) and solanaceous species (potato). Thus far, it has been difficult to evaluate the relative performance of different crops for industrial or pharmaceutical Molecular Farming, because this requires the production of the same protein in a range of hosts, using a ‘standardized’ expression construct. The performance of an expression construct across species is itself difficult to judge since the same promoter (or other regulatory sequence) may have a different intrinsic level of activity in different genetic backgrounds. Therefore, different research groups and companies have concentrated instead on optimising their ‘favourite’ system, i.e. the host species for which there is the greatest in-house expertise and experience.

Biological and geographical factors are also important, and these should be evaluated on a case-by-case basis taking into account the market value of the recombinant protein. Such factors include:

- *Set up costs*: The set-up cost for any transgenic crop is generally high, reflecting the requirement for controlled environment rooms and greenhouses during plant regeneration. The actual time required depends on the species, and can be several months in the case of cereals and legumes. These costs are minimal for transient expression systems, such as agroinfiltration or virus infection. For cell suspension cultures, the cost of fermenters and media has to be included.

- *Scale-up and maintenance costs*: The costs associated with scaling up and maintaining crops of transgenic plants are minimal because standard farming practices are sufficient. The choice of crop may depend on geographical factors such as the available land, the cost of labour and the distance to the nearest processing plant or distribution centre. Conversely, scaling up and maintaining agroinfiltration or fermenter-based systems can be very expensive. The advantages of transgenic plants therefore increase in proportion to the scale of production.
- *Length of production cycle*: The disadvantages of low yields and high running costs can in some cases be balanced by shorter and more frequent production cycles. This is particularly the case for fermenter-based systems where the costs are high but the production cycle can be reduced to a matter of days. When comparing different transgenic crops, it may be wise to consider the length of the growth cycle, the number of times per year a species can be grown and harvested. Tobacco and alfalfa, for example, can each be harvested several times in a year.
- *Biomass yield*: Although the level of recombinant protein production varies only moderately among different species, the actual biomass produced per hectare of plants varies considerably. For example, a comparison of tomato and pea shows that, due to the high biomass yield of tomato, for every hectare of peas only one third of a hectare of tomatoes would be required to produce the same amount of protein, even though the yield of recombinant protein per unit biomass is lower in tomato than in pea. Tobacco has the highest biomass yield of all crop plants used for Molecular Farming.
- *Costs of processing*: The downstream processing of recombinant proteins (extraction, purification and characterization) can make up 80% or more of total production costs (Kusnadi et al. 1998). Here, minimizing the costs of processing is a priority that can be achieved by choosing a host species for which processing infrastructure is already locally available, and choosing a host system from which protein extraction is easy. It is easier to extract proteins from watery tissues, such as tomato fruits than it is from dry material, such as cereal grains, although recombinant proteins can be modified by proteases and phenolic compounds released from watery plant tissue, while these tend to be present in lower amounts in cereal grains. Tobacco, while advantageous in terms of biomass yield, can contain toxic metabolites that have to be removed. This is not a problem with edible crops. Ease of extraction is also a major advantage of cell suspension cultures, especially when the recombinant protein is secreted into the medium (Hellwig et al. 2004).

- *Edibility*: For certain recombinant proteins, such as vaccines and antibodies, it may be advantageous to use edible plant organs as production vehicle (e.g. tomato fruits, potato tubers) as this allows direct oral administration with no processing costs at all. The same applies to industrial proteins, such as phytase and α -amylase, which are used to increase the nutritional value of animal feed.
- *Costs of storage and distribution*: This takes into consideration the nature of the processing and distribution network. If there is a short distance between the field and the processing plant, and the distribution network is small, storage and distribution costs are low. The converse applies if the distances are larger. If this is a critical economic consideration, then the production of recombinant proteins in cereal seeds, which can be stored for months or even years at ambient temperatures without the protein losing activity, is better than production in tomatoes, which must be stored and transported in chilled containers, or tobacco and alfalfa leaves, which must be desiccated or frozen to preserve protein stability (Khouidi et al. 1999).
- *Costs of containment*: Where containment is an issue, plant cell cultures grown in industrial scale fermenters are optimal since these are closed vessels. However, tomatoes are also attractive since these are grown in greenhouses. In most crop species, chloroplast-expression of the transgene will result in natural containment since functional chloroplast DNA is not transmitted through the pollen, but chloroplast transformation has only been achieved in a few species, and not in any of the cereals. The compromise between production costs and profit is likely to be a key issue in selecting the most suitable species for Molecular Farming because most pharmaceuticals will be produced by industry. We predict that these costs will dictate which crop or crops become generally accepted for recombinant antibody production.

Constraints on the product yields

The yield of recombinant proteins produced in a plant system depends on three factors: the intrinsic limitations of the production host and expression system, limitations imposed by the level of transgene expression, and limitations imposed by the stability of the recombinant protein. The intrinsic yield potential of the production crop depends partly on its biomass yield per hectare, partly on the protein content of the plant tissue (which is highest in legume seeds) and partly on the extent to

which the endogenous protein synthesis machinery can be diverted to produce the recombinant protein of interest. However, when considering a production host, it is also necessary to take into account factors such as the availability of agricultural infrastructure and processing technology, the throughput and efficiency of first generation transformation and regeneration, and the identification of high producer lines that perform stably in the field. Such lines should comply with all relevant biosafety and regulatory standards (Commandeur et al. 2003). Factors affecting the level of transgene expression in plants include the promoter activity and specificity, the optimization of mRNA stability and translational efficiency, and the removal of spurious AU-rich sequences that may act as cryptic splice sites, all of which can be controlled by expression cassette design (Schillberg et al. 2003). Other factors, such as transgene copy number and organization are more difficult to control in this manner, and still the best method remains to generate a population of transgenic lines and select those with the best performance. Protein stability is probably the single most important factor limiting yields in Molecular Farming, and this can be addressed at least in part by appropriate sub-cellular targeting. For example, recombinant antibodies targeted to the secretory system generally accumulate to much higher levels (>1000-fold) than those synthesized in the cytosol, and further yield increases occur when they are retained in the endoplasmic reticulum rather than secreted to the apoplast. It is also important to remember that the ability of the host plant to produce a recombinant protein depends on its spare metabolic capacity. For example, a recombinant protein that is particularly demanding for a rare amino acid is unlikely to accumulate to high levels.

Control of product quality

The quality of the product depends on its authenticity, i.e. similarity to the native counterpart. Unless a fusion tag of some description is used, the amino acid sequences of a plant-derived recombinant protein and the equivalent native protein are usually the same. However, certain forms of posttranslational modification are not carried out in plants (e.g. hydroxylation of proline residues) and there are subtle differences in glycan chain structures, such as the absence of sialic acid and the presence of core $\alpha(1,3)$ xylose and $\beta(1,2)$ fucose residues (Gomord et al. 2005). Glycans affect the structure, folding and interactions of glycoproteins, and may thus influence their distribution, longevity and activity. Foreign glycan structures may also

be immunogenic. As well as the glycan structure *per se*, the homogeneity of plant-derived glycoproteins is also important for batch-to-batch consistency. This can be improved using bioreactor systems (such as *Chlamydomonas reinhardtii* or *Lemna minor*) where growth conditions can be controlled. The presence of fusion tags also affects the activity and structure of recombinant proteins, and these are not considered acceptable for therapeutic proteins. Therefore, if a fusion is used to control targeting or facilitate purification, it must be removed during the processing steps before the product is used.

Biosafety concerns

The biosafety of transgenic plants producing recombinant pharmaceuticals has a major impact on public opinion and, in turn, influences the political and regulatory framework governing pharmaceutical production and biotechnology in general. Specific biosafety risks fall into two categories – the risk of transgene escape and the risk of unintended exposure to the recombinant protein (Commandeur et al. 2003). The risk of transgene spread reflects the potential for transgene DNA sequences to spread outside the intended host plants and production site. This can result in the growth of transgenic crops in other cultivated fields or in non-cultivated areas, the spread of foreign DNA to other plants (and possibly to microbes and animals) and the uncontrolled production of recombinant proteins in natural settings. Mechanisms of transgene spread include the dispersal of transgenic plants or seeds by human and animal activities or the weather, and outcrossing via transgenic pollen. The risk of unintended exposure concerns the potential for any organism (including humans) to come into contact with the recombinant protein produced by a transgenic plant. Many different mechanisms can be involved, including herbivory and parasitism, the exposure of pollinating insects to transgenic pollen, the exposure of microbes in the rhizosphere to root exudates, the exposure of non-target microbes and animals to proteins secreted in the leaf guttation fluid, the release of recombinant proteins by dead and decaying transgenic plant material, and the contamination of food or feed crops during harvesting, transport, processing and/or waste disposal.

An appropriate choice of production species can go a long way to prevent or minimize transgene spread by dispersal or vertical gene transfer. Certain plants have been singled out as inappropriate hosts by regulatory organizations. For example,

alfalfa and rapeseed have been highlighted as unsuitable for field cultivation because they are bee-pollinated, sexually compatible with abundant and local weed species and the seeds can lie dormant for several years, making volunteer plants difficult to isolate and destroy (Figure 1). Note that this does not compromise their merits as production hosts if they are grown under containment. Other species have been more readily accepted because of the lower risks of transgene spread e.g. potato (male sterile), sugar beet and rice (self-pollinating). The major current production crops – maize and tobacco – have intermediate status.

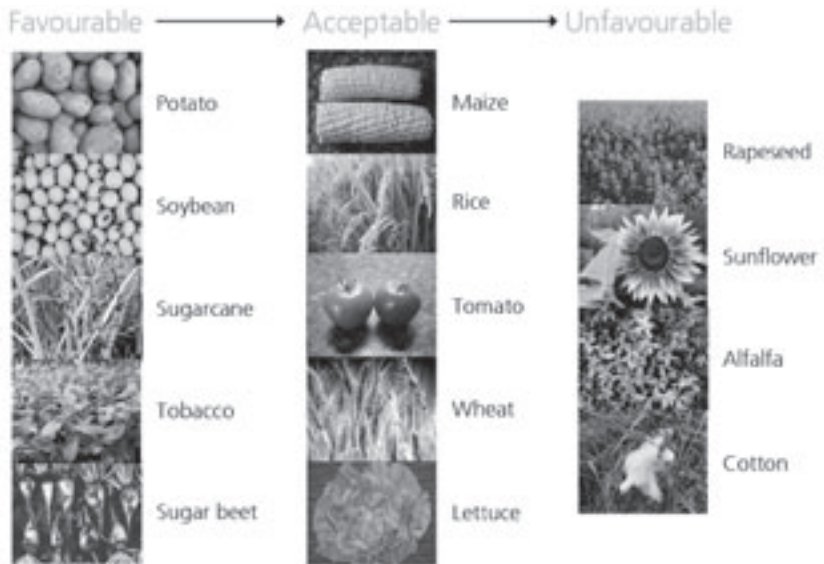


Figure 1: Suitability of different crops for the production recombinant proteins, from a regulatory perspective. The most favourable crops produced have beneficial features for environmental safety and regulatory compliance (e.g. male-sterility in potato, self-pollination in rice). Sugar beet is only favourable in the first year, when it undergoes vegetative growth. The least favourable plants show lower yields and have undesirable features such as open pollination, sexually-compatible wild relatives etc. Note that the most suitable species in terms of biosafety are not necessarily those with the best features for production (e.g. alfalfa, which is advantageous due to its homogenous glycans, is bee-pollinated and is sexually compatible with local wild relatives, while soybeans, which are self-pollinating and isolated, suffer from excessive protein degradation).

Given an appropriate choice of host species, the only way to fully avoid transgene spread from field plants to compatible crops and wild species is by containment. The aim of containment is to prevent seed and pollen dispersal, prevent the survival of dispersed seeds and pollen, or prevent gene flow from viable pollen. The containment may be physical and based on habitat barriers. For example, transgenic plants can be maintained in greenhouses, in artificially-irrigated desert plots miles from any other plants, or in underground caverns and caves. Alternatively, the physical containment may be focused on individual plants. For example, flowers can be emasculated before viable pollen has developed (not an option for seed- or fruit-based production, but suitable for leafy or vegetable crops), or the flowers/fruits may be concealed in plastic bags. Isolation zones are often placed around transgenic crops. These can be barren, but a more suitable alternative for insect-pollinated crops is to provide a zone of non-insect-pollinated plants which would discourage the insects from leaving the transgenic zone. Barrier crops, i.e. a border of non-GM plants of the same species as the transgenic crop, are also useful as these can absorb much of the pollen released by transgenic plants and can then be destroyed after flowering.

Biological containment measures provide additional barriers to gene flow and many different strategies have been tested. In some cases, natural genetic barriers have been exploited. For example, pharmaceutical production in self-pollinating species (e.g. rice, wheat and pea) or crops with no sexually compatible wild relatives near the site of production provide a first level of defence against gene flow. Similarly, crops with asynchronous flowering times or atypical growing seasons are useful. Cleistogamy (self-fertilization before flower opening) is an extension of the above, and could be engineered into crops used for molecular farming by modifying the architecture of flower development. In practice, however, there is always a residual risk of outcrossing. Another potential strategy, yet to be fully explored, is the exploitation of apomixis (embryo development in the absence of fertilization). Transformation strategies can also be adapted to take advantage of natural barriers, e.g. chloroplast transformation (which prevents gene flow by outcrossing, see above) and genomic incompatibility, which is suitable for polyploid species such as wheat that hybridize with wild relatives (in this approach, the transgene is placed on a wheat chromosome that does not contribute to the genome of the hybrid offspring). These natural mechanisms may be augmented with artificial genetic strategies including male sterility, transgene mitigation (tight linkage between the transgene encoding the recombinant protein and another gene that con-

fers a selective disadvantage on wild plants carrying the gene, but not those cultivated under defined conditions) and genetically controlled seed sterility. As well as the transgenes encoding the pharmaceutical products of interest, marker genes used to facilitate plant transformation may also spread by the mechanisms discussed above. However, unlike the pharmaceutical transgenes, such markers are no longer necessary once the transgenic line has been established. For this reason, a suitable strategy to prevent the spread of marker genes is to excise these genes from the transgenic lines.

There are numerous genetic strategies to avoid unintended exposure both by ‘natural’ processes such as adventitious herbivory, and by human activities such as the unintentional mixing of transgenic and non-transgenic crops during harvesting, transport, refining and processing. To avoid contamination by human error, there should be a clear distinction between pharmaceutical and food plant material. The best way to ensure segregation is through the use of non-food crops like tobacco for production, since these never come into contact with food. Where food crops are used, a rigorous series of regulatory practices should be in place from the farm to the factory, ensuring complete isolation of transgenic material during growth, harvesting, transport, storage, processing, extraction and waste disposal, and this should be supported by validated procedures for cleaning shared equipment. An important step towards segregation is identity preservation through the use of visually distinct non-food varieties for pharmaceutical production, such as purple maize. The health impacts of the products of Molecular Farming are addressed in detail through human clinical trials. This is identical to the procedures used to assess the clinical efficacy and safety of any other type of drug, and it is notable that more than 25% of our current drugs are derived from plants.

Extraction and processing

Not all recombinant proteins produced in plants need processing to the same extent. At one extreme, there are proteins intended for intravenous use in humans which must be purified to the highest standards. At the other extreme, there are proteins that can be utilized in raw, unprocessed plant material (e.g. vaccine candidates and industrial enzymes used for food processing). Between the extremes, there are proteins that need greater or lesser degrees of purification for their intended uses. The purification strategies employed, and the bottlenecks encountered, depend on the

expression host and tissue. Leaves, seeds, fruits and vegetables can all be processed in much the same manner, but the processing of leaves must take place immediately after harvest (or they must be dried or frozen) to avoid protein degradation, while fruits can be chilled, and vegetables and seeds can be stored for long periods at room temperature without significant loss of activity.

To make protein production in plants competitive and sustainable, it is important to reduce the amount of bio-waste and to dispose properly of all the buffers and reagents used during extraction and processing. For example, leafy crops can be dried to restrict the buffer volumes necessary for extraction, and the reagents used in downstream processing could be regenerated and recycled, e.g., through the use of immobilized enzymes.

