



EUROPÄISCHE AKADEMIE

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

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Pharming

Promises and risks of biopharmaceuticals
derived from genetically modified plants
and animals



Springer

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ISBN: 978-3-540-85792-1

e-ISBN: 978-3-540-85793-8

Ethics of Science and Technology Assessment ISSN: 1860-4803
e-ISSN: 1860-4811

Library of Congress Control Number: 2008935322

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Cover design: eStudio Calamar S.L.

Typesetting: Lambertz Druck, Köln, Germany

Printed on acid-free paper

9 8 7 6 5 4 3 2 1

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Preface

The Europäische Akademie deals with the scientific study of the consequences of scientific and technological advances for individuals and society, as well as for the natural environment with the lifesciences being an important focus of its work.

The application of bio- and genetechonology for medical purposes has been a hot spot of research in the lifesciences for several decades. One major field is the development and production of biopharmaceuticals, with therapeutic hormones and antibodies as prominent examples. They are pharmaceutical proteins that have to be isolated from biological material or be produced by genetically modified organisms. Besides the use of fermenter grown recombinant cell cultures for their production, it is now also possible to use higher organisms (plants and animals) for this purpose. This new application of genetechonology – called “pharming” – seems to be a promising strategy to produce a broad variety of biopharmaceuticals in large quantities at comparatively low costs. It attracted special attention due to its potential for profitable investments by the pharmaceutical industry.

However, taking into account the generally cautious attitudes of at least the European public towards gene- and biotechnology it is obvious that pharming should undergo a thorough evaluation of its ethical, legal, and social aspects and implications. For this task the Europäische Akademie set up an interdisciplinary and international project group that produced the report at hand. Besides it should be noted that the group consisted of senior and junior scientists contributing to the joint project on an absolutely equal footing. This show that intergenerational scientific collaboration can well transcend the often denounced state of dependence of younger scientists – given an adequate institutional framework is provided.

I would like to thank the authors Dr. Margret Engelhard; Kristin Hagen, Ph.D.; Rikke Bagger Jørgensen, Ph.D.; Professor Dr. Rafael Pardo-Avellaneda; Professor Angelika Schnieke, Ph.D.; Dr. Felix Thiele, and in particular the chair Professor Dr. Eckard Rehbinder, for their dedication to this project.

The Federal Ministry of Education and Research (Bundesministerium für Bildung und Forschung, BMBF) is hereby acknowledged for the funding of the project. In addition, the Banco Bilbao Vizcaya Argentaria (BBVA) foundation in Spain is thanked for their support that made the fieldwork of chapter 5 possible.

Foreword

Among the many products of modern scientific and technological innovation, gene technology has from the very beginning been highly controversial, especially for moral and environmental reasons. In the public debate, stem cell research, cloning of animals and cultivation of genetically modified plants are dominant themes. However, it is now also possible to produce biopharmaceuticals in genetically modified plants and animals. This new biotechnological method, which is called “pharming”, has a great potential on the growing market for biopharmaceuticals. It has important technical advantages over existing production methods and offers the prospect of much lower prices for pharmaceuticals, although its economic competitiveness remains to be seen. Besides benefits for producers, patients and health care systems, pharming also raises a number of complex environmental, health-related, moral, legal and social questions that have as yet not been thoroughly discussed. The degree of public awareness of the problems associated with pharming has been low. Now that the first biopharmaceuticals produced in transgenic animals have been authorized or are close to authorization in Europe and the United States, it is time to enter into an open fundamental debate about the issues raised by pharming.

To evaluate the potentials and risks associated with pharming and to determine the need for, and means of, legal regulation and policy action for the responsible further development of pharming, the Europäische Akademie zur Erforschung von Folgen wissenschaftlich-technischer Entwicklungen established an international, interdisciplinary project group in 2006. Disciplines represented in and members of the group were plant biotechnology (Dr. M. Engelhard, Bad Neuenahr-Ahrweiler, project coordinator), livestock biotechnology (Professor A. Schnieke, Ph.D., Freising), ecology (R. B. Jørgensen, Ph.D., Roskilde), animal welfare (K. Hagen, Ph.D., Bad Neuenahr-Ahrweiler), social science (Professor R. Pardo-Avellaneda, Ph.D., Madrid), ethics (Dr. F. Thiele, Bad Neuenahr-Ahrweiler) and environmental law (Professor Dr. E. Rehbinder, Frankfurt a. M., chair).