Purification strategies may be based on standard chromatographic techniques which fractionate proteins by size, charge or hydrophobicity, but methods can also be devised to affinity purify specific products (e.g. using Protein A or immobilized antigens to purify recombinant antibodies, or the development of stable and cheap synthetic ligands to purify proteins with particular fusion tags). One of the most promising of these is the oleosin fusion platform developed at SemBioSys Genetics Inc., in which recombinant proteins are expressed as fusions with the oil-body-specific endogenous protein oleosin in rapeseed and safflower. This is followed by a simple and inexpensive purification scheme involving the separation of oil bodies. As discussed above, the presence of fusion proteins is incompatible with therapeutic use, and the tag must be removed. In the oleosin technology, this is achieved by *in vitro* endoproteolytic processing.

Regulatory landscape

One of the greatest uncertainties surrounding the use of plants for the production of pharmaceuticals is the regulatory landscape. While plants are grown in glasshouses and in enclosed bioreactors, the production of pharmaceuticals is regulated in the same way for other production systems, and comes under the authority of the FDA and equivalent agencies in other parts of the world. The switch to open-field conditions adds another layer of regulatory complexity, because the transgenic plants then come under the authority of APHIS (part of the USDA) or their counterparts in Europe and other regions. The involvement of multiple regulatory agencies makes

the production process more complex, although recent guidelines published by EMEA suggest that production of pharmaceutical proteins in plants will become feasible even when these plants are grown in the field (EMEA, 2006).

However, all recombinant pharmaceuticals, including those derived from plants, need to comply with the national and international GMP standards for product safety, quality, potency and efficacy. It is not clear at which stage GMP requirements should come into effect when plants are used as the production system, since the strict rules governing defined growth conditions are difficult to implement in the field where variables such as the weather, differences in soil quality and the presence of other organisms need to be considered. This is increasingly important now that European regulatory requirements regarding GMP-compliance for the manufacture of medicinal products have extended to the production of clinical trial material (Directive 2001/20/EC).

Examples

A number of pharmaceutical proteins with commercial potential have been produced in plants and four case studies are described briefly below.

1. A plant-based vaccine to protect poultry from Newcastle disease virus (NDV), a contagious and fatal viral disease affecting poultry, was developed by Dow Agro-Sciences and approved by the USDA-APHIS' Center for Veterinary Biologics in February 2006. This is a notable milestone because it is the first-ever plant-based vaccine to gain regulatory approval. This vaccine is not expressed in whole plants, but is produced in plant suspension cells in steel fermenters, a production choice that resolves many issues related to containment. There are no current plans to market the vaccine, but approval from the regulators showed that making pharmaceuticals in plant cells, rather than in animal cells or whole plants, is a viable strategy.
2. A monoclonal antibody has been produced in transgenic plants and will be used to affinity purify an antigen (not produced in plants) that is used as a vaccine in humans. This antibody was approved by the Cuban authorities in June 2006. The license was obtained from the National Center of Biological Safety, which is part of the Cuban Ministry of Science, Technology and the Environment. The antibody is used to capture the active pharmaceutical ingredient (API) of the hepatitis B vaccine produced in Cuba by Havana's Genetic Engineering and Biotechnology Center (CIGB), sold under the trademark of Heberbiovac-HB.

3. The Canadian company SemBioSys uses safflower to produce human insulin. Through its oleosin expression technology the company is able to target the recombinant insulin to oil bodies maximizing accumulation and facilitating purification. Insulin therefore accumulates at up to 1.2% of total protein in safflower seeds which is commercially viable. The company envisages producing material for human clinical trials and filing an Investigational New Drug application with the FDA in 2007/2008. By following an abbreviated approval pathway reserved for products that have already been approved using a different production process, SemBioSys aims to market safflower-produced insulin as early as 2009/2010.
4. A chimeric secretory IgG-IgA antibody produced in transgenic tobacco plants has been developed to prevent the oral bacterial infection that contributes to dental caries (Ma et al. 1998). The antibody can prevent recolonization of the buccal cavity by *Streptococcus mutans*, the organism responsible for tooth decay in humans. This results in the replacement of the pathogenic organism with endogenous flora. The antibody recognizes a surface adhesion molecule which is essential for the bacteria to adhere to teeth. Phase II clinical trials of this antibody are underway.

The Pharma-Planta consortium

Pharma-Planta is a consortium of 39 principal scientists from academic and industrial institutions representing twelve European countries and South Africa. Pharma-Planta has been funded for five years, by the European Commission as part of the Sixth Framework Programme in the area “Plant platforms for immunotherapeutic biomolecule production”. The project began in February 2004.

Many reports have been published demonstrating proof-of-principle for the small- to medium-scale production of a variety of proteins in plants. Pharma-Planta aims to move beyond conceptual studies and develop candidate products for clinical evaluation in Phase I human trials. This will include compliance with all regulatory requirements, good manufacturing practice (GMP) standards and pre-clinical toxicity testing. The consortium is developing robust risk assessment practices for recombinant pharmaceutical molecules produced in plants, based on health and environmental impact, and is working closely with the appropriate regulatory authorities (Sparrow et al. 2007). Finally, the consortium is developing a coordinated program for securing and managing intellectual property which will facilitate the availability of high priority plant-derived recombinant pharmaceuticals to the poor in developing countries.

The major objectives of the five year project are as follows:

- To produce two recombinant pharmaceutical molecules in transgenic plants. These will be developed through all regulatory requirements, Good Manufacturing Practice (GMP) standards and pre-clinical toxicity testing. They will then be evaluated in Phase I human clinical trials.
- To develop robust risk assessment practices for recombinant pharmaceutical molecules produced in plants, based on health and environmental impact. Pharma-Planta will work with regulatory authorities within the EU as well as public groups to ensure that the production systems are as safe and as acceptable as possible, and that they comply with all biosafety regulations.
- To define and carry out a coordinated program for securing and managing intellectual property that will facilitate the availability of high priority plant derived recombinant pharmaceuticals to the poor in developing countries.
- To develop and refine new strategies for the expression of recombinant pharmaceuticals in plants which can be used on a generic basis for molecules that normally are expressed poorly.
- To develop and generate transgenic plants expressing the second generation of recombinant molecules that will be used in future clinical trials.

The Pharma-Planta project is divided into six workpackages. Four monoclonal antibodies were selected to be fast-tracked through the key elements of risk assessment, plant production, scale-up and regulatory affairs, with the aim of selecting two for clinical trials within the lifetime of the project. A selection of medically relevant antigens was also chosen for development, and these have entered a “development loop” in which new technologies are assessed for efficacy in model systems, for environmental and medical safety, for public acceptability, and for scale-up. It is unlikely that any of these second-generation molecules will reach clinical trials in this project, but they will contribute to the pipeline of products that will encompass the newest developments in plant pharmaceutical production technology. The two development pathways are mutually beneficial. The “fast track” brings together the developers and the regulators to address the regulatory pathway that is necessary for product development. In turn, the development loop is the vehicle for generating new knowledge, intellectual property and training that strengthen the commercial base established for production of the first-generation antibodies.

The principal fast-track molecules in the Pharma-Planta project are two monoclonal antibodies that bind to the human immunodeficiency virus (HIV). Previous studies have shown that these HIV-neutralizing antibodies, produced in animal cells, can prevent HIV transmission in rhesus macaques by topical application. Since the annual requirement for such a topical vaginal microbicide is very high (5 mg/dose, i.e. 5,000 kg/year/10 Mio. women) plants are probably the only platform that can produce sufficient amounts of these HIV-specific antibodies at an acceptable cost. Up to 120 mg of recombinant antibody per kg of biomass has been produced in tobacco leaves, tobacco suspension cells and maize kernels. The plant-produced human monoclonal antibodies showed broadly neutralizing activity against HIV (Sack et al. 2007).

Conclusions

We are facing a growing demand for protein diagnostics and therapeutics, but lack the capacity to meet those demands using established facilities. Moreover, recombinant proteins will become more important as high throughput genomics, proteomics, metabolomics and glycomics projects spawn new product candidates, disease targets and eventually new remedies. A shift to plant bioreactors may therefore become necessary within the next few years. However, the production of pharmaceutical proteins in plants will only realize its huge potential if the products achieve consistent highest quality standards, enabling the provision of clinical grade proteins that will gain regulatory approval and can be used routinely in clinical trials and treatments. The achievement of these goals is conditional on the development of technologies for improving yields, ensuring product sustainability and quality, including extraction and processing steps that comply with current good manufacturing practice (cGMP) standards. Moreover, there are several further challenges concerning the environmental impact, biosafety and risk assessment of Molecular Farming which reflect the release of transgenic plants as well the safety of the plant-derived products themselves.

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Commercial Pharming: Managing the Challenges of Drug Manufacturing in Plants and Animals

Margaret L. Eaton

Introduction

For over ten years, research has demonstrated the feasibility of using plant and animal systems as sources for drug production, a process that has come to be called ‘pharming’.¹ The expected benefits of producing drugs this way are numerous and one need only to consider one example, vaccines derived from plant cell culture, to show pharming’s promise. The cell growth media of conventionally made animal-derived vaccines can become contaminated with viruses and, also, the attenuation processes for vaccines from live viruses can fail and actually cause the disease the vaccine was intended to prevent. Producing vaccine in plants can eliminate these problems and, additionally, alleviate a vaccine manufacturing capacity problem, enhance the flexibility of manufacturing by simply altering acreage under production, simplify extraction and purification, and cost less to manufacture. Research has shown that similar potential benefits exist for drugs and other biologics derived from plants and animals. This research has progressed to the point that a pharming company has recently obtained the first regulatory approval for a “pharmed” human drug – a recombinant human antithrombin protein trade named Atryn[®] developed by U.S.-based GTC Biotherapeutics.² What makes this a pharming product is that it is

¹ For the purpose of this paper, the term ‘pharming’ refers to the branch of biotechnology that genetically engineers plants or animals to become living “factories” or “bioreactors” to produce pharmaceuticals.

² Antithrombin is a plasma protein with anticoagulant properties and, therefore, antithrombin deficiency conditions cause abnormal blood clotting. GTC Biotherapeutics, based in Framingham, Massachusetts, USA, is devoted to the development, production, and commercialization of therapeutic proteins through transgenic animal technology. GTC’s Atryn is in Phase III study in the United States in preparation for regulatory approval for hereditary antithrombin deficiency. GTC is also conducting Atryn studies to support marketing approvals for use in acquired antithrombin deficiency – blood clotting which can result from a wide array of conditions such as burns, disseminated intravascular coagulation, sepsis, cardiopulmonary bypass surgery, or acute liver failure. In addition, GTC is developing a recombinant human serum albumin, a malaria vaccine, and a CD137 monoclonal antibody to solid tumors. GTC also collaborates with other entities to develop and manufacture products such as monoclonal antibodies and immunoglobulin fusion proteins that are difficult to produce in significant quantities from conventional recombinant production systems. Intended targets for these products include conditions such as rheumatoid arthritis, HIV/AIDS and cancer. See <http://www.gtc-bio.com>, May 2007.

derived from goats whose milk protein promoting gene has been genetically altered to produce the human antithrombin protein in the milk of the animal. Until this drug was approved for human use³ by the European Medicines Evaluations Agency (EMA) on August 6, 2006, any focus on pharming's clinical potential was primarily speculative and limited to the scientists, medical policymakers, and others involved in transgenic experiments. That will soon change as this and other pharming drugs come to market.

Behind Atryn[®] in the pharming pipeline are a series of other products heading for regulatory approval application. Most of these are being developed by Pharming Group NV, a Dutch company specializing in the development of drugs and nutraceuticals in the milk of cattle and rabbits. The company's most advanced drug and the one closest to U.S. approval is recombinant human C1 inhibitor (rhC1INH) for the treatment of hereditary angioedema⁴ which is in Phase III (*i.e.*, late stage) human clinical trials. In earlier stages of development at Pharming Group are: recombinant human lactoferrin (rhLF), a naturally occurring human protein believed to strengthen the body's immune system and intended as a nutraceutical or food supplement; recombinant human fibrinogen (rhFIB) to stop excessive bleeding during surgical procedures or after traumatic injury; and recombinant human collagen type 1 (rhCOL), a biomaterial with potential uses as a hemostat, vascular and tissue sealant, implant coating, artificial skin, wound dressing and similar applications. Dow AgroSciences has also developed a tobacco source for Newcastle disease⁵ vaccine which was approved by the U.S. Department of Agriculture's Veterinary Biologics in April 2006. Canadian company SemBioSys Genetics is preparing to file an Investigational New Drug (IND) application for safflower-produced human insulin. It is also developing safflower as a source for apolipoprotein AI which can be used to reduce the plaque associated with stroke and heart attack. Origin Biotherapeutics is in the early stages of developing transgenic chickens to manufacture drugs. Applied Phytologics, Inc. is creating genetically engineered cereal products for medical, nutritional or industrial uses. Planet Biotechnology is field testing transgenic tobacco as

³ The drug was approved for the prophylaxis of venous thromboembolism in surgical patients with congenital antithrombin deficiency.

⁴ Hereditary angioedema is a life threatening human genetic disease that causes recurrent attacks of edema (swelling) of body tissues.

⁵ Newcastle is a contagious and often fatal viral disease of poultry for which there is no treatment but for which other effective vaccines exist.

a source for a monoclonal antibody against tooth decay (CaroRx[®]), a fusion protein that blocks rhinovirus, the major virus responsible for the common cold (RhinoRx[®]), and a neutralizing anti-doxorubicin antibody to prevent chemotherapy-induced hair loss (DoxoRx[®]).⁶

In the midst of all of this commercial pharming activity, it should be noted that the industry leader in this field, PPL Therapeutics PLC, once the largest company dedicated to production of human proteins from transgenic animals,⁷ shut down its pharming program and the company was later sold because of financial and management difficulties. A second pharming company that did not succeed was Large Scale Biology Corporation (LSBC) which was using genetically modified tobacco mosaic virus to infect tobacco plants which then produce a vaccine for preventing recurrence of non-Hodgkin's lymphoma. Epicyte Pharmaceutical in San Diego, California, which intended to genetically engineer corn crops to produce medicines, suffered research delays and setbacks and was eventually sold. While these and other pharming companies have failed, the ones mentioned in the paragraph above represent a sample of what is to come if the early products live up to their promise of being bio-equivalent to natural proteins, safe, effective, and more economical to develop and manufacture than the mammalian cell culture production methods used for other biotechnology drugs.

Now that a pharming product exists on the market and others are on their way, attention to these types of products is sure to increase as regulatory agencies, doctors and patients, financial analysts, the policy and activist communities, the press, and, eventually, the public comes to learn about the technology, its uses, and its atten-

⁶ Information about these investigational products is from company websites and trade journals. Since 1991, at least 125 applications to grow plants genetically modified to produce drugs or industrial proteins have been approved by the U.S. Department of Agriculture (USDA). The author has no reliable data on the current number of animal pharming product applications. Therefore, this paragraph does not contain a complete list of corporate-sponsored pharming products under development. The information may also be outdated at the time this paper is published. The paragraph is intended only to present a representative sample of corporate-sponsored research in this area. Other pharming products are being investigated by academic researchers and include monoclonal antibodies in corn for herpes treatment, gastric lipase enzyme in corn to treat cystic fibrosis, GM corn used as a human contraceptive, and a blood anticoagulant grown in canola. See, Position Paper: Pharmaceutical and Industrial Crops, Union of Concerned Scientists, October, 2006. Available from URL: <http://www.ucsusa.org>, May 2007.

⁷ PPL's primary pharming product was human α 1-antitrypsin (AAT) produced in the milk of genetically altered sheep. Patients with AAT deficiency, which is rare, develop life threatening emphysema. Cystic fibrosis was another target for this protein.

dant risks and benefits.⁸ As this happens, there are sure to be comparisons made to other genetically modified organisms (GMOs), many of which have encountered significant resistance when they entered the marketplace. The history of this resistance is as old as genetic engineering technology and is exemplified in the concern expressed to U.S. President Jimmy Carter in a 1980 letter from several high ranking religious leaders:

We are rapidly moving into a new era of fundamental danger, triggered by the rapid growth of genetic engineering. Albeit, there may be opportunity for doing good, the very term suggests the danger. Who shall determine how human good is best served when new life forms are being engineered? Who shall control genetic experimentation and its results which could have untold implications for human survival? Who will benefit and who will bear any adverse consequences, directly or indirectly? These are not ordinary questions. These are moral, ethical, and religious questions. They deal with the fundamental nature of human life and the dignity and worth of the individual being. (President's Commission for the Study of Ethical Problems 1982)

When corporations become involved to commercialize the products of new biotechnologies, the above questions take on a different character and a segment of the population has never been comfortable when business interests influence how these products eventually reach patients. At the same time, others believe that scientists do not always pay sufficient attention to the consequences of their research. The need for broader influences in the process was voiced early on when James Watson, the co-discoverer of DNA structure and Nobel Laureate, presciently anticipated the difficulties associated with both unfettered biotechnology and business when he said:

This [genetic engineering] is a matter far too important to be left solely in the hands of the scientific and medical communities. The belief that [...] science always moves forward represents a form of *laissez-faire* nonsense dismally reminiscent of the credo that American business if left to itself will solve everybody's problems. Just as the success of a corporate body in making money need not set the human condition ahead, neither does every scientific advance automatically make our lives more 'meaningful'. (Watson 1978)

Despite how long ago these comments were made, the concerns expressed remain current and will probably affect the pharming market. Since the first biotechnology-derived crops were commercialized in 1996, widespread rejection of and concern about the products has challenged regulatory agencies, energized activists, and created a lay press intent on scrutinizing the possible harms and ethical questions asso-

⁸ See, for example: Pew Initiative on Food and Biotechnology (2002).

ciated with genetically modified products. The cloning of Dolly the sheep stimulated similar debates about the possible harmful effects of pharming. (Pennisi 1998) The control of genetically engineered plants and animals in the hands of corporations has also become an issue for people who fear that business imperatives rather than safety and efficacy drive the entire process from R&D, regulatory approval, and marketing. As a result, a perception has been created that the benefits of genetically engineered products accrue mainly to the corporations and their commercial customers with the risks being borne by people, animals, the environment, and societies. An anti-corporate backlash from this kind of perspective is inevitable. (Manning 2004) Some companies, such as California's Ventria Bioscience, were so concerned about vandalism by militant environmentalists that it refused to reveal where it intended to plant its rice plants engineered to produce anti-microbial proteins. (Lee, Lau 2004) While this antagonistic state of affairs is unfortunate, given the significant health benefits that can come from pharming, the negative focus provides a rich history from which lessons can be drawn in order to guide the marketing of future products. With this as its goal, this paper will recount the past difficulties faced by companies that have introduced genetically modified organisms to the marketplace and then make recommendations for pharming companies interested in avoiding the problems seen in the past.

Human Safety

First and foremost among the concerns about using genetic technology to produce products for human consumption (food or drugs) has always been human safety. In part the fear stems from the unknown – how can there be assurance that products from a new genetic technology are safe when the technology is first introduced? It is a reasonable question and one that is not satisfied by reliance on current scientific understanding. Late-identified adverse reactions to drugs and chemicals occur frequently enough to generate wariness about new products and technologies. Therefore, although the body of scientific evidence has found that the risks posed by biotechnology products are roughly equivalent to their traditionally produced counterparts, this finding does not necessarily reassure the public. The problem is exacerbated by the fact that some genetically engineered products have come on the market without extensive human safety data. There are two main reasons for this lack of data. The first is that, in the U.S. where many of the first GMO products were

commercialized, the Food and Drug Administration (FDA) imposed a regulatory policy in 1992 for biotechnology (including GM foods) that focused on the nature of the product and not on the process used to derive the product. Therefore, the fact that biotechnologies were used to create the product did not generate any special requirements so long as the corporate sponsor could convince the FDA that the product was substantially equivalent to its natural counterpart.⁹ The second reason is that, in contrast to large pharmaceutical companies that often seek so-called blockbuster markets, biotechnology companies tend to develop drugs used in small populations of patients. These populations are often so small as to qualify for orphan drug status in the U.S.¹⁰ One difficulty in developing orphan drugs is that not many patients are available for clinical trials, and the patients who are available often live far apart. The shortage of human subjects and the research difficulties often mean that it is only possible to collect a relatively small set of safety data. Some examples provide insight into the problems these situations create for companies.

When Monsanto submitted a marketing application to the FDA for the first bio-engineered animal drug, recombinant bovine somatotropin (rbST),¹¹ the company was required to satisfy two major requirements: the drug was safe for animals and the milk from cows injected with rbST was substantially equivalent to milk from untreated cows. Therefore, the FDA did not require extensive human safety tests before approving the use of the drug. Even though it was not required to do so, Monsanto voluntarily submitted additional human safety data and studies that showed that any rbST or related hormones that remained in the milk would not be biologically active in humans. The studies were sufficient for the National Institutes of Health to conclude in 1990 that the composition and nutritional value of milk from rbST-treated cows was essentially the same as milk from untreated cows. (National Institutes of Health Technology Assessment Conference Statement 1990)

⁹ The Coordinated Framework for the Regulation of Biotechnology, promulgated initially by the Office of Science and Technology Policy and adopted by the FDA, is based on the principle that techniques of biotechnology are not inherently risky and that biotechnology should not be regulated as a process, but rather that the products of biotechnology should be regulated in the same way as products of other technologies. (Office of Science and Technology Policy 2002)

¹⁰ In the U.S., orphan drug status is given to drugs used to treat diseases that affect fewer than 200,000 patients. To induce drug companies to develop drugs for these small populations, the Orphan Drug Act provides incentives, the primary ones being a seven-year period of market exclusivity following approval of an orphan drug by FDA and a 50% tax credit for certain clinical research expenses involved in developing an orphan drug.

¹¹ rbST is an injectable growth hormone that can increase milk production in dairy cows by as much as 20%.

In 1993, the FDA ruled that milk and meat from rbST-injected cows were safe for humans and allowed milk and meat from rbST-supplemented cows to enter the commercial food supply. Marketing approval was controversial, however, and had not gone smoothly. Sufficient public attention had been generated in this process that critics continued to voice concerns about the product after it was approved.¹² The primary concern related to human safety. Despite the study data provided to the FDA, there was significant lay concern that increased amounts of growth and other hormones present in the milk of treated cows could produce harmful effects, particularly abnormal growth patterns and high blood pressure in children. Many did not believe that Monsanto had produced sufficient data to show that milk from rbST-treated cows was safe either in adults or children, especially with long term use. Monsanto had also convinced the FDA that labels identifying dairy products as coming from rbST-treated cows were not needed. Both Monsanto and the FDA agreed that this kind of labeling would falsely imply that products from rbST animals were inferior. Monsanto also resisted organic and other producers that wished to label their dairy products as “rbST-free”. As a result of the safety and labeling controversies (and also concerns about animal health, see below), Monsanto faced product boycotts from dairy producers, grocers, schools, and chefs. Activists petitioned Congress and the FDA to ban the product and they also staged high profile anti-rbST campaigns, which included newspaper and magazine ads and highway billboards. Some states demanded that milk from treated cows be labeled and forced the FDA to perform a safety re-assessment. Both the EU and Canada instituted moratoria on the use of rbST. Lawsuits resulted between Monsanto and those dairy producers and states that placed labels on dairy products stating that they came from rbST-treated cows. (Marden 1998) The press coverage was very negative. U.S. media studies at the time showed that 70% of all GM food stories featured the negative aspects of products. All of these difficulties caused rbST sales to fall far short of what had been projected.

The lack of trust in the human safety of rbST was attributable to two major uncertainties – that Monsanto had decided what safety data was sufficient and that the FDA, following their substantial equivalence policy, had not required Monsanto to submit more data. In this climate, it was easy for people to believe the negative medical and lay news reports that followed rbST’s approval. These included con-

¹² Information about the marketing of rbST is from Eaton (2004).

cerns related to the growth factor called IGF-1, which had been found in slightly higher levels in the milk of rbST-treated cows. At the time that the product was approved, Monsanto and other scientists relied on data that showed that IGF-1 was destroyed by digestion in the mouth and stomach, was not absorbed into the blood, and so would have no physiologic effect. Subsequently, however, researchers found that, in the presence of the milk protein casein, IGF-1 largely survives digestion and passes intact into the intestine, where it is absorbed into the bloodstream, again in small amounts. Later studies were published linking high blood levels of IGF-1 with both prostate and breast cancers. (Chan 1998 and Hankinson 1998) Despite the lack of data on the clinical significance of this finding and that the FDA had reaffirmed rbST's safety, (Steyer 1999) the breast cancer story became nationally prominent after it was aired on CBS television news. Even more serious, critics claimed, was the fact that no long-term or chronic toxicology studies had been done on rbST prior to marketing nor were they requested by the FDA. Given this situation, a significant number of people were not willing to believe that the product was safe.

Companies that had developed genetically modified foods shared similar problems. Both Calgene and Zeneca produced GM tomatoes that, respectively, prevented shipping damage and increased viscosity thereby making a superior sauce tomato. However, both tomatoes contained marker genes that conferred resistance to the antibiotic kanamycin. Since this was a medicine used to treat infections and because there had been no long term studies, consuming the tomatoes was thought by some to pose a risk of inducing kanamycin-resistant bacterial infections. Although there were other reasons, this safety issue contributed to the fact that both products were withdrawn from the market not long after approval. In both cases, revenues on product sales did not approach the costs of development. (Manning 2004) In another example, pharming's first human drug product recombinant α_1 -antitrypsin (AAT) from PPL Therapeutics, failed in its first human safety trial despite over 15 years of study. Since the drug was to treat the lung condition attributable to AAT deficiency, it was tested in an inhaled form with the expectation of good results. However, the trial was stopped because of concerns about hypersensitivity pneumonitis ascribed to minute amounts of animal protein contaminating the product. (Spencer, Humphries, Brantly 2005) Atryn may also face difficulties because of a lack of extensive safety data. GTC Biotherapeutics had conducted safety and efficacy testing in humans but, given

the small number of patients with hereditary antithrombin deficiency undergoing surgeries,¹³ GTC's EMEA submission included only five surgical cases. Based on this limited data, the EMEA Committee first rejected GTC's application but after GTC appealed and asked for inclusion of nine childbirth cases, the drug was re-reviewed and then finally approved. With so few research patients, however, it may take some time on the market for the full safety profile of this recombinant drug to become evident.

Failure to contain the transgenic animals or plants used in pharming may also result in consequences to human health if the genetically modified products end up in the food supply. This concern is currently strong with plant pharming and the potential hazard was first articulated after it was determined that the edible cereal grains would be a viable drug production system. (Vaquero 2000) The concern is exacerbated by the fact that tests for commercial pharmed plant DNA are proprietary and so cannot be verified or independently tested. Several "escapes" of genetically modified food plants have put the public on high alert for this problem. For instance, when Adventis CropScience announced that traces of its Starlink[®] GM corn were discovered in numerous food products, comments such as this appeared in biotechnology policy journals:

The troubling fact was that a GM crop *not* approved in the US for human consumption found its way onto dining tables. The adventitious presence of Starlink in tacos had no consequences for human health, but could the same be said of a crop variety designed for biopharmaceutical production? (Nature Biotechnology 20:527, 2002)

In a lay science magazine, this quote followed reports of the ProdiGene incident (described below) where corn containing a transgene to make pig vaccine spread to neighboring corn fields:

...more importantly, the leak shook the public's confidence in the technology. So far, no one has shown that current GM crops carry any health risks. But pharma crops, the new generation of GM plants, raise the safety stakes: the proteins spliced into these plants are specifically chosen to target physiological function. ...A consensus about how worried people should be about contamination seems unlikely to emerge in the near future. When it comes to the risk of drugs making their way into the food sup-

¹³ To recruit patients for its Atryn clinical studies submitted to EMEA, GTC Biotherapeutics contacted 23,000 physicians in multiple countries to identify 500 who treated patients with antithrombin deficiency. From this pool, it took 18 months to enroll 14 patients who fit the study enrollment criteria, since patients with hereditary antithrombin deficiency only need supplementation during high risk situations or when pregnant and giving birth. See Scotland (2005).

ply, says Ellstrand [Norman Ellstrand, a plant geneticist at the University of California at Riverdale and director of the Biology Impacts Center], “I wouldn’t say zero tolerance for all pharmaceuticals, because presumably some of those things would be totally benign if they got into the food supply.” Those products that might not be harmless, he advises, “should be put into nonfoods, grown inside of buildings, or simply shouldn’t be created in plants at all.” Margaret Mellon, head of [Union of Concerned Scientists] food biotechnology program, disagrees. “We can’t have a policy which only allows safe drugs in our food. It has to be no drugs.” (Katsnelson 2004)

The debate about whether transgene flow into the food supply affects human health is exacerbated by the fact that DNA detection technology has become so sophisticated that minute amounts of contamination can be detected. The presence of such small amounts of contamination can be either worrisome or so small that it is difficult to believe that any effects will occur. In addition, the testing is most often for the transgene with the concomitant finding that the food in question does not contain the protein that the DNA codes for. Without the protein, in many cases it is assumed that the presence of the DNA is harmless. (Katsnelson 2004) Nonetheless, this fear that pharmed drugs can accidentally become part of the food supply has already contributed to the demise of at least one pharming company. In 2005, Large Scale Biology Corporation went out of business citing as main reasons the doubts from investors about food contamination and safety and about the large pharmaceutical companies that LSBC intended as development partners. The fact that LSBC was using a non-food crop (tobacco) as its source plant and that the methods used to insert transgenes prevented spread by pollen was not sufficient to allay concerns. (Pollack 2005)

Based on the experience with previously approved genetically modified products, scientists have identified areas of potential human safety risks and these have been incorporated into regulatory guidelines for consideration by companies developing pharming products (U.S. Food and Drug Administration, Center for Biologics and Research 1995): The risks include allergenicity and contamination from animal and plant care products such as herbicides, food additives, pesticides, drugs and vaccines. Infection with animal pathogens such as viruses, bacteria, mycoplasma, or transmissible spongiform encephalopathy agents is also high on the list of concerns. Various biosecurity controls are imposed to prevent such zoonotic and other animal-based risks and these controls cover both the raising and handling of animals and the purification of the drug from the milk of the animal. The extent to which current biosecurity measures are reassuring, however, is periodically undermined by

studies that show how difficult it is to detect some infectious agents such as prions and how easily some animal pathogens such as endogenous retroviruses are transmissible to humans. (Paradis 1999) It is also probable that, unlike traditional biotechnology cell culture processes, these problems may appear inconsistently and generate considerable lot-to-lot variation in both quality and purity of the product. The fact that serious problems such as these are covered by guidelines in the U.S. rather than strict and consistent regulations may contribute to less than full trust in product safety.