Over a period of two and a half years the project group held 13 internal meetings. In addition two workshops with external experts took place in Berlin in September 2006 and September 2007. The contributions of the colleagues involved profoundly enriched the study and in this respect the authors’ special thanks go to: N. S. Andersen (Roskilde), Professor Dr. D. Birnbacher (Düsseldorf), Privatdozent Dr. B. Breckling (Bremen), Profes-

sor M. Eaton, Pharm.D., J.D. (Stanford), Dr. T. Fahrendorf (Langförden), A. Kind, Ph.D. (Freising) (who has in addition made specific contributions to chapter 2.3), Professor Dr. J. Luy (Berlin), Professor Dr. P. Sandøe (Kopenhagen), Dr. J. Schiemann (Braunschweig), Dr. S. Schillberg (Aachen), Dr. E. Schmitt (Darmstadt), Professor Dr. R. Müller-Terpitz (Passau), Professor B. Whitelaw, Ph.D. (Roslin), and Professor Dr. G. Winter (Bremen). For a fruitful discussion in the course of the symposium “New applications of genetic engineering in livestock”, that took place in September 2007 in Berlin, we also thank Professor Dr. L.-M. Houdebine (Jouy en Josas), Professor Dr. M. Kaiser (Oslo), Professor Dr. H. Niemann (Neustadt), Dr. C. Van Reenen (Lelystad), Professor G. Walsh, Ph.D. (Limerick), and Professor Dr. A. Zanella (Oslo) as invited speakers. Most papers of the workshops were published in 2007 in the Graue Reihe of the Europäische Akademie. Contributions of the symposium are being published parallel to this project in the same book series.

For the editing I express my gratitude to I. Rochlitz, Ph.D. (Herts), K. Mader, M.A., and F. Wütscher from the Europäische Akademie. I also thank the numerous people who helped the group in organising the various meetings that took place outside the academy’s seat in Berlin, Bilbao, Bonn, Frankfurt, Freising, Madrid and Roskilde.

Frankfurt am Main, July 2008

Eckard Rehbinder

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1 Introduction

Proteins are an important subclass of pharmaceuticals in medicine. Most pharmaceutical proteins, however, cannot easily be synthesized chemically and are called biopharmaceuticals. Until recently these were either derived from biological material such as donated blood, or produced in genetically engineered bacteria, yeast or animal cell lines¹. It is now also possible to produce biopharmaceuticals in genetically modified plants and animals: recombinant human proteins have, for example, been expressed in maize kernels, tobacco leaves, goats' milk and chickens' eggs.

Throughout the book this new technology is termed '*pharming*'², composed of *pharmaceutical* and *farming*. Other terms sometimes used include 'biopharming', 'gene farming', and for plants only: 'pharm crops', 'molecular farming'. Reflecting common practice, the term 'plant pharming' will be used here to refer to the use of whole plants, plant cell cultures, hairy root cultures, and algae, while 'animal pharming' refers to whole animals, but not animal cell cultures.

The market for biopharmaceuticals is large and growing, with an estimated global value of \$33 billion in 2004, \$40 billion in 2007 and forecast to reach \$70 billion by the end of the decade. There is huge potential for novel medications, significant research and development spending, and a rising number of biopharmaceutical products on the market for human use: 170 in 2007, with more than 2,000 in clinical trials³. The growing market of biopharmaceuticals includes many products, including antibodies, that could be produced by pharming.

Factors contributing to the growth of the biopharmaceutical market include increases in the number of medical indications for protein therapies, and the number of patients with illnesses usually treated with pharmaceutical proteins. The provision of insulin for diabetes is one example. It has been estimated that in the year 2000, about 171 million people worldwide suffered from diabetes types I and II, and this number is projected

¹ See chapter 2.1 for a brief introduction to biopharmaceuticals and biotechnology.