Complaints about the lack of safety data prior to the introduction of GM foods led to statements such as by a Food First spokesperson who said that genetically modified foods represent “the largest ecological and human health experiment in history. The U.S. public and environment are the guinea pigs right now.” (Coale 2000) It would be unfortunate if that view spilled over to pharming products. Currently, with only one pharming product on the market, human safety risks are theoretical, yet it would be imprudent to ignore the possibility of risk. The first time that an approved pharming product is responsible for a human adverse event or drug-producing plant DNA is found in the food supply, it may be difficult to underestimate the damage that will be done to the pharming industry, impacted industries, regulators, and the technology. To illustrate the point, one member of the U.S.-based National Food Processors Association told a pharmaceutical plant workshop, “This represents something we never want to see” and then showed a mock headline reading “Medical Carrots Containing Vaccine Found in Baby Food: Recall Underway.” (Pew Initiative on Food and Biotechnology, the U.S. Food and Drug Administration, and the Cooperative State Research, Education and Extension Service of the U.S. Department of Agriculture 2002)

Perceived Benefit

There is no doubt that the purpose of a genetically modified product heavily influences the speed and degree of its regulatory and public acceptance. History has shown that a drug, for instance, for an unmet medical need gains approval and acceptance much more readily than a genetically modified food for which there is no felt need. Two 1980's era products exemplify this difference. The first genetically engineered drug, insulin, gained acceptance because of the difficulties of

obtaining insulin from animal sources and the problems associated with human allergenicity to the animal proteins. The second genetically engineered drug, recombinant human growth hormone (rhGH), replaced the use of scarce and sometimes prion-contaminated human cadaver sources. Because of these benefits, regulatory agencies welcomed the marketing applications and physicians readily prescribed the drugs despite lingering 1970s-era concerns that bioengineering techniques would generate mutant organisms that could escape the lab, contaminate the environment, and harm humans. It is likely that any therapeutic that is currently harvested from human blood will also receive a favorable reception given the chronic shortages, the cost of obtaining and processing blood, and the problems with infectious risks. The lack of perceived need, in contrast, was a factor in the widespread rejection of Monsanto's rbST. Illustrative protests against the drug included this quote, "What person in their right mind would choose to ingest a bioengineered hormone – whose long-term effects have not been studied – so cows could produce more milk that we don't need." (Mason, Milk 1994) For reasons most likely having to do with feasibility of execution, products developed from new genetically modified technologies are frequently of the sort that, initially at least, seem to offer little. Calgene's Flavr Savr tomato described above is a case in point. It was an anticipated success since the genetic alteration produced a tomato that could be ripened on the vine longer and still withstand shipping damage. The tomato is relatively easy to modify genetically, and it was hoped that the experience of manipulating tomato ripening could be used for other fruits. The problem, however, was that these tomatoes tasted more bland than their natural counterparts and were rejected by consumers. After spending ten years and more than \$200 million in R&D, the Flavr Savr tomato was withdrawn in 1997 after only three years on the market.

For both regulatory approval and medical and patient acceptance, tolerance for risk usually rises with the benefit perceived. Given this axiom, GM human drugs and vaccines will generally fare better than will GM neutraceuticals, animal drugs, foods, and food additives. Interesting exceptions may be a pharmed drug available from other methods or foods that can be produced in countries that are prone to famine or nutritional deficiencies. For instance, in the near future, insulin will probably be available from both cell culture and safflower plants and it will be enlightening to see if the perceived benefit-to-risk ratio will differ between the two because of their

methods of derivation. Syngenta's Golden Rice¹⁴ is an example of a transgenic product with great therapeutic and nutritional promise – to alleviate the vitamin A deficiency and resultant blindness and other illnesses that are common in malnutrition. The potential benefit is obvious since an estimated 1–2 million children die each year for lack of vitamin A. When this product first came on the market, however, the promise of benefit was not fulfilled since not enough vitamin A could be obtained in the normal amount of rice eaten. (Christensen 2000) If this problem cannot be remedied and the rice becomes just an enriched crop valued in developed countries for its antioxidant properties, it is doubtful that this food will be able to provide enough benefit to overcome doubts about the risks associated with GM crops. Finally, saying that high benefit can significantly increase risk tolerance does not mean that at some point there will be a reversal of the ratio. The magnitude of the risk posed by a pharmed product can overcome even significant benefit especially if those risks concern persons other than the patient (such as with zoonotic infections) or the environment (such as with gene flow contamination).

Transparency, Consent, and Choice

Another difference between pharmed drugs and other genetically modified products is the degree to which patients or consumers choose to accept them and do so fully informed of the consequences. Genetically modified foods suffered in this regard in the U.S. since these foods were widely planted and in the food supply well before most American consumers were aware of their presence. This public ignorance was largely the result of the prevailing practice in the U.S. where, in order to protect confidential business information, USDA permits for commercial GM plants rarely disclosed the type of GM plant or how much acreage was under cultivation. As a result, several years ago when the USDA was estimating that more than 60 percent of corn, 83 percent of cotton, and almost 89 percent of soybeans grown in the United States were genetically modified for various traits (including herbicide tolerance and insect resistance), and that up to 70 percent of all processed foods in grocery stores contained GM ingredients, (California Department of Food and Agriculture 2003) U.S. polls were showing that 60 percent of respondents thought that less than

¹⁴ Golden Rice is genetically modified to contain a daffodil gene that creates beta-carotene, a pro-vitamin A. See, Biofortified rice; a contribution to the alleviation of life-threatening micronutrient deficiencies in developing countries. Available from URL: <http://www.goldenrice.org>, May 2007.

half of the processed food in grocery stores contained GM ingredients and only 19 percent felt they had eaten GM foods. And, while 55 percent of responders had heard “not much” or “nothing” about GM foods, 75 percent wanted to know if their food was genetically modified. (Pew Initiative on Food and Biotechnology 2001)

Given these disparities, some consumers came to resent the fact that genetically modified foods had been introduced into the food supply without their knowledge, acquiescence, or consent. (Bailey, Lappe 2002) These were usually the same consumers who remained uncertain about the safety of GMOs and wanted the ability to avoid them. They demanded labels that identify the product as containing GM ingredients (these do not exist in the U.S.) or at least have the ability to purchase products labeled “GMO free” (which is generally allowed in the U.S. and is becoming a more widespread practice (Arnoldy 2006)). Although fewer in number, others want to avoid GM foods for religious or cultural reasons. There are also some physicians who want labels so that they can identify any new illness caused by genetically engineered food. Others believe that corporate interests influence the judgment of company scientists and that too many regulators are biased in industry’s favor, both of which undermines product safety. All of these factors entered into the opposition Monsanto faced when marketing their GM foods and rbST. Monsanto’s marketing practices and its opposition to labeling was viewed by some as an attempt to force products on the market. (Reynold 1999) Despite the FDA’s agreement that GMO labels falsely imply a safety issue, demands for labels persists mainly because consumers want to exercise choice in their food selections. Rebuffing the argument that there is no scientific data or reason to support a safety concern, those who wish to avoid GM foods counter that scientists have been wrong in the past and paying a little extra to have foods labeled is worth it to avoid the risk, even though small, that long-term consumption of GM foods will create a health hazard for themselves or their children.

In contrast, consumers of drugs (*i.e.*, patients) are afforded the opportunity to accept or reject recommended drug treatment. Current medical, ethical, and legal requirements call for the physician to inform the patient about the risks, benefits and alternatives of any recommended treatment and patients have the right to refuse any recommended drug except under certain emergency or psychiatric situations. Pharmacists in the U.S. are also required in most states to provide patients with information about dispensed drugs. In both situations, patients are being advised by independ-

ent professionals whose ethics require them to place primary importance on the welfare of their patients. Although patients probably rarely exercise their right to refuse recommended drug treatment, the fact that they have the right to do so under informed conditions affords a measure of control and freedom that is not often available when choosing whether to accept or reject GM food, which can also be perceived to as fundamental to health.

In the case of pharming products, the drug and vaccine products will be offered and dispensed under the prevailing medical conditions. What is not known at this point is whether the regulatory agencies will require the products to be labeled or patients informed about the animal or plant source. If past policy and practice is any indication, the answer to this question will be “no”. Most drugs are (or were, initially) plant (digitalis) or animal (insulin) or human (growth hormone) derived without patients being informed of this fact. That their drug is a product of biotechnology processes is also probably not known by many patients. Since there is no demand for this information, there is no reason to expect that the situation will change for pharmed drugs. The *status quo* may change, however, if patients come to believe that their plant-derived drug is harmful to the environment or animal rights activists protest the use of animals as bio-factories for drugs. While patients may continue to seek access to unique pharmed drugs, if there is a non-pharmed drug available, some will undoubtedly choose it.

Impact on Animals

Prior to the arrival of rbST and informing the debate about it, animal rights activists had protested the use of horses as a source of hormones used to treat the symptoms of menopause.¹⁵ When animal rights activists and the public became aware that over 35,000 female horses in the U.S. and Canada were impregnated each year and confined in stalls to collect urine for estrogen, concern rose for the welfare of these animals and their foals, which are often sent to feed lots and then slaughtered for meat. Women’s groups such as Canada’s Women’s Health and Ethics Coalition, citing health, environmental, and animal welfare issues, called for the end of the prac-

¹⁵ The estrogen products used in many hormone replacement treatments comes from the urine of pregnant mares, hence the trade name of the drug product Premarin®. Animal rights groups that object to this use of horses include HorseAid which sponsors the website <http://www.Premarin.org>, May 2007. This website exists to protest the use of horses in the manufacture of estrogens for human use.

tice and, in response, individual women spoke up about their decisions to discontinue post-menopausal hormone replacement drugs because they did not want to be a party to the use of horses for this purpose. (MacInnis 1996) News reports began to appear that rescue farms were created to shelter the foals. (Montgomery 1997)

Soon after this issue had been reported in the lay press, rbST was targeted for opposition because of the possibility that injected cows would suffer from the use of the drug. At the time that rbST was first considered for approval in the U.S., the data on animal safety was insufficient to dispel questions about the fate of the cows injected with the drug. Activist groups such as People for the Ethical Treatment of Animals (PETA) demanded more data and were skillful in convincing regulators of the potential for animal harm. The studies that had been done showed that rbST use increased the metabolic demands on the animal and led to weight loss, stress, and shortened life span. Other adverse reactions included reproductive problems, calving irregularities, digestive disorders, lameness, and mastitis, the latter necessitating the increased use of antibiotics which theoretically could come up in the milk. Empathy for rbST animals prompted comments like this, made by a newspaper reporter writing about the drug: “Any nursing mother knows about a certain physiological overload of hunger, fatigue and engorgement with natural lactation. And then to have your chemistry skewed to produce about 20 percent more? No wonder rBGH-injected cows suffer from what is called a ‘prolonged negative energy balance,’ resulting in weight loss, among other things.” (Mason 1994) The regulatory agencies did not ignore these concerns and animal health issues delayed the approval of rbST in the U.S. and prevented approval in Canada.

Heightened animal welfare awareness from these incidents is likely to attach to animal pharming. Two issues have already surfaced – the fact that many animals are killed in the process of producing the transgenic herd and, as was the case when PPL’s 6,500 transgenic sheep were no longer needed, every animal must be destroyed to prevent any gene spread after pharming uses end. (Timons 2000) The natural regret over the destruction of otherwise healthy animals has already caused difficulties for Pharming Group. Public complaints were voiced over the fate of the company’s first genetically engineered bull, Herman, which was created in 1990 so that its female offspring could produce lactoferrin. When the experiment was abandoned in the mid-1990s, Dutch law required that Herman and his offspring be killed to prevent the accidental release of transgenic organisms. The Dutch Society for the Protection

of Animals and members of the public were vigorous in their attempts to save Herman so that he could live out his life in peace in his familiar surroundings. (Science 295:437, 2002) Pharming Group's prolonged negotiations between the legal requirements, the activists' demands, and the public pressures over one research animal is an example of how diverting animal welfare issues can be for companies.

In general, regulatory agencies responsible for animal welfare attempt to ensure healthful surroundings, proper medical treatment, the discovery of any special management measures needed, and freedom from pain and suffering. Specific to pharming animals, regulators are grappling with the possibility that a transgene could be activated in places other than the mammary gland, with the resulting protein being toxic to the animal. (Gillespie) In addition, the FDA has stated that it will consider whether the health or usefulness of pharmed animals could be damaged by high levels of protein expression or an affect on the expression of endogenous proteins. (U.S. Food and Drug Administration, Center for Biologics and Research 1995) Whether any of these animal welfare concerns impact the approval and acceptance of pharmed drugs remains to be seen as does the acceptance of animal pharming products once on the market.

Impact on the Environment

In 2002, more than 100 million acres of bioengineered crops were planted in the world. (Bren 2003) The potential environmental harm from this much planting has received widespread attention. Primary among the concerns is the so-called genetic pollution that occurs when transgenes from GM plants escape to or co-mingle with other wild or crop plants. Ways in which this can happen include mistakes such as: GM seed is left in the field to germinate in following years, pollen from GM plants flows to non-GM crops, GM and non-GM plants are co-mingled during harvesting or processing. Soil microorganisms and water supplies can also be affected when transgenes escape into the environment. Whether animals and insects feeding on GM crops can be harmed is also being studied. Reduction in biological diversity is also a potential risk if genetic modifications are spread too widely. Additionally, ecological systems can be disrupted if, for instance, GM pesticide resistant plants result in pesticide resistant pests. (PEW Initiative on Food and Biotechnology 2004) A major fear (and a difference between pollution from GM organisms and that from chemi-

cal or nuclear contaminants) is that, once released into the environment, genetically modified organisms cannot be removed.

These fears have been magnified by several instances of the inability to manage gene flow and co-mingling that of GM plants. Examples include these incidents:

- 1999: The Swiss Department of Agriculture announced that two of Pioneer Hi-Bred's non-GM corn seed varieties were contaminated with foreign genes. As a result, many cornfields were burnt or destroyed and the Swiss seed importer was required to offer payments of 700 Swiss Francs per hectare to compensate affected farmers. (Furst 1999)
- 2000: The StarLink incident involved the finding that small amounts of StarLink GM corn, which contained a gene expressing an insecticidal protein and not approved for human use because of its allergenicity potential, was found in many food products including taco shells and cereals. (Dorey 2000) Although no documented human health problems were reported and there was scientific data indicating that StarLink was not allergenic, there was widespread unwillingness to believe that the contamination was benign. The resulting negative publicity was widespread and StarLink was recalled, costing the industry (Aventis CropScience, corn producers and processors, food stores) hundreds of millions of dollars, some estimates as high as \$1 billion. Lawsuits seeking compensation for depressed corn prices and trade moratoria on imports added to the costs of this incident. (Nelkin, Marden 2004)
- 2000: The EU found that canola seed imported by Canada's Advanta contained small amounts of unapproved GM traits. Advanta's investigation revealed that, despite having followed all of the required isolation rules, the contamination had resulted from gene flow from a neighboring field and the genes moved into the conventional foundation seed. Again, protests were lodged by environmental groups and government officials and reported in the media. The costs associated with the incident included plowing under all of the Advanta canola plants in France and a ban on the selling of any of the canola grown in Sweden. (Smyth 2002)
- 2002: Monsanto notified the FDA that a GM canola oil marketed by the company might be contaminated with a different strain of GM canola oil that had not been reviewed or approved for food uses. Instead of being forced to recall the product, however, Monsanto was allowed to consider the event as a voluntary

consultation with the FDA to review the contaminant GM canola oil for human consumption. The FDA eventually ruled that the GM canola oil was safe for humans to eat and that no mandatory FDA approval was required to sell the oil. (Killman, Carroll 2002)

- 2002: Pollination of Canadian organic canola crops with GM material disqualified growers from organic certification. As a result, the Saskatchewan Organic Directorate initiated a class action suit against Monsanto and Aventis Crop-Science to seek compensatory damages for revenues lost. (Bouchie 2002)
- 2002: Human error was attributed to the spread of corn genetically modified by ProdiGene, Inc. to contain a vaccine against transmissible pig gastroenteritis. ProdiGene was fined \$250,000, over 150 acres of corn fields in Iowa and Nebraska were burned, and, when it was discovered that the GM corn was harvested along with soybeans, 500,000 bushels of soybeans were burned also at a cost to the company of \$3 million.
- 2004: The Union of Concerned Scientists published a pilot study that found DNA genetically engineered to resist herbicides had contaminated traditional seeds of three major U.S. crops, corn, soybean, and canola. The UCS concluded that “seed contamination, if left unchecked, could disrupt agricultural trade, unfairly burden the organic industry, and allow hazardous materials into the food supply.” (Union of Concerned Scientists 2004)

In the most recent example in 2006, Bayer CropScience notified the FDA and the USDA that trace amounts of a genetically modified experimental rice (called Liberty Link 601 or LL601) were found in commercial rice seed and had entered the U.S. and EU food supply. This rice had been bioengineered to be tolerant to Liberty® herbicide, was considered experimental and not intended for commercialization,¹⁶ had exceeded USDA growing and field test biocontainment requirements, and had not been submitted to FDA for evaluation under the voluntary biotechnology consultation process. Later, the FDA concluded that the presence of this bioengineered rice variety in foods and feeds posed no safety concerns. (Food and Drug Administration 2006) This conclusion was the result of the FDA having previously approved the protein found in LL601 and having reviewed its safety in food and feed for other crops. However, previous containment failures such as those above and the fact that no one