² The term 'pharming' is also used on the internet to denote hackers' attacks that redirect a website's traffic to a bogus website in order to steal identity information.

³ Lawrence 2005; Pavlou and Reichert 2004; Pavlou and Belsey 2005; Walsh 2006; Ernst & Young 2007.

to increase to 366 million by 2030⁴. Although only a fraction of diabetics require insulin, the need for this protein will certainly increase. Changes in practice, such as the adoption of oral delivery rather than injection, may contribute to increased demand because substantially larger doses of insulin are required. Plant pharming has been explored as a means of supplying insulin at a reasonable price. The concept was realized in *Arabidopsis thaliana* in 2006⁵ and since extended to commercial production in safflower by SemBioSys (Calgary, Canada). The company is currently planning to start clinical trials, with a projected US launch of the product in 2011. By using safflower as production platform, SemBioSys hopes to reduce insulin unit costs by 40 % or more, and capital costs by up to 70 % compared with the production in traditional expression systems, and to provide a production system that allows easy and cheap scale-ups to meet growing demands⁶.

Another example is monoclonal antibodies, currently mainly produced in cell culture. Production costs per gram have been estimated as \$300–3,000 in mammalian cell culture, \$105 in transgenic goats and \$50 in transgenic corn⁷. Monoclonals with applications in cancer are currently some of the most promising new drugs, with a large potential market in which pharming may become important. Pharming also offers savings in capital investment, because of the ease with which production can be scaled up. Growing more transgenic crops or breeding more transgenic animals is simpler and cheaper than constructing additional culture facilities for bacteria, yeast or animal cell culture. A recent study estimated the capital investment for bulk antibody production in mammalian cell culture to be at least double than that required for transgenic goats⁸.

Pharming, particularly animal pharming, also provides a means of producing proteins which are difficult to make by other means. Many of the more complex human proteins require post-translational modifications for their assembly and bioactivity, which most microorganisms are unable to carry out. Cultured mammalian cells are able to fulfill many but not all of these functions. For example, several blood clotting factors require γ -carboxylation of glutamate residues; this is carried out poorly by chinese hamster ovary (CHO) cells, but successfully by the lactating mammary gland.

The addition of sugars to proteins, termed glycosylation, is another important type of post-translational modification. Glycosylation patterns are quite different between bacteria, yeast, plants and mammals and this can have important pharmacological consequences for proteins produced

⁴ Wild *et al.* 2004.

⁵ Nykiforuk *et al.* 2006.

⁶ <http://www.sembiosys.com/Main.aspx?id=14> (July 2008).

⁷ Farid 2007; costs per gram estimated at a production rate of 100kg/year. At higher production rates, the savings estimates become even more pronounced.

⁸ Lawrence 2007.

in each, for example affecting bioactivity, clearing rate and immunogenicity. Post-translational modifications are therefore an important determinant in choosing particular species and cell types as an expression system (see chapter 2).

In August 2006 the industry achieved a significant breakthrough when the European Commission authorized Genzyme Europe⁹ to market human antithrombin III (ATryn[®]) produced in the milk of transgenic goats. Antithrombin is used for the prophylaxis of venous thromboembolism for patients with congenital antithrombin deficiency undergoing surgery.

This advance however came very late compared with early industry expectations. The companies that pioneered pharming and developed the technology (PPL Therapeutics, GTC Biotherapeutics, Genfarm/Pharming) were founded in the late 1980s and had expected to bring the first product to market after five to seven years. Nevertheless, it has with hindsight been a big achievement to proceed from a theoretical possibility to market approval in less than two decades.

Despite the market authorization, proof of principle and an increasing number of pharming field and clinical trials in progress (see tables 2.1, 2.7), there is still a long way to go before pharming products are accepted and used. Although pharming might offer a method of producing valuable proteins, and might realize important advantages over existing methods, its economic competitiveness remains to be proven, not least because competing technologies are also developing, for example the increasing availability of mammalian cell cultures and addition of post-translational modifications to yeast-produced proteins. Furthermore, pharming also raises a number of ecological, moral, legal and social questions.