¹⁶ LL601 rice was tested on U.S. farms between 1998 and 2001, but the company decided not to market the product and never submitted a request for regulatory approval. There were no allegations, except in the EU, where the importation of GM rice was banned, that any laws were broken.

could explain how LL601 had contaminated regular rice has fueled fears that containment of genetically modified food plants might be impossible and that contamination of the food supply with non-food GMO's is inevitable. (Nature Biotechnology 20:527, 2002) According to Joseph Burris, an emeritus professor of seed science at Iowa State University, "Our fields are factories without walls. We can't control the environment." (Katnelson 2004)

These experiences have contributed to the view that we are unable to predict the potential environment impacts of growing, harvesting, and processing GM plants. Also, the economic costs of gene contamination are potentially very high since not only is the GM source usually recalled and destroyed but value is also ruined for all of the contaminated products. Organic farmers in particular are fearful that the inability to prevent gene contamination can destroy their entire industry. In all of these situations, regulatory systems lose credibility and trade disputes and lawsuits are inevitable and highly disruptive. (Smyth et al. 2002) While many European countries have restricted the growing and/or selling of GM crops, the U.S. has been relatively permissive in this regard. That situation may change, however, especially with the advent of pharming. Concern about human and environment safety have begun to influence American jurisdictions when voter initiatives to ban the planting of any GMOs have started appearing on the ballots and some have passed. (Wasserman 2005) The GMO containment problem was also addressed by the U.S. National Academy of Sciences which, while of the opinion that most GMO contamination poses little risk, advised that those GMOs that do pose risks (presumably pharmed drugs) require more stringent, integrated, and redundant bioconfinement methods instituted at the beginning of the development of the plant or animal. (National Academy of Sciences) The possibility that a pharming plant could pass on its drug-making capabilities to other plants is of great concern and has prompted activists and industry groups to demand strict controls. The activist group Greenpeace has demanded that crops that are genetically engineered to produce pharmaceutical or industrial proteins should be grown only in contained facilities. (Greenpeace 2001) A food industry alliance led by the Grocery Manufacturers of America has also called for a ban on using food crops for pharming purposes. (Grocery Manufacturers of America 2003)

In the meantime, while policy groups and regulators are working on viable options, plant pharming continues. SemBioSys Genetics, for instance, predicts that the com-

pany can meet the world's total projected insulin demand in 2010 with less than 16,000 acres of GM safflower crop.¹⁷ Despite company assurances that the biology of safflower pollination patterns facilitates containment, with this amount of acreage being planted, the environmental impact of this GM crop will be closely watched.

Regulatory Proficiency and Corporate Conflicts of Interest

The ability of regulators is always challenged when they are asked to review and approve medical products that have been produced using new technologies. In most cases, there are inevitable tensions between the company's need to get a product to market and the agency's need to protect the public health by doing a very thorough safety and efficacy review. In the case of drugs that result from pharming, the agency that regulates drugs and biologics will also have to face the additional challenge of interfacing with the agencies that regulate animal welfare, agriculture, and the environment. It is common in complex situations like this to see differences of opinion expressed about the ability, competency, rigor, currency, speed, and flexibility of the regulatory system. (*Nature Biotechnology* 22:527, 2004) And there is no doubt that pharming will put the regulatory systems to a strenuous test.

In the U.S., for instance, the USDA issued new regulations in 1993 that required a permit to field test genetically modified plants intended to produce drugs. In September 2002 and in response to public concerns, the USDA and the FDA jointly published a guidance document outlining their expectations for drugs, biologics, and medical devices derived from bioengineered plants.¹⁸ However, the ProdiGene contamination incident in 2002 prompted the USDA to again revise and strengthen its oversight rules. This process resulted in a new draft guidance issued in 2006. (USDA, APHIS 2006) Companies are now required to use designated equipment for planting and harvesting pharming plants, provide better crop containment training for growers, use wider buffer zones between GM and other crops, plant pharming crops before or after surrounding crops, conduct post-harvest monitoring, and undergo at least five inspections a year. In addition to USDA rules, the FDA will also set standards for field operations, in essence regulating the field as a manufacturing facility as it does for traditional drug manufacturing. Both agencies will also interface with

¹⁷ <http://www.sembiosys.com>, May 2007.

¹⁸ See: <http://www.fda.gov/cber/gdlns/bioplant.htm>, May 2007.

the Environmental Protection Agency in regulating pharming products. How effectively the various agencies will be able to coordinate review and oversight remains to be seen. In addition, although these new requirements are intended to prevent future contaminations, food industry, consumer, and environmental advocates and some scientists have complained that, while better, the new rules are not stringent enough to prevent contamination of the food supply. Some skeptics are even less confident since they hold the view that the USDA favors the biotechnology industry and the Midwestern growers who see pharming as a new economic opportunity. (Pew Initiative on Food Biotechnology 2004, Karnelson 2004)

Only time and experience will tell if the new guidelines are effective and, in the meantime if history is any indication, the regulatory agencies will suffer further loss of trust with each subsequent incident of environmental or containment problem. After the StarLink incident, the public learned that an activist group had discovered the contamination, not a regulatory authority, and a Pew Initiative on Food and Biotechnology public opinion poll at the time showed that 45% of American were “not confident” in their regulators. When the FDA announced in 2002 that it would rely on the USDA to regulate the field testing phase of pharmed plant production, (FDA 2002) there were questions about the wisdom of ceding this authority. Questions are also raised because of the differences between countries in their biotechnology regulatory decisions. The EU, for instance, tends to rely on the Precautionary Principle which, in its most general definition, states that where there is doubt about safety, a technology should be avoided or at least limited. In the U.S., regulators of GMO’s have tended to focus on the characteristics of the products of biotechnology and assume that biotechnology processes *per se* are not a reason to impose more rigorous requirements. With such different regulatory policies, consumers often wonder if their system is too liberal or too strict.

The fact that the U.S. GMO regulations and guidelines have been more liberal and are revised after biotechnology processes are shown to produce harm is seen by some as commendable flexibility and others as a sign of laxity. One example highlights this difference. In 1989, Pharming Group was ordered by the Dutch government to stop all animal cloning experiments that it was conducting to boost the efficiency of drug protein production in cows. The reason behind the government’s move was to support the policy that genetic engineering and animal cloning is permitted only when there are no feasible alternatives in lower organisms and when the benefits to socie-

ty outweigh animal suffering. (Enserink 1998) In response, Pharming Group announced that it would move its cloning research to the U.S., under the assumption of encountering a more permissive regulatory climate. In cases such as this, when regulators in one country are seen as more permissive or more hospitable to corporate interests than others, it forces the question of which regulatory scheme better serves the public interest. Regulatory agencies and the governments that control them are not blind to this kind of public issue. Therefore, GTC Biotherapeutics may encounter more scrutiny when it submits its limited Atryn clinical data to the FDA. Also, SemBioSys has stated that, because its genetically modified safflower will be producing insulin, a drug with a long history of human safety, and because of the FDA policy to focus on the product and not on the bioengineering process (at least with animal drugs), it expects an abbreviated regulatory approval process. In a climate where environmental and food safety groups are calling for more stringent regulations for pharming products and a ban on using food crops to produce drugs, SemBioSys and pharming companies like it may encounter more regulatory friction than expected.

Price and Access

Whenever drug prices are high, the issue of equitable access emerges and forces companies to deal with demands for lower and affordable prices. On the face of it, drugs produced from pharming methods may seem to have an advantage when it comes to pricing. One of the benefits of pharmed products and a major reason for their commercialization is the expected cost savings that can be achieved by using plants and animals rather than using existing biotechnology cell culture processes or obtaining therapeutic proteins from human blood. For instance, GTC Biotherapeutics has estimated that the capital costs for a mammalian cell fermentation system that generates 100 kilograms of drug a year would run from \$300 to \$500 million, but 150 of GTC's goats can produce roughly the same amount of drug and cost a tenth as much. (Choix 2006) SemBioSys believes its safflower-produced insulin can reduce capital costs compared to existing insulin manufacturing by 70% and product costs by 40%.¹⁹ An executive at Centocor, Inc. estimates that producing 1,000 kg of human antibodies in hamster cells costs about \$105 to \$175 per gram while transgenic plants might be able to produce the same amount

¹⁹ Press Release, Sembiosys achieves major milestone, July 18, 2006. See <http://www.sembiosys.ca>, May 2007.

for \$15 to \$190 per gram. (Pew Initiative on Food and Biotechnology 2002) Pharming also promises to supply a reliable and cheaper source for blood products currently obtained from human donors, a system where shortages are common and costs are high.

Even though the cost of pharming development and manufacturer may be lower than cell fermentation, cheaper drugs are not necessarily the result. One reason is that many pharmed drugs will be biologics for small and orphan markets, such as Atryn's market for congenital antithrombin deficiency. Manufacturers in these situations will have to charge an amount high enough to recoup R&D and production costs and the smaller the market, the higher the drug price will be. Another reason not to expect low drug prices is that companies marketing new technologies must insure against uncertainties and liabilities such as lawsuits that may come as a result of a biocontainment failure. Costs such as this need to be incorporated into the price of the product. A third reason is that many pharming companies (so far, at least) are development companies that will seek big pharma partners when it comes time to market the drug. Traditional big pharma pricing practices do not automatically result in lower drugs prices when the company is able to achieve manufacturing efficiencies. Finally, prices for pharmed drugs may stay high longer than other drugs since pharming companies will probably not encounter the generic competition that causes drug prices to fall after patent expiration. Reasons for the lack of generic competition include the fact that pharming plants and animals and the techniques and skills to derive drugs from them are difficult to acquire. A case in point is Wyeth-Ayerst's Premarin, which lost patent protection over 20 years ago, but still faces no generic competition. Attempts at generic competition have failed because competitors, avoiding the difficulties of raising and maintaining the herds of horses required to manufacture the drug, have developed synthetic versions which Wyeth-Ayerst has demonstrated lack the same composition and biopharmaceutic/pharmacokinetic characteristics. In addition, debates currently exist about whether generic equivalents of biotech drugs are even possible²⁰ and this debate will surely extend to pharming generics.

²⁰ Biologics are typically large molecules, the manufacturing processes for which are complex and can easily introduce changes in the resulting drug product such as immunogenicity. As a result, it is more difficult to ascertain the efficacy and safety of generic versions. Regulatory agencies are currently struggling to generate acceptable bioequivalency standards. (Jonietz 2004)

Recommendations

What protects pharming from many of the challenges faced by GM foods is the fact that the end product is a human drug that must undergo strict regulatory review and the submission of safety and efficacy data prior to marketing. The risk:benefit calculus more easily swings in favor of benefit for drugs and the risks are more tolerable especially when the drug targets a disease that has no other effective treatment. However, because the technology is so new, pharming manufacturers should not assume that product utility will prevent the negative reactions that have plagued prior GM products. In the background as these technologies are being developed are public opinion polls that reveal a strong ambivalence about the benefits of biotechnology.²¹ In such a climate, one of the most valuable exercises for any company that wishes to avoid the problems of the past is to know and understand this GM product history. Hopefully, this paper will be a useful starting place in this regard. Deriving lessons and turning them into recommendations is the next step in this process.

The first recommendation is that companies will obtain the most benefit if they conduct some planning of social and ethical consequences and stakeholder analysis at the beginning of product development rather than later in the product life cycle. Monsanto's experience with its so-called terminator seed technology illustrates the value of such an approach. The terminator genes were intended to be used with Monsanto's GM seeds and caused the seeds from the GM plants to be sterile. This meant that customers who wanted to keep planting the superior GM seeds would need to buy new seeds each year. Monsanto acquired the terminator patents in the late 1990s to meet a business need which was to protect its patents on GM seed and ensure a continuing market for them by preventing farmers from saving and replanting (or even selling) the subsequently harvested GM seeds. (Patterson 2006) While Monsanto may have viewed this practice as seed piracy, farmers, especially subsistence farmers, had long relied on seed saving to avoid the expense of buying new seed each year. Critics also thought that pollen from terminator plants could fertilize nearby native plants and make them sterile. These concerns were so deeply felt that the debate about the terminator seeds became widespread, polarized, and emotional. Opposition from farmers, environmentalists and others included protest rallies at

²¹ In one U.S. poll, 55% of respondents agreed that scientific research has created as many problems for society as it has solutions and 63% agreed that scientific research does not pay attention to the moral values of society. (Virginia Commonwealth University 2003)

the company and destruction of fields where terminator crops were rumored to be growing. (Weiss 1999) In reporting this story, comments such as this were made in the mainstream press: “The Terminator will allow companies like Monsanto to privatize one of the last great commons in nature – the genetics of the crop plants that civilization has developed over the past 10,000 years.” (Pollan 2006) After encountering this resistance, Monsanto decided to halt the commercialization of the terminator technology until a full airing of the issues was complete and the company had the time to respond publicly to the concerns raised.²² In making this decision, Monsanto had the benefit of encountering the early reaction to an intended product and thereby most likely avoided the expense of continued commercialization of a product that would have failed on the market. Monsanto’s terminator experience suggests that companies can benefit by seeking public reactions to potentially controversial products as early as possible to preserve the ability to adapt the product or the commercialization process. Seeking public input also shows respect for stakeholders and avoids the problem of customers and consumers feeling blindsided by a new biotechnology as they did when GM crops were first marketed.

In assessing the potential consequences of developing new products, starting with a broad definition of consequences and including all of the impacted stakeholders will also provide insights that can guide product development. For instance, stakeholder consequence analysis should include the usual groups that concern any pharmaceutical company (physician customers, patients, etc) but, given the GM product history, should also include regulators (who may not be sufficiently knowledgeable about the product technology or who have not generated sufficiently specific guidelines or regulations), the farmers who will raise the transgenic plants and animals (who need education and very precise rules on how to manage transgenic product farming and some of whom will be the subject of activist protest), transgenic animals that produce the company’s drugs (for whom suffering needs to be kept at a minimum), the environment (which can sustain harmful disruption from pharming activities and gene flow), the technology (whose social promise should not be ruined by ill-considered corporate action), organic and non-pharming farmers and food vendors (whose crops or animals and livelihood may be damaged by pharming practices), environmental and animal rights activists (whose objections can create prod-

²² Unless otherwise specified, this and subsequent comments about Monsanto’s programs to address the ethical concerns about its GM products are from Bensimon (2005:267–300).

uct acceptance and public relations problems), and the public (who are concerned about the consequences of encountering GM products).