After an introductory technology chapter and an overview of potential applications, this book will assess risks and hurdles, and recommend appropriate measures for safe, acceptable and useful development of the technology. After a brief introduction to biopharmaceutical biotechnology (section 2.1), the technology of plant pharming is described in section 2.2: the methods of generating plants for the production of recombinant biopharmaceuticals, cultivation strategies and purification methods of biopharmaceuticals from transgenic plants. Section 2.3 provides an outline of basic recombinant DNA technology used in animal pharming, reviews methods of generating transgenic animals, describes technical issues affecting the choice of species and tissue used for production and briefly describes the purification of protein products from transgenic animals.

Risks to humans consuming pharmaceuticals are discussed in chapter 2. Biological risks to the environment are described in chapter 3, as are the control measures necessary for agricultural coexistence between pharming and non-pharming crops. Pharming often makes use of conventional crop

⁹ Current authorization holder: Leo Pharma, Ballerup, Denmark.

plants and animals that are normally used as food or feed. 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 will be crucial. The plausibility of a scenario of food chain contamination is demonstrated by the first documented pharming accident in 2002 in the USA, when 13,000 tonnes of soy beans were contaminated with vaccine from co-min-gled genetically modified maize volunteers¹⁰.

It presently remains unclear whether confinement strategies are suitable to avoid plant pharming having consequences for nearby flora, fauna and soil microbiology. Often the knowledge of the potential interactions between the pharming crop and the environment is limited. This lack of knowledge leads to a risk assessment with a large degree of uncertainty (dealt with in chapter 3 on risk assessment and chapters 6 and 8, on ethics and law, respectively). With animal pharming, confinement is not considered to be a major problem.

Animal pharming and plant pharming differ in a number of ways that will be touched on throughout the book. One important difference is that the animal species that are considered for pharming are generally considered to be sentient, and their potential suffering thus has to be taken into account. Chapter 4 reports on current knowledge and management suggestions with regard to adverse effects on animals in the experimental phase (making and evaluating transgenic founder animals) and in the production phase (husbandry and protein collection).

The contrasting views on animal and plant pharming are an important aspect of chapter 5, in which the profile of public attitudes to pharming is presented, relying on new data from a major multi-country comparative survey of public perceptions of biotechnology. The commonalities, the national differences and also the singularities in views and acceptance of pharming are offered, illustrating the areas of consensus and disagreement across a number of European societies that may have regulatory implications as barriers and also as facilitating components for future harmonized regulation. The aim of the analysis in this chapter is to offer, for the first time, a map of attitudes to pharming in the context of general perceptions of biotechnology and science and technology at large. The explanatory role of general and highly specific variables will also be explored. Among the large set of variables for characterizing public views of pharming, a few are of prime interest: knowledge of and proximity to science, world views (particularly, views of the promise of and reservations about science, images of nature and its transformation by humans, views on animals), risk perceptions, evaluation of the genetic modification of the plants, animals and humans, the hierarchy of acceptability of different medical and socio-economic goals potentially reachable through pharming, and views on the use

¹⁰ Fox 2003; Sauter 2005; Spök 2007.

of different types of plants or animals. Finally, the current predisposition to take medicines produced by pharming will be charted.

Chapter 6 addresses moral conflicts about pharming caused by discrepancies between the far-reaching medical and economic hopes connected to pharming, public attitudes to it, and moral concerns regarding amongst other things the moral status of animals and plants, the naturalness or unnaturalness of pharming, and the aims and means of using animals and plants for pharming. In addition, the difficulties of performing a systematic risk-benefit assessment of both animal and plant pharming are considered. The goal of the chapter is first to clarify how certain moral standpoints on pharming are structured. Given this map of moral arguments for and against pharming, a second goal chapter 6 will be to develop recommendations for mastering moral controversies on pharming.