When it comes to addressing the safety and consent issues about this new technology, different approaches can be taken. The first is to rely on a steady history of safety to gradually assuage the concerns of the skeptics and critics. Monsanto took this approach with its GM crops and rbST but eventually decided that it was insufficient and too slow to achieve adequate sales. After encountering years of resistance, Monsanto changed its tactics and decided that trust in its GM products would not be achieved with a paternalistic approach that said, in essence, the public can rely on our assurances about the safety of our products. To learn from their mistakes, company executives challenged a primary assumption within the company, that people would agree that biotechnology promises more sustainable agriculture and improved well-being. According to one executive, “It was naïve arrogance. We had a naïve sense that our view would be unanimously accepted. We were arrogant by making decisions about what people would or should want and what they don’t want.” Another manager acknowledged that “We parachuted products onto society without showing that they are safe. We were not sensitive to our stakeholders and came to the conclusion that we had to change our behaviour.” (Bensimon 2005:285;277)

Monsanto’s strategic change included the adoption in 2000 of the New Monsanto Pledge which, regardless of one’s view about Monsanto, can serve as a model for how to approach GM product development. The New Monsanto Pledge was a public declaration to stakeholders that contained five main elements – dialogue, respect, transparency, sharing, and benefits. Briefly, these concepts were translated into a pledge to engage in dialogue with both stakeholders and opponents, to listen carefully and respect different points of view about products and their effects, to consider the potential negative impacts of products, to share proprietary genomic sequencing data and other technology with public researchers, non-profit organizations and local farmers around the world, to provide product information (including safety data) so that it is available, accessible, and understandable, to operate in a more transparent manner, and to conduct more widespread education about the environmental, agricultural and economic benefits of biotechnology.²³

Taking lessons from Monsanto and other company experiences, it is also worth considering the adoption of a broader view of the benefit and risk of products. This

²³ See URL: http://www.monsanto.com/monsanto/layout/our_pledge/letter_grant.asp, May 2007.

means an attempt to balance human benefit and risk with the impact on animals and environment. Companies should avoid the assumption that there is general agreement that benefit to humans and the company justifies any use of animals. Fully understanding in advance, for instance, what will have to be done to animals to obtain commercial quantities of a product will allow companies to adjust technology processes or choice of animal to reduce animal suffering while still maintaining product viability. Any harm (human, animal, environmental), when it is expected, should be minimized and/or justified in advance or, if this is not possible, alternative methods should be sought. For instance, if the risks of gene flow from a pharming plant are unacceptable, a company can study the feasibility of using non-food plants or non-edible parts of food plants, inserting terminator genes, growing plants in indoor environments, or using plant cell cultures. Having to make these adjustments later in the product development process can destroy the promise of the drug and even the company. Also, researching and acknowledging likely problems before they occur will avoid reactions of surprise and dismay when they happen. For instance, if it is true, it is better to publicly state that a minimum of cross-pollination of transgenic field plants cannot be avoided and then address why this gene flow will not pose a risk to human health or the environment. It is possible that gene flow from a pharming plant will not be problematic because the effects of ingesting minute amounts in food have no health effects. However, any company that takes this position must support it with independent, highly credible and rigorously obtained research data. The next task in this process is to assure that the company will not solely rely on this research but will continue to diligently monitor for these adverse events. Promising bio-security and then failing to monitor for its loss invites product failure and litigation. Companies developing new genetic technologies should also plan (and have the resources for) a more extensive R&D process than if it were developing a drug using more mature technology. Acting more like a university laboratory than a commercial entity avoids what in retrospect is determined to be premature and hasty marketing. Dow AgroSciences made such a research commitment when, with no marketing intentions, it fully developed its Newcastle and other poultry vaccines in tobacco to ensure the feasibility, effectiveness, and safety of using this plant system. (Mihaliak, Webb 2005)

Companies also need to recognize the legitimacy of demands for broad regulatory assessment of new drug technologies. As a regulatory affairs executive from DowA-

groSciences has recognized, “we need regulations tough and we need them transparent.” (Pew Initiative on Food and Biotechnology 2002) Firms that take the opposite view and successfully resist stringent regulatory assessment may obtain short term gains but may also experience failures when the lack of data hinders product acceptance or the drug is recalled because of late discovered adverse effects. Regulatory antagonism never serves a company well. Rather, a company’s long term interests are better served by adopting a practice of participating and assisting in the generation of sustainable regulatory standards and maybe even exceeding these standards. In contrast, companies should avoid opposition to regulations based solely on development cost and delay, and should not assume that one country’s regulations are unreasonable because they are more stringent than another. There are several reasons for these recommendations. Each country has a sovereign right to protect public health and safety and this right should be respected in the process of seeking marketing approval. Agencies and companies that discount public safety concerns also risk the loss of trust that is necessary for them to function effectively. Additionally, denigrating the regulators can result in a backlash against the company and the product. For instance, when a company receives a publicly available letter from regulators chastising its behavior, the company can suffer significant public relations and legal harm. Companies also need to avoid the view that regulatory agencies own the final responsibility for insuring product safety prior to marketing. When Monsanto’s Director of Corporate Communications told the *New York Times* that “Monsanto should not have to vouchsafe the safety of biotech food. Our interest is in selling as much of it as possible. Assuring its safety is the F.D.A.’s job.”, (Pollan 1998) this comment had a greater potential of undermining trust in the technology and the company than almost anything else that Monsanto could say.

After product approval, companies should also be willing to conduct post-market surveillance whether or not they are required to do so. It serves companies well to operate with the understanding that scientific knowledge is not static and that no product is ever approved with a full appreciation of how it will behave once on the open market. Consequently, a continuous collection of data about new products derived from novel technologies should be a standard practice.

With regard to maintaining an openness about the new technologies, what is clear is that people often feel suspicious of and at-risk from companies that deprive them of information that is considered valuable. This is especially true now with an

increasingly educated and Internet-connected public that expects to be able to obtain information. With the intense scrutiny being focused on companies that make GM products, it is also more likely that controversial information will be revealed by an outside source which further enhances the impression that the company is trying to hide information. During drug development, transparency is difficult since the technology and data are often considered confidential business information that allows the company to compete effectively. However, engaging in a careful balancing of the need for confidentiality and openness may well convince the company that can be more forthcoming. After marketing approval, product labels will be a primary source of product information, but openness about products needs to be pervasive. So, for instance, when pharming companies issue press releases about a product, there is no good reason not to disclose the fact that it comes from a genetically modified plant or animal. If that revelation invites criticism, engaging in a dialogue about the issue will help allay distrust and provide valuable insight for the company about how their products are perceived. In addition, a company is less likely to suffer public relations problems when adverse events occur (as they inevitably do even with the greatest of care) if the company has adhered to a practice openness and dialogue. Finally, when the company discloses information or takes a position about a controversial technology, statements should be as accurate, balanced, and objective as possible. “Spinning” disclosures to prevent loss of market share or investor confidence is usually detected and detracts from the impression that companies are a source of reliable product information. For instance, Monsanto was criticized when it developed GM seed priced for wealthy commercial farmers but seemed to justify its product development by citing third world hunger and the global need for more food. The fact that the seed was not affordable in the countries that needed food the most created a disconnect between the activity and the justification message. By glossing over a controversial price issue rather than dealing with it directly, Monsanto again was inviting mistrust. The final reasons that openness is good corporate policy is that it shows respect for customers and other stakeholders – acknowledging that they are entitled to information and can make good use of it – and fosters confidence in the company and its products.

Another mind set that companies should avoid is that negative public reaction to GMOs is irrational and not worthy of comment. These views may well be irrational but are also likely to be a result of uncertainty of the unknown where caution is a

rational reaction. Monsanto is probably correct that the longer a product is on the market without causing an adverse event, the more likely it is that resistance will fade. Ultimate acceptance, however, will be hastened with education about new technologies and products, education that addresses both the benefits and risks, and the certainty of the data that supports the benefit/risk conclusions. No one will be surprised by a statement that knowledge about new technologies inevitably develops over time and fewer people will be troubled if that statement is accompanied by another that pledges the company to a vigilance that maximizes its ability to recognize new benefits and risks. Business managers may also be reluctant to go beyond addressing concerns about product technology and business practices. However, in the GM product arena, companies have been asked to address fundamental ethical, religious, and cultural questions about the technology such as whether scientists are “playing God”, breaking down inviolate boundaries in nature, or redefining the relationship between humans and animals. Given the newness and power of the technology and how it has the potential to re-define nature, companies will necessarily encounter these questions and should be prepared to address them.

Conclusion

Modern expressions of resistance to GM products include a mixture of uncertainty about how the product will behave environmentally, fears about animal and human safety, concerns that regulatory agencies are unprepared to review the technology and are overly influenced by commercial sponsors, criticisms that companies have failed to fully inform the public about the nature of products, and unease about the propriety of genetic manipulation. The corporate misjudgments and the inconsistent and delayed regulatory responses about GM foods and animal drugs have certainly put pharming companies at a disadvantage, possibly requiring them to proceed more cautiously than they otherwise might have. However, GMO commercialization history can also serve as an opportunity for pharming companies to learn from and avoid past mistakes. The medical potential and market expectations for pharming products will be significantly enhanced if companies can achieve this goal.

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Pharming – Ethical Aspects

Dieter Birnbacher

1. Pharming – perspectives and risks

Though “pharming” in the sense of the production of pharmaceuticals by transgenic organisms and agricultural methods has been practised on a small scale for years the practice is as little known as the term “pharming” itself. On the Internet, “pharming” is primarily used for a recent method of Internet fraud, and there have been only a limited number of scientific articles internationally. It does not come as a surprise, therefore, that bioethics has not yet reacted to pharming. In fact, it has scarcely taken notice. Pharming has come on to the scene more or less surreptitiously.

This is not as it should be. Pharming should interest bioethicists because it raises a number of serious ethical issues – even though these issues are not specific but well known from other forms of advanced biotechnology. Pharming is of ethical interest primarily for the risk problems it shares with other forms of growing transgenic plants and breeding transgenic livestock on a large scale. But it is of ethical interest also for the chances it promises for the future. Pharming can be expected to lead to a number of new medicines, or at least new components of medicines. It might become a particularly efficient way of producing pharmaceuticals – medicines, vaccines, sera – that cannot be synthesised, or only at high costs, outside of biological organisms. This is not only of economic but also of ethical significance. By opening up prospects of providing cheaper medicines it might not only help to solve some of the financial problems of the medical system of industrialised countries but also to improve the accessibility to medicines of the inhabitants of poor countries who now suffer from heavy deficiencies in the supply of medical services.

Extrapolating from the bioethical discussions on the production and cultivation of transgenic plants and animals, the ethical objections to pharming can be expected to be directed primarily at the risks created by this way of production for humans, animals, and the environment. The main problem lies in the novelty of these methods and the corresponding uncertainty about the dimensions and the exact nature of the risks associated with them. Both factors should teach us caution in introducing additional risks and to handle the new strategies with relatively strict safeguards. Though

there has been quite a long period of time in which the consequences of horizontal gene transfer from transgenic crop plants have been monitored, pharming is a special case because transgenic plants used for pharming are not grown for the production of food but for the production of chemicals not contained in their natural or normal varieties. Not only the substances to be harvested from them may be toxic or otherwise dangerous to the health of man and animals, but also their by-products and the compounds resulting from their interaction with the environment. One central question of pharming on an industrial scale will therefore be how the pharmaceuticals and the organisms that produce them can be kept separate from food-and-feed-organisms (transgenic or not). We know that it is hard to control horizontal gene transfer, especially if pollens are likely to be transported over long distances. On the other hand, containing the respective crops in greenhouses to prevent contamination of other crops, as seems imperative on the precautionary principle, might be incompatible with using this procedure on a scale large enough to make it economically interesting.

With zoopharming, the risk profile is different, the main problem being the contamination of the pharmaceuticals themselves. This problem is similar to those discussed in the context of xenotransplantation. The pharmaceuticals produced might be contaminated by animal pathogens dangerous for humans (or which become so by interaction with endogenous substances), not only for the users of the pharmaceuticals but also for persons coming into contact with them in the context of production (such as agricultural workers) or in the context of consumption (such as nurses).

Risks resulting in the course of the production, distribution and consumption of pharming products constitute the primary ethical concern with pharming. However grave these risks may be, the principles relevant to the estimation and management of these risks are not in any way special. They are of the same sort as for other risks imposed by transgenic organisms on humans and animals. In both cases, the focus of ethical concern should be on welfare issues, both in humans and animals. The welfare of animals might be compromised by pharming either directly, by the substances they are expected to produce in their organisms, or indirectly by changes resulting from the presence of these substances in their organisms or from their altered genome. In each individual case of a transgenic animal it has to be examined whether the risks for the welfare of the animal by introducing changes in its genome and by breeding and keeping it for human purposes are proportional to the expected benefits.

There is a risk of *underestimating* these risks, but there is also a risk of *overestimating* them by giving unproportional weight to the “artificiality” of these risks. There is a respectable body of evidence for a widespread human tendency to overestimate anthropogenic risks and to underestimate natural risks (cf. Birnbacher 2006:17ff). Moreover, negative events that are caused by human interventions tend to be assigned more negative value than negative events of a purely natural origin. Natural disasters like earthquakes, avalanches or floods are more readily accepted than crimes, wars and technical catastrophes. This phenomenon is closely related to a phenomenon known as *omission bias*: People often prefer a greater natural risk for which nobody in particular can be made responsible to a smaller anthropogenic risk caused by a human intervention. A case in point is the so-called “seeding” of hurricanes. While interventions as a rule mitigate the impact of a hurricane, they occasionally make things worse than they would otherwise be. Only in this case the consequences of the failed intervention are attributed to the authorities that decided on the operation. In the case of non-intervention the harmful consequences of the hurricane are attributed to nature rather than to a human failure to intervene (Howard et al. 1972:1197).

This is relevant to the issue of judging the risks of transgenic plants and animals since changes introduced in nature by means of gene technology are usually judged to be more “artificial” than the changes introduced by conventional breeding. In consequence, there may be a tendency to overestimate the risks of gene-technological interventions in plants and animals in comparison to the risks of conventional breeding – despite the fact that conventional breeding constitutes a wilful introduction of genetic changes in natural organisms no less than genetic changes effected by recombinant methods, of only more indirectly. This does not mean that there are more and other sources of risks that make transgenic plants and animals more dangerous to human and animal health than conventionally bred varieties. It only means that realistic estimations of risks should be wary of not being misled by popular misperceptions.

2. Objections to pharming based on a principle of naturalness

One potential source of objections against pharming comes from a strong principle of *naturalness*. Principles of naturalness are not valued very highly in the mainstream of philosophical ethics. In everyday morality, however, this is different. The

relevance of the distinction between the natural and the anthropogenic or artificial continues to make itself felt even within the framework of a secularised morality. In everyday moral thinking, the natural is explicitly or implicitly preferred to the artificial. What has come to exist in the course of nature is systematically privileged over what has been produced or created by man. There is a simple test that indicates that a principle of naturalness is involved in an argument or an attitude: its incompatibility with the “principle of agency” formulated by James Rachels. This principle says: “If it would be good for a particular state of affairs to occur “naturally”, without being brought about by human action, then it is permissible to act so as to bring it about.” (Rachels 1998:154)

This principle is *not* accepted in areas in which the main problems of bioethics are to be found, e. g. in human reproduction and human dying where technical interventions are under close critical scrutiny whereas the results of the “natural lottery” are usually accepted without further ado. While the realisation of positively valued states in the course of nature is welcomed as a heavenly gift, human interventions that aim at the realisation of the same states often meet with ambivalent feelings if not with outright rejection.

Any principle of naturalness, however, is confronted with a dilemma. It either postulates that the natural is morally privileged because there are further values of high priority that are realised by “letting nature take its course”, or it postulates that the natural is valuable independently of all further values that may be associated with it. In the first case, the justification of the value of the natural is extrinsic; in the latter case it is intrinsic. Both alternatives, however, raise serious problems.

The problem of the first alternative is that it makes the relation between the natural and the values that are assumed to be intrinsically valuable purely contingent. If the intrinsic value does not lie in being natural but in being in conformity with a divine plan of creation, in anthropocentric values like safety, quality of life or sustainability, or in aesthetic values like natural beauty, the relation between these values and nature become merely contingent. If you have to choose between a natural and an “artificial” option, choosing the natural option may very well be the morally superior option. On this alternative, however, this will be not because it is *natural*, but because it exhibits these other values. There are no doubt good prudential reasons to prefer the natural. Natural processes may be less risky than human technical interventions since nature had much more time to eliminate extreme and catastrophic

dangers in the course of its evolutionary “experience”. Furthermore, nature has the advantage of being absolutely neutral. Differently from human agents, nature knows no affects and especially no negative affects like sadism and revengefulness. Even if the ways of nature are often destructive and cruel, she does not know resentment and hate and does not pursue anyone in particular with criminal energy, as humans do.

In this respect, then, there are perfectly good reasons *not* to accept Rachels’ “principle of agency”. Permitting human agents to realise what is rightly welcomed in nature would often be imprudent. Such permission might have unwanted side-effects (such as misuse and abuse) that we do not expect from the natural course of events.

The problem for the defender of a principle of naturalness of this kind is, however, that it is not clear why the principle he defends is a principle of *naturalness*: What is specifically valued in nature is only extrinsic. Nature is regarded as a value purely as a manifestation or source of intrinsic values other than naturalness. Moreover, most of these values are accepted by nearly everyone, including non-naturalists.