Intellectual property rights have a major impact on the development of biotechnology: Many biotechnological procedures relevant for developing marketable biotechnological products, including biopharmaceuticals, are protected by patents. In chapter 7 the framework of intellectual property rights relevant to pharming is introduced. Furthermore it is assessed whether – and if so why – patents are morally, legally, or economically questionable with respect to pharming.

Chapter 8 analyses the legal situation with regard to pharming, with a focus on the situation in Europe. The development and manufacture of pharmaceuticals derived by recombinant DNA technology is regulated by different and highly complex European regulations and directives as well as by member state laws. Consequently, the relevant activities lie within the responsibility of a number of political and administrative institutions. For example, plant pharming represents for the first time a merger of green and red biotechnology, with the consequence that different regulatory regimes are applicable and different authorities are responsible. The contained use and the deliberate release, through cultivation of genetically modified organisms from which the recombinant pharmaceuticals are derived, is regulated by two EC directives and member state law on gene technology law that implements the directives. The same is true for animal pharming. The production of developmental recombinant pharmaceuticals and the placing on the market of the final preparation are covered by an EC regulation and supplementary national law. The placing on the market also requires an authorization from the European Medicines Agency. Furthermore, although pharming products are not intended to be used as food or feed, due to the risk of contamination of the food and feed chain pointed out above, there may be a need for preventive regulation under an EC regulation relating to genetically modified food and feed. Animal welfare law must be considered with respect to the use of transgenic animals for the development and – to a certain extent – the production of recombinant pharmaceuticals.

Chapter 8 in addition analyses the relevant regulatory texts and administrative practice from the perspective of their adequacy for tackling the risks and considering the potential benefits of pharming. In particular, what steps regulatory institutions are presently taking in order to reduce the risks associated with pharming and whether this action is sufficiently protective of human health, the environment and animal welfare, will be discussed.

In the final chapter of the book the implications of the analyses are presented, and recommendations for policy action are derived with a view to the responsible further development of pharming.

9 Conclusions and recommendations

9.1 *Pharming technology and its market*

The manufacture of biopharmaceuticals using genetically modified cultured cells and microorganisms is an established and successful industry. Using genetically modified whole animals and plants as a production platform is a more recent development that has sprung from radical innovations in the genetic manipulation of plants and animals, and reproductive technology in animals, over the past 10 to 20 years. The first two pharming products have gained market authorization. The world market for biopharmaceuticals is large, as is an important subset of biopharmaceutical products, including antibodies that could be produced by pharming. For certain proteins, pharming may be the most cost-effective means of production and could increase the availability of valuable medicines. It may also be the only way of producing useful quantities of a particular protein, thereby allowing the development of entirely new medicines.

Experience will continue to be gained regarding the suitability of the different production platforms for producing particular proteins. Technical advances in pharming continue to be made across a broad front, both in the industry and in academia. Currently available evidence indicates that pharming is capable of competing on equal terms with other methods of manufacturing pharmaceutical proteins. It has advantages due to the possibility of producing large, complex proteins with appropriate patterns of post-translational protein modification, and the comparatively low scale-up costs. However, these advantages will be relative to the development of the competing technologies, for example the increasing availability of mammalian cell cultures and the possibility of adding post-translational modifications to yeast-produced proteins.

Pharming is a viable and potentially competitive means of producing important biopharmaceuticals. In some cases, pharming may be the most efficient, or even the only, way of producing a particular protein.

Intellectual property rights have had a major impact on access to key technologies and potential products. While some patents covering valuable resources are due to expire, intellectual property restrictions are likely to

be very important in the short to mid term. Practices such as the granting of excessive and protectionist claims by national governments are a significant negative influence that stifles innovation.

The pharming industry in Europe requires a transparent, rational and stable regulatory environment in which to operate if it is to attract the long-term investment necessary for economic viability. Until now legislation has been made in reaction to rapid scientific advance and has been motivated mainly by a need to manage potential risk. The regulatory framework is fragmented and in important respects uncertain. Uncertainties regarding the application of the existing regulation, as well as their future development, are a significant disincentive to the development of new products. It is now timely to consolidate the regulatory framework and decrease the level of uncertainty. The outcome would also lead to equality of competition for pharming with other forms of manufacturing biopharmaceuticals.

A clearer regulatory framework for pharming is needed in order to decrease economic risks and secure equality of competitive conditions.

9.2 Public attitudes and moral evaluation

9.2.1 Attitudes

Potential controversy on pharming revolves mainly around the means, not the goals. The perception of the means -genetic modification of plants and animals- has two main components, one of a cognitive nature (basic knowledge of genetics) and the other of an evaluative character (views and feelings about purposely changing the blueprint of plants and/or animals). At present, the dominant profile of perceptions of biotechnology in general and pharming in particular is heavily dependent on the second component. Lack of knowledge, misunderstandings and misrepresentations of basic genetic concepts are observed in most advanced societies and particularly in Europe. A higher level of knowledge does not automatically translate into more positive attitudes, but at a minimum will certainly help to remove unfounded fears and empower individuals to make informed choices about accepting or rejecting pharming. The acceptance or rejection could also become less holistic, giving way to a more fine-grained evaluation, depending on the specifics of the goals and the means, such as the type of plant or animal to be used and the purpose of the biomedical application. Special attention should be paid to offering unbiased basic information about genetics and about pharming procedures to the public.

The scientific community and the policy makers should foster a climate of open dialogue with society at large, without taking for granted that any intervention at the genetic level of life has to be perceived by the public as a “good

thing” and, even less, that all forms of opposition or cautious stand on the part of the public are a mere function of ignorance about the means and the risks. Public’s views, values and preferences about nature and its genetic modification for different goals should be taken seriously by the scientific community, companies and regulators, and these actors should be better equipped to understand and engage in a productive debate with the public and the organizations concerned with nature preservation and animal defence.

A higher level of salience, independence, transparent regulatory procedures, openness and accountability of these agencies and public bodies could significantly increase the level of public trust in the authorization of specific pharming applications (both processes and products). It could decrease the immense cognitive demands on individuals for personally evaluating the usefulness, risks and implications of advances in pharming. In doing so it could reduce the potential both for adversarial and promotional campaigns on pharming mounted by single-issue organizations and lobbies.

The scientific community and the policy makers should foster transfer of knowledge of biology and genetics to the public, a climate of open dialogue with society at large, and a higher level of salience, independence, transparency, and accountability of regulatory agencies.

9.2.2 Moral evaluation

In assessing the moral concerns expressed in public attitudes and in the bioethical literature, the goal of the chapter on the moral evaluation of pharming has not been to search for true or objective answers. Rather, the aim is to come up with recommendations for a morally acceptable, but also socially accepted development of the field of pharming. The focus has been on conflicts about pharming caused by discrepancies between far-reaching medical and economic hopes, public attitudes, and moral concerns regarding amongst other things the moral status of animals and plants, the naturalness and unnaturalness of pharming, and the aims and means of using animals and plants for pharming. In addition, the difficulties of performing a systematic risk-benefit assessment of pharming have been analysed.

Having taken into account both the argumentative strength of the various criteria proposed for the moral evaluation of pharming and their potential for mastering conflicts on pharming, it is proposed that i) in developing pharming, more weight should be given to avoiding the infliction of suffering on animals, compared with concerns regarding the unnaturalness of pharming or the infringed integrity of pharming animals and plants, ii) in evaluating pharming projects one should take into account the specific aims for which the animals and plants are used, and iii) in view of the scientific uncertainties in performing a systematic risk-benefit assessment of

both animal and plant pharming, there should be a careful case by case analysis of pharming projects using the precautionary principle.

The moral evaluation of pharming should consider:

- the potential suffering inflicted on pharming animals;
- the purpose of, and need for, the specific products for which the animals or plants are used;
- the precautionary principle in view of the available scientific evidence and its limitations, and the difficulties in performing a systematic risk-benefit assessment of both animal and plant pharming.