The second alternative is no less problematic, though for other reasons. If the natural is taken to be valuable intrinsically, it is valued independently of what it expresses and independently of consequences. In this case, however, it is intuitively implausible to assign to nature a positive value or even, as Ludwig Siep maintains, “a value of high priority” (Siep 2004:312) since this value would have to be assigned also under counterfactual conditions. If nature is intrinsically valuable it would be valuable even under conditions in which it were the product of a *deus malignus* (as some forms of Buddhism and Schopenhauer’s metaphysics of will have it) e. g. by imposing on man not only a life of pure suffering, but also by implanting in him the instinct of procreation, but by perpetuating this suffering indefinitely. Could the natural be a value of high priority even in such a diabolical world? Could naturalness be a value if it exhibited no aesthetic value whatsoever, and the beautiful and the sublime in nature were exclusively the product of human art?

Because of their inherent weaknesses, principles of naturalness do not seem to be a suitable basis for ethical objections to pharming. In the case of pharming, appeals to naturalness even have a further weakness: Though genetic modification is a particularly deep and radical interference with nature, the plant and animal species used for pharming purposes are among the most “artificial” entities in the realm of the living already now. The plants and animals of which pharming makes use are conventional domestic plants and domestic animals that are the products of the

efforts of a long history of breeding efforts. Even in their genetically unmodified forms, they are the results of purposeful human modifications of nature. The modifications to which these plants and animals will be subjected for serving as organic factories are only a small further step in the same direction. Thus, even supposing that principles of naturalness have more force than they in fact have, they would be much less compelling in the case of domestic races of plants and animals than in the case of wild species. It is improbable that a new transgenic race of tobacco or of pigs meets with ethical objections or misgivings of the same intensity as a transgenic race of ice-bears.

There is a further reason to assume that, in contrast to other applications of gene technology, in the case of pharming the appeal to a principle of naturalness will not cut much ice: Pharming is exclusively undertaken with direct or indirect *therapeutic* intentions. Therefore, even a defender of a strong principle of naturalness will have to balance the negative value of what, for him, is a massive intervention in nature, against the undisputed positive value of the good it might mean to patients. Experience shows that even massive interventions, not only in *nature* but also in *human nature* (such as organ transplantation or the implantation of neuroprostheses) are accepted without much discussion provided the motivation behind these interventions is primarily or exclusively therapeutic. Even “bioconservatives” do not in general object to radical interventions in nature when these constitute therapeutic or preventive options or serve the compensation or correction of abnormalities. They object to such interventions only in case these are undertaken for non-health-related purposes, such as for the enhancement of physical or mental faculties or for lifestyle options.

3. Ethics of dignity: Objections to “instrumentalising” animals

Animal activists will possibly object to pharming on the ground that breeding genetically modified animals for the sole purpose of producing pharmaceuticals constitutes a particularly radical form of instrumentalisation.

One should distinguish carefully between the concern that using transgenic animals as “living chemical factories” might negatively affect their welfare or functioning, and the concern that using them for the production of pharmaceuticals is ethically problematic *per se*, irrespective of how they are affected by them. The latter position

is the “anti-instrumentalisation” position whose most prominent representative has been Tom Regan. Regan rejects even the most “humane” forms of agricultural use of higher animals as incompatible with the inherent dignity of these animals. He would no doubt reject zoopharming for the same reasons. What is problematic about pharming for a Regan-like animal activist is not the suffering or the harm inflicted on animals by instrumentalising them for food, research or the production of pharmaceuticals, but the act of making them instruments for human purposes in the first place. Making them “mere means” for human purposes violates their right to “respectful treatment” (Regan 1983:327).

Regan’s position on instrumentalisation of animals is a very rigid position indeed. I personally think that it is too rigid. Furthermore, it is an open question whether the dignity Regan attributes to higher animals (“inherent worth”) is sufficient to exclude any kind of instrumentalisation. Contrary to what is often thought, not every form of instrumentalising someone can be interpreted as a violation of his or her dignity, neither in the human nor in the animal world. Making use of the work force of an employee makes him or her means to purposes which are not his or her own. But this does not mean that they are made a “mere means” in the sense of a morally objectionable act of exploitation. Whether this is the case depends on further factors, among others on how much freedom the employee has, whether he or she is adequately paid for the services rendered, whether the work they are made to do is detrimental to their health and well-being, and whether they have the right to reject work that is incompatible with their moral principles. Analogously, not every higher animal that is used for purposes not its own is thereby made a “mere means”. Whether this description is adequate depends on how it is dealt with during its whole life time – whether it is made to suffer pain, fear, stress or severe frustration, whether it is adequately cared for, whether it is kept under suitable conditions, and whether it is sufficiently free to live out its physical and social needs.

It cannot, therefore, be said that pharming is *inherently* “instrumentalising” in a morally indefensible way. At least, it cannot be more morally indefensible than raising and keeping conventional domestic animals for other purposes. Nor can this description be justified by the mere fact that “instrumentalising” domestic animals in this case involves their genetic modification. They are, as I said above, highly “artificial” results of human breeding anyway. Their genome has been pushed in a direction that promises to be useful to human purposes in the same way as the genome

of transgenic animals is, if only indirectly. And, finally, differently from meat production, pharming does not in general involve the killing of animals for the sole purpose of making use of their bodies. In pharming, pharmaceuticals such as antibodies or hormones are in general derived from the milk, the eggs or the urine of transgenic animals and not from their carcasses. If pharming means instrumentalising animals, this aspect is present in pharming only in an exceptionally mild form.

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The Use of Genetically Modified Animals for the Production of Pharmaceuticals – Legal Considerations from an Animal Welfare Perspective

Ralf Müller-Terpitz

A. Introductory Remarks

I. Animal Gene Pharming – Some Background Information

Animal gene pharming aims at the creation of transgenic animals that carry a (human) gene for the production of active ingredients like (mostly) therapeutical proteins. These ingredients shall be extracted from the blood, milk or urine of such transgenic animals and subsequently be processed to pharmaceuticals. In future, this concept may be optimised by the technique of cell nuclear transfer cloning (CNT) in order to “replicate” a high quantity of efficient “bioreactors” with specific transgenic characteristics.

There are several advantages that are expected from animal gene pharming: firstly, it shall serve to produce pharmaceuticals that can at present not (or not satisfactorily) be manufactured by a conventional chemical synthesis or with the help of recombinant cell cultures. And secondly, these pharmaceuticals shall be produced in a higher quality and quantity at moderate cost, particularly if compared to fermenter grown recombinant cell cultures.

Though animal gene pharming seems to be a promising technique for the production of specific pharmaceuticals, one has to emphasise that it is still in its beginnings. Up to now, animal gene pharming must primarily be considered as an issue of scientific experimentation and research. Thus, there are only few examples of a successful creation of transgenic animals used for the production of pharmaceutical ingredients: In 2004, e.g., scientists of the universities of Tübingen, Munich and Vienna managed to create transgenic rabbits and a herd of nine cloned transgenic calves producing a bispecific single-chain antibody for T-cell-mediated tumor cell killing in their blood. The gene to produce this protein was infiltrated in the animals' embryonal connective tissue. Apparently, the animals are not affected by their use

as transgenic “bioreactors” (cf. Grosse-Hovest et al. 2004). Furthermore, in August 2006, after successful clinical trial the European Agency for the Evaluation of Medicinal Products (EMA) recommended EC-admission of an active ingredient – the blood clotting inhibitor “ATryn” by GTC Biotherapeutics Inc. – which is extracted from the milk of transgenic goats.¹

II. Legal Topics Raised by Animal Gene Pharming with Regard to Animal Welfare Protection

When assessing the above sketched concept of animal gene pharming from an animal welfare perspective one has to distinguish between different legal topics:

- Firstly, producing pharmaceuticals via transgenic animals requires the *creation* of transgenic strains. At present, the creation of such strains can only be realised by animal experimentation (cf. Kluge 2002:§ 7, no. 22). Hence, legal regulations regarding the experimental use of animals have to be observed.
- Secondly, the concept of animal gene pharming is based on a continuing reproduction of animals with specific altered genetic characteristics. Therefore, legal provisions regarding the *breeding* of such animals have to be taken into consideration.
- And finally, as in future animal gene pharming may be optimised by the technique of CNT-cloning, it has to be analysed what provisions animal welfare regulation stipulates with regard to this relatively new method of artificial reproduction.

However, it has to be highlighted that such a legal analysis is still based on a narrow fundament of facts. Therefore, jurisdiction or an intensive legal debate on animal welfare subjects related to the creation of genetically modified animals for the production of pharmaceuticals is still missing or concerns patent issues which are not of interest for the context at hand. Consequently, the following considerations are to be considered as a first attempt to identify some legal aspects of relevance from an animal welfare perspective which have to be specified in the future.

¹ For further details on this case cf. the article by Eaton in this volume.

B. Legal Assessment of Animal Gene Pharming from an Animal Welfare Perspective

I. General Concerns about a Genetic Modification and Cloning of Animals

Especially the animal welfare organisations have expressed some general legal concerns with regard to a genetic modification and cloning of animals. Highly visible, these concerns are influenced by the ethical debate on this subject.

First of all, critics hold that such modifications infringe the “creature’s dignity” if they are carried out to the sole advantage of mankind. Especially the technique of cloning is considered to be an unacceptable instrumentalisation of animals. Furthermore, it is argued that the effects of genetic transfers on the physiology and metabolism of modified animals and their offspring are not sufficiently predictable. As a matter of fact, negative impacts on the expression of important genes or through the expression of transgenes at the wrong place cannot be definitely excluded. Moreover, through the insertion of foreign genetic information the receiving organism could be infected with pathogens. (Cf. Hirt et al. 2003:§ 7 no. 51; Idel 1998:107) And finally, critics claim that genetic modifications of animals might cause a loss of biodiversity, especially if this process is combined with the technique of CNT-cloning. Therefore, animal welfare activists are of the opinion that a genetic modification of animals for whatsoever purposes is already inconsistent with existing international or national animal welfare regulation or should at least be rigorously prohibited. (Cf. Bündnis 90/Die Grünen 1997; Amann and Goetschel 1999; Goetschel 1998)

As will be shown subsequently, none of these objections is suitable to rule out or materially restrict the creation, breeding or cloning of genetically modified animals for the production of pharmaceutical ingredients. Though legally protected by the international, supranational and national law, animals are not considered to be a person enjoying fundamental rights such as the right of dignity or life. Thus, animals may be modified or used to the advantage of man as long as the latter can indicate “good reasons” for such a treatment. Nevertheless, there are legal restrictions that have to be observed. In a first step, these restrictions shall be described for the international and supranational level (I.). In both legal orders, minimum animal welfare standards have been established that are not only binding for the Federal Republic of Germany but for all other member states of the European Union as well. In a second step, it shall be examined whether the German legislation exceeds or perhaps even falls below these standards (II.).

II. Animal Gene Pharming under International and Supranational Law

1. The International Level

On the international level, a closer look has to be taken at the UN-Convention on Biological Diversity (a), the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (b) and the European Convention for the Protection of Animals Kept for Farming Purposes (c).

a) The UN-Convention on Biological Diversity

The UN-Convention on Biological Diversity of 5 June 1992 (1760 United Nations Treaty Series 79; 31(1992) ILM 818), which is binding for 189 parties including the European Community and the Federal Republic of Germany, aims, amongst others, at the conservation of genetic biological diversity “in situ”. This objective comprehends the conservation of wildlife *and* domesticated or cultivated species (like e.g. farm animals) in the surroundings where they have developed their distinctive properties.²

However, animal gene pharming does not endanger this objective, even if in future the technique of CNT-cloning will be used. At first, it has to be stressed that the Convention does not rule out the application of this technique as it was still largely unknown at the time of the Convention’s adoption. Furthermore, the genetic modification of animals for pharming purposes will most likely not result in an expulsion of other domesticated or cultivated species. Whereas the cloning of animals for farming purposes, i.e. the artificial creation of a high amount of transgenic animals for food production reasons by CNT, might lead to a gradual substitution of a variety of genetically different farm animals by only few genetic strains, animal gene *pharming* aims at the creation of only few and small transgenic animal populations with specific genetic characteristics. Thus, it is unlikely that the concept of animal gene pharming will damage biological diversity in the long run. Hence, the Convention does not inhibit or even stipulate any obstacles to this pharmaceutical concept.

b) The European Convention for the Protection of Experimental Animals

By contrast, the Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes of 18 March 1986³, as amended by the Pro-

² Cf. article 1 and 2 of the Convention.

³ European Treaty Series No. 123.

TOCOL of 22 June 1998⁴, needs a closer examination. This Convention was drafted and adopted under the auspices of the Council of Europe in Strasbourg. To date, it has been signed by 23 of its 46 members, including the European Community and Germany.

The Convention stipulates minimum standards only⁵. Amongst others, its main subjects of regulation are the conduct of scientific experiments with vertebrate animals following the “3R-approach” (replace – reduce – refine) and the authorisation procedure for such experiments.⁶ As far as the Convention also sets out guidelines regarding the accommodation and breeding of vertebrate animals⁷, they are only related to animals used for experimental or other scientific purposes.⁸ Thus, these provisions are not of relevance for the present subject.

The Convention applies to any vertebrate animal used or intended for use in any experimental or other scientific procedure where that procedure may cause pain, suffering, distress or lasting harm.⁹ The term “procedure” is defined as any experimental or other scientific use of an animal which may cause it pain, suffering, distress or lasting harm, including any course of action intended to, or liable to, result in the birth of an animal in any such conditions. However, the elimination of these conditions by a successful use of anaesthesia, analgesia or other methods does not place the use of an animal outside the scope of this definition.¹⁰ Inter alia, such experimental procedures may be performed for the avoidance and prevention of (human or animal) disease, including the production of drugs, substances or products, and the diagnosis or treatment of such disease.¹¹ Where it is planned to subject an animal to a procedure in which it will or may experience *severe and enduring* pain, that procedure must be specifically declared and justified to or specifically authorised by the responsible authority.¹² Furthermore, the states being party to the Convention are obliged to take appropriate measures in order to ensure that no

⁴ European Treaty Series No. 170. However, this Protocol has not entered into force yet.

⁵ Cf. article 4 of the Convention.

⁶ Cf. article 6–13 of the Convention.

⁷ Cf. article 5 and article 14–17 of the Convention.

⁸ Consequentially, article 1 paragraph 1 sentence 2 of the Convention explicitly excludes non-experimental agricultural or clinical practice from its scope of application.

⁹ Article 1 paragraph 1 sentence 1 of the Convention.

¹⁰ Article 1 paragraph 2 letter c) of the Convention.

¹¹ Cf. Article 2 letter a) of the Convention.

¹² Article 9 paragraph 1 of the Convention.

such procedure is carried out *unnecessarily*. From the subsequent provision it can be reasoned that the necessity of such experimental procedures depends amongst others on a satisfactory declaration to the responsible authority that the intended scientific experiment is of *sufficient importance* for meeting essential needs of man or animal.¹³

What conclusions can be drawn from the preceding overview with regard to the concept of animal gene pharming? Firstly, at present the *creation* of transgenic animals for gene pharming purposes has as a rule to be considered as an animal experiment covered by the Convention because it cannot be definitely excluded that the genetic intervention may cause pain, suffering, distress or lasting harm to the affected animals or their offspring. This interpretation is backed by a resolution, adopted during a multilateral consultation of the contracting parties in 1992 which explicitly extends the Convention's scope to genetically engineered animals and their offspring. As the technique of genetic modifications cannot be controlled sufficiently yet and thus may cause the negative effects described in the introduction, the initial generation of a transgenic strain for animal gene pharming (or other) purposes is to be considered as an experimental procedure. In addition, it has to be emphasised that this understanding of the European Convention also influences the interpretation of the supranational and thus the national law, as both, the European Community and the Federal Republic of Germany, have adhered to this international treaty.