9.3 *The assessment and management of risks associated with pharming*

9.3.1 *Principles*

9.3.1.1 *Case by case*

A clearer regulatory framework for pharming is needed, not only in order to decrease economic risks but also in order to effectively manage risks to humans, animals and the environment. The striking problem in risk assessment is that pharming plants and animals lead to new combinations of trait (transgene), organisms, and environment, so that it is hardly possible to draw on existing experience. Assessment and management of risks associated with plant or animal pharming have different emphases – welfare in the case of animals, risks to the environment in the case of plants. This is reflected in the sections below.

In plants, unless the transgene modifies traits associated with reproduction - which is rarely the case - the mode of gene dispersal will not be changed within a given species, and therefore the dispersal of pharming plants is identical to that of non-GM plants and other GM plants. However, the fact that proteins are intentionally produced in very high concentrations in pharming plants makes it much more complicated to evaluate the probability of possible unwanted effects. This is also true of transgenic animals, leading to animal welfare concerns. Therefore, although general recommendations on risk assessment of pharming plants and animals would probably fail to address all pharming plants and animals in an appropriate way, we will below propose some general measures in addition to the case by case approach necessitated by the diversity of scenarios.

The risk assessment of pharming requires a case by case approach. However, we also propose some general measures for handling high levels of uncertainty.

9.3.1.2 Risk-benefit evaluation

Risk assessment of pharming plants and animals can be quite uncertain. This uncertainty calls for a broad regulation of GM pharming plants and animals, in which ethical and social considerations regarding the production should accompany the traditional natural science-based risk assessment. This is in particular true of highly bioactive products. Both with respect to experimental releases and cultivation of pharming plants and experimental releases and the keeping of pharming animals, the grant of authorization should be conditional not only on a positive risk assessment considering proportionality between risks and costs, but also on a positive risk-benefit evaluation. Such an evaluation is an expression of the principle of “ecological proportionality”. It is already recognized in the regulation of pharmaceuticals, pesticides, biocides, and particularly dangerous chemicals for general use, and should also be introduced with regard to pharming activities.

Risk-benefit evaluation – not only a risk assessment – should be made a precondition of authorization, both with respect to the experimental and the production phase.

9.3.1.3 Independent risk assessment research

Presently, the authorities base their risk assessment mainly on experimental results provided by the GM producer. Allocation of more funds to independent risk assessment research is necessary; presently these research activities are minimal. In order to provide an independent assessment and research on potential risks associated with pharming, researchers who are not dependent in any way on transgenic plant or animal producers or associated parties should have better access to material on pharming GM plants and animals. Procedures regarding the conditions of access and protection of trade secrets must be worked out based on a public discussion.

Access to information necessary for independent risk assessment research should be improved and better funding should be made available for this research.

9.3.1.4 Transparent procedures and independence of risk assessment bodies

Although existing law affords concerned citizens an opportunity to comment on a proposed release and gives them access to information relating to the risk assessment, the present level of transparency in the risk assessment

procedures is not sufficient to ensure informed and effective participation. The quality of information on the risk assessment procedures available to the public should be higher. There should be access not just to monitoring plans, but also to monitoring results. Arguments on which the evaluation of risk and decisions on risk management are based, including assumptions regarding science, values, world views etc. should be made public. Avenues that the public have for expressing their opinion should be improved. An open register giving sites of releases and production should be available in all EU member states. It should be mandatory to inform adjacent farmers about planned releases. However, trade secrets must be protected. This is in particular necessary in the experimental phase. Confidential gene constructs deserve protection throughout the development and production phases.

In view of concerns about trust in the institutions, members of the EU and national risk assessment bodies should be required to declare their associations with private companies (all collaborative projects, committee memberships, etc.) when assessing particular products, and if advisable, be prohibited from making particular assessments.

Procedures ensuring such higher levels of transparency should be worked out for the risk assessment bodies based on a public discussion.

There should be stronger requirements for transparency in risk assessment procedures.