Consequently, the creation of a transgenic animal for the production of pharmaceutical ingredients has to meet the above described requirements for the realisation of animal experiments. However, as long as such ingredients cannot be satisfactorily generated by other means, like e.g. chemical synthesis or cell cultures, and as long as the procedure of genetic modification is of sufficient importance for the essential needs of man or animal, these restrictions can be overcome even if the procedure may cause severe and enduring pain to the modified animals. Nevertheless, it has to be highlighted that these requirements are not met if the genetic modification only pursues cost reducing effects, i.e. if the creation of a transgenic strain only aims at the production of an already available pharmaceutical ingredient at lower costs. The experimental genetic modification of an animal for pure cost cutting reasons would not satisfy the criteria of a "sufficient importance for meeting the essential needs of

¹³ Cf. article 9 paragraph 2 of the Convention.

man or animal”. This formulation has to be interpreted in the light of article 2 of the Convention, defining the admissible objectives of animal experiments such as avoidance, prevention, diagnosis or treatment of disease or basic scientific research. Cost aspects are not mentioned in this catalogue. Furthermore, such a procedure would conflict with the principle of replacement as laid down in article 6 of the Convention. According to this provision, a procedure shall not be performed for any of the purposes referred to in article 2, if another scientifically satisfactory method, not entailing the use of an animal, is “reasonably and practicably available”. Therefore, an animal experiment being solely carried out for cost cutting reasons could only be admissible if an alternative method to produce a specific pharmaceutical ingredient (e.g. via cell cultures) would be so expensive that patients could not or not sufficiently be supplied with this substance. However, if the genetic modification will in all probability *not* cause pain or lasting harm, such treatment could also be performed for pure cost reduction purposes because in this case the modification would not be covered by the Convention’s scope.¹⁴

And finally, the question has to be analysed whether the Convention stipulates any guidelines for the issue of *cloning*: Unlike the technique of embryo-splitting the technique of CNT-cloning is still of experimental nature because it is characterised by a high rate of failure in terms of abortion and mortality as well as a high rate of morbidity, like e.g. immunity deficiency, dyspnea or arthrosis (cf. Braun 2002:138ff.). Therefore, at present it cannot be excluded that the use of this technique might cause the cloned animal pain, suffering or lasting harm. Nevertheless, the question whether the act of CNT-cloning falls inside the Convention’s scope is discussed controversially. Some authors neglect the applicability of the Convention arguing that its article 1 paragraph 2 letter a) defines the term “animal” as any live non-human vertebrate *except for their foetal or embryonic forms*. As the process of cloning is not carried out on born animals but on embryos – so the argumentation – it does not fall inside the scope of the Convention (cf. Braun 2002:145). However, the definition of the term “procedure” in article 1 paragraph 2 letter c) of the Convention militates in favour of the opposite opinion: According to this provision, a scientific experiment does not only comprehend the use of an already born animal but also “any course of action intended to, or liable to, result in the birth of an animal in any such con-

¹⁴ Cf. again article 1 paragraph 1 sentence 1 of the Convention.

ditions” (i.e. suffering pain, distress or lasting harm). Thus, not only experimental procedures that are carried out on already born animals, but also scientific measures that might lead to the birth of an animal suffering pain, distress or lasting harm are covered by the Convention. Hence, the wording of article 1 paragraph 2 letter c) is open enough to enclose the technique of CNT-cloning, as this one “is liable to result in the birth of an animal (...)” suffering from the described conditions. However, as already mentioned, this interpretation is discussed controversially.

c) The European Convention for the Protection of Farm Animals

The European Convention for the Protection of Animals Kept for Farming Purposes of 10 March 1976¹⁵ was also drafted and adopted under the auspices of the Council of Europe. Again, the European Community as well as the Federal Republic of Germany are parties to this Convention. On 6 February 1992, it has been amended by a Protocol¹⁶ which explicitly extends the scope of the Convention to biotechnology issues such as the creation of animals as a result of genetic modifications or novel genetic combinations.

According to Article 2 of the Protocol, natural or artificial breeding or breeding procedures which cause or are likely to cause suffering or injury to any of the animals involved shall not be practised. Furthermore, no animal shall be kept for farming purposes unless it can be reasonably expected, on the basis of its phenotype or genotype, that it can be kept without detrimental effects on its health or welfare.

Though it cannot be definitely excluded that genetic modifications or the technique of CNT-cloning might cause suffering or detrimental effects to the animals concerned, Art. 2 of the Protocol is not or at least not yet applicable to the concept of animal gene pharming: At first, it has to be highlighted that the Protocol is still out of force.¹⁷ Furthermore, the Convention applies to animals that are bred or kept for the production of food, wool, skin, fur or other conventional farming purposes. Thus, it is unlikely that its scope can be extended to the breeding and keeping of animals having been genetically modified for *pharming* purposes, i.e. for the production of pharmaceutical ingredients. The term “breeding procedure” traditionally refers to a procedure of *sexual* reproduction. Hence, it is at least doubtful whether this

¹⁵ European Treaty Series No. 87.

¹⁶ European Treaty Series No. 145.

¹⁷ To come into force, the Protocol has to be ratified by further 16 contracting parties.

term also encloses the technique of CNT-cloning, especially as it was still largely unknown at the time of the Protocol's adoption.¹⁸

2. The Supranational Level

In European Community law, animal welfare issues as such do not yet constitute an integral part of the Community objectives (Art. 2 EC Treaty), activities (Art 3 EC Treaty) and legislative competences. However, in 1997 the EC Treaty was amended by the so-called Amsterdam Protocol on the Protection and Welfare of Animals which stipulates that “in formulating and implementing the Community’s agriculture, transport, internal market and research policies the Community and the Member States shall pay full regard to the requirements of animal welfare, while respecting the legislative or administrative provisions and customs of member States in particular to religious, cultural and regional heritage.”¹⁹

In its secondary law, the European Community has paid regard to this objective of animal welfare in its Council Directive 86/609/EEC of 24 November 1986 regarding the protection of animals used for experimental and other scientific purposes (Official Journal of the European Communities 1986 No. L 358/1), the Council Directive 98/58/EC of 20 July 1998 concerning the protection of animals kept for farming purposes (Official Journal of the European Communities 1998 No. L 221/23) and the Council Regulation 1804/1999 of 19 July 1999 supplementing Regulation 2092/91 on organic production of agricultural products and indications referring thereto on agricultural products and foodstuffs to include livestock production (Official Journal of the European Communities 1999 No. L 222/1).

The directives regarding animal experiments and the protection of farm animals simply transfer the European Conventions sketched above into Community law and therefore mainly assume – even literally – their provisions. Consequently, they approximate the legal situation on the international and supranational level. Again, the Community legislation just stipulates minimum standards respecting the right of the Member States to adopt stricter measures with regard to animal protection.²⁰

¹⁸ According to Braun 2002:146, the Protocol shall not be applicable to the issue of cloning because it would not be proven yet that this technique causes pain or injuries to the affected animals.

¹⁹ According to article 311, the protocols annexed to the EC Treaty by common accord of the Member States shall form an integral part thereof. In future, the Amsterdam Protocol on the Protection and Welfare of Animals shall pass into article III-121 of the Treaty establishing a Constitution for Europe.

²⁰ Cf. article 24 of the Council Directive 86/609/EEC and article 10 paragraph 2 of the Council Directive 98/58/EG.

However, it extends these minimum standards to those Member States of the European Union that are not party to the European Conventions.

In contrast to the legal guidelines presented so far, the Council Regulation on organic production contains a provision that is applicable to the issue of *cloning*. According to its article 6 paragraph 1 in conjunction with annex I no. 6.1.1., the reproduction of organically reared livestock should be based on natural methods. Therefore, with the exception of artificial insemination, other forms of artificial or assisted reproduction such as the embryo transfer or the different methods of cloning (embryo-splitting, CNT) are prohibited. Nevertheless, it has to be emphasised that this prohibition only applies to *organic farming* and thus not to the issue of animal *gene pharming*.

III. Animal Gene Pharming under National Law

Finally, it has to be analysed whether the German animal welfare legislation exceeds the minimum standards as established by international and supranational law.

As on European level, under German constitutional law animals are not considered to be beneficiaries of fundamental rights. However, since 2002 they are subject of a constitutional protection clause (Art. 20a Basic Law) providing that “(...) the state shall protect the natural bases of life and the animals by legislation and, in accordance with law and justice, by executive and judicial action, all within the framework of the constitutional order”. Thus, animals are beneficiaries of legislative protection, but only in accordance with other conflicting constitutional rights (such as the freedom of research or the right to physical integrity) and pursuant to legislative concretion. In Germany, animal protection issues have been concretised by the Animal Welfare Act of 18th May 2006 (Federal Law Gazette I:1206). According to section 1 sentence 1, it is the aim of this act to protect the lives and well-being of animals, based on the responsibility of man for their fellow creatures. Nevertheless, section 1 sentence 2 as well as the subsequent provisions regarding animal husbandry, killing, experiments on animals or animal breeding reveal that this is not an absolute but only a relative protection as – generally speaking – “good (anthropocentric) reasons” may justify pain, suffering or harm inflicted upon animals. As will be shown subsequently, animal gene pharming basically constitutes such a “good reason”.

Again, one has to distinguish between the *creation* of a genetic strain and the *breeding* of transgenic animals. At first, some remarks to the creation of genetically modified animals: According to section 7 paragraph 1 no. 2 Animal Welfare Act, the expression “experiments on animals” means any operation or treatment on the animal genotype which may cause the genetically modified animals or their carriers pain, suffering or harm. As the effects of genetic modifications cannot be definitely predicted, the creation of a genetically modified animal has – as a rule – to be considered as an animal experiment under the German animal welfare law. Therefore, such genetic modifications may only be carried out if they are “indispensable” (amongst others) for the prevention, diagnosis or treatment of human diseases. The decision whether experiments on animals are indispensable shall be based in particular on the scientific findings available at the time and on checks whether the same purpose can be achieved by other methods or procedures.²¹ Thus, if the purpose of genetic engineering – the production of a pharmaceutical ingredient – may be achieved by other means (like e.g. through cell cultures), the genetic modification of an animal is not “indispensable” in the sense of the quoted provision, even if the same objective could only be realised at much higher costs. Again, pure cost cutting reasons are – notwithstanding the supra mentioned exceptions – unsuitable to justify animal experiments (cf. Caspar 1999:454ff; Hirt et al. 2003, § 7 no. 15). In addition, experiments on vertebrates may only be carried out if the pain, suffering or harm is “ethically justifiable” in view of the experiment’s purpose. Experiments causing lasting or repeated severe pain or suffering to vertebrates may only be performed if the results are expected to be of “outstanding importance” for the fundamental needs of human beings or animals.²² In principle, genetic modifications on animals for pharmaceutical reasons can satisfy these restrictions. However, such a question can be definitely answered only with regard to a concrete experiment, i.e. on a case-by-case basis.

Moreover, the question has to be analysed whether reproductive *CNT-cloning* is to be considered as an animal experiment pursuant to the German animal welfare law. In contrast to the international and supranational level, this question has to be clearly denied: according to section 7 paragraph 1 Animal Welfare Act, an experiment on animals is defined as any operation or treatment *on animals* or *on*

²¹ Section 7 paragraph 2 sentence 1 no. 1 and sentence 2.

²² Section 7 paragraph 3 of the Animal Welfare Act.

the animal genotype. Hence, the German provisions regarding animal experiments are only applicable to already existing (living) animals and their embryonic forms but not to their *creation*, even if this act of creation has – like in the case of CNT-cloning – experimental character. Furthermore, the complete replacement of the ovule’s cell nucleus by the nucleus of a somatic cell cannot be understood as a “treatment on the animal genotype”, as cloning is a technique to reproduce living entities but not a technique to modify their genetic constitution.²³ Thus, the legal situation in Germany is not consistent with the legal guidelines as stipulated by the European Convention for Animal Experiments and the Council Directive 86/609/EEC. Accordingly, the legal situation in Germany has to be adjusted to the international and supranational level. However, as already mentioned earlier, there does not yet exist a consensus about the application of the European Convention (and the Council Directive) on CNT-cloning. In addition, even on the national level, the interpretation of the Animal Welfare Act just presented has not remained unchallenged.²⁴

At last, it has to be noted that the Animal Welfare Act contains a detailed provision regarding the issue of *breeding*. The reproduction of transgenic animals from the third generation on is considered to be breeding. From that moment, the creation of a transgenic strain passes the border from an animal experiment to continuing breeding (cf. Hirt et al. 2003, § 7 no. 2; Kluge 2002, § 7 no. 8). According to section 11b paragraph 1 Animal Welfare Act such breeding or changing of vertebrates through procedures of biotechnology or genetic engineering shall be prohibited if it must be expected that the offspring, the animals altered by technology or genetic engineering, or their offspring, due to hereditary factors are lacking parts of the body or organs for species-specific use, or they are unfit or deformed, and thereby caused pain, suffering or harm. Section 11b paragraph 2 extends this prohibition to biotechnological changes that might lead to behavioural abnormalities, disturbances of species-specific contacts or keeping problems. However, it can only be judged on a case-by-case basis if the breeding of genetically modified animals is in compliance with the restrictions presented. And finally, it has to be stressed that the CNT-cloning of genetically

²³ This conclusion is also shared by Braun 2002:139 et seq.; Löwer 2001:193 et seq.; Vesting and Simon 1998:263.

²⁴ According to the Bundesregierung 2005:18, Caspar 1999:434, Hirt et al. 2003, § 7 no. 2 and Kluge 2002, § 11b no. 8, CNT-cloning is supposed to be a treatment of the genotype for experimental purposes and thus an animal experiment according to Section 7 paragraph 1 no. 2 of the Animal Welfare Act.

animals already altered is not covered by this provision.²⁵ Whereas the term “breeding” only refers to sexual forms of reproduction (cf. Hirt et al. 2003, § 11b no. 2), the “change (of vertebrates) through procedures of biotechnology or genetic engineering” can only be accomplished on an already existing animal or on its embryonic form. Furthermore, the pure transfer of a cell nucleus cannot be considered as such a genetic modification. Again, though, this interpretation is controversial.²⁶

C. General Conclusions and Outlook

What general conclusions can be drawn from the foregoing?

- The creation of transgenic animals and their breeding for gene pharming purposes is basically compatible with international, supranational and national animal welfare law. None of these legal orders establish an overall prohibition of this concept. In contrary, animal gene pharming is considered to be an “ordinary” *animal welfare issue* that has to be subsumed under the already existing animal welfare regulation.
- The *creation* of transgenic animals (transgenic strains) is primarily a scientific experiment that has to (and can) meet the international, supranational and national restrictions with regard to animal experimentation, especially if the experiment is of outstanding importance for the health of man. However, neither the international and supranational nor the national law allow such experiments for pure cost-cutting reasons.
- The legal treatment of *reproductive CNT-cloning* is still a question not definitely answered. Whereas on the international and supranational levels this technique could be subsumed under the provisions regarding animal experiments, such an interpretation seems to be impossible for the national level. Thus, the German Animal Welfare Act has to be adjusted to the international and supranational law. However, it has to be stressed that there is no consensus about this interpretation yet. Consequently, other authors argue that CNT-cloning is not covered by the existing international and supranational animal welfare regulation or vice versa that this technique has to be treated as an animal experiment on all legal levels.

²⁵ Again, this conclusion is shared by Braun 2002:142 et seq.

²⁶ According to the Bundesregierung 2005:18, and Hirt et al. 2003, § 11b no. 8, section 11b can basically also be applied to the technique of CNT-cloning, at least when this technique will have lost its experimental character. However, the cited authors do not present an argument for this opinion.

By contrast, the *breeding* of transgenic animals for gene pharming purposes is not a subject of international and supranational law yet. The national law contains a provision which can also be applied to the concept of animal gene pharming, at least when sexual breeding techniques are used. Again, the application to asexual techniques (cloning) is discussed controversially.

These conclusions lead to three questions that ask for further analysis:

Form a biological as well as ethical point of view it should be examined if it is appropriate to apply the general animal welfare provisions to the creation and breeding of transgenic animals or if such modifications require specific legal standards (e.g. a specific ethical justification of such experiments because of their penetrative and lasting character, a specific qualification of the staff handling such animals, an observation of transgenic animals and their offspring over several generations, a specific data collection on such animals, etc.).

This question (specific legal regime for animal experiments) is closely connected to the question whether it is necessary or at least desirable to extend and to update the provisions regarding the breeding of genetically modified animals, especially where such provisions are – like on the European level – still missing.

And finally, the technique of CNT-cloning needs further observation. Again, the question has to be answered if it is necessary or at least desirable to establish a legal framework for CNT-cloning of animals on the European and national level. If this question is answered affirmatively, a decision about the major content of such a regulation has to be taken.

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