9.3.2 Product safety and information

9.3.2.1 Measures to prevent contamination and ensure product quality

The development and production of pharming medicinal products does not only require the protection of the environment from risks associated with the release of GMOs, but also the protection of the production process from risks originating from the environment, for example viral and other infectious agents, or pesticides.

The requisite safety measures for ensuring an appropriate safety and quality of developmental and final pharmaceutical products are not necessarily such that an open release with confinement cannot be used under pharmaceuticals regulations. The producer should be allowed to lay the emphasis on safety and control measures regarding the gaining and processing of the crude bulk material and the manufacture of the medicinal product. Strict containment may in some, but not all, instances be necessary. From economic and animal welfare aspects, containment would be a disadvantage.

Other potential quality and safety problems associated with the use of transgenic plants and animals for the production of pharmaceuticals, such as instability, immunogenicity, impurities and host cell contaminants can be tackled by applying the normal authorization prerequisites and procedures.

Adequate safety measures must be taken in order to prevent the contamination of pharming products by environmental factors, such as viral agents. If production is not performed with containment, special care is required regarding the gaining and processing of the crude bulk material and the manufacture of the finished pharmaceutical.

9.3.2.2 *New guidelines on pharming medicinal products and European Medicines Agency (EMA) committee on pharming products*

In view of more recent scientific and economic developments in the field of pharming, the existing EMA guidelines are outdated. To ensure product safety and quality also of pharmaceuticals that do not consist of, or contain, GMOs but are derived from recombinant protein, the adoption of modern guidelines is warranted. A special committee on pharming should be established within the agency in order to ensure a greater familiarity of the EMA with the specific problems of pharmaceutical quality and safety (for example aspects of immunogenicity) presented by pharming products.

New EMA guidelines on pharming products are needed. A special committee on pharming should be established within the agency.

9.3.2.3 *Labelling and consumer information*

To afford patients and doctors a free choice of pharmaceuticals within the constraints of the public health system, two measures are advisable. Firstly, labelling containing information on the relevant production method should be permissible and encouraged by the authorities, as it is unclear whether this can be done under existing law. Secondly, there should be a general individual right to information on the production method against the manufacturer.

Voluntary labelling should be permissible and encouraged. Individuals should have the right to information on the production method.

9.3.3 Risks to the environment and food and feed chains

9.3.3.1 Experiments and cultivation with containment, and deliberate releases

Two legal avenues can be used for the production and use of genetically modified organisms: experiments and cultivation with containment under the contained use directive, or deliberate release under the release directive. In case of production in the open environment it should be clarified if a part B procedure under the release directive (normally used for field experiments) or a part C procedure (an authorization for placing on the market) must be secured.

Compared with plants, accidental escape of large animals (excluding fish) is unlikely, and there are good chances of retrievability. Therefore, the rest of this section is concerned with plants. In most cases some degree of containment or confinement is imposed for experimental releases or regular cultivation of GM plants. A residual risk of transgene leakage remains in all cases. This means that dispersal of plants or plant parts (for example gametes and seeds) is always a possibility. However, the different containment, confinement and isolation measures offer differing degrees of safety. As regards risks to the environment, including risks to human health, there is a clear choice between development and production in strict containment (bioreactors, special glass-houses or closed animal units) or in the open environment provided that adequate genetic containment, or confinement, and protection measures are taken.

In some cases of particularly high risk or great uncertainty, development and production under strict containment may be warranted. However, the imposition of strict containment is not warranted on a general basis. It will always be the combination of the transgenic character, the recipient plant and the receiving environment that determines, together with the principle of proportionality, to what extent, and which type of, containment or confinement should be applied from the point of view of ecological risks.

All types of genetic or physical plant containment, confinement and isolation systems may be leaky at some point. The different containment, confinement and isolation measures can offer differing degrees of safety. The choice between completely avoiding release or applying more or less stringent containment, confinement and isolation measures should be guided by factors such as the degree of risk and uncertainty, the safety that can be achieved and proportionality.

It is necessary to be extra cautious particularly during the first experimental releases of a pharming plant, as knowledge about the interaction between the pharming plant and the environment is probably limited at

this point. During the release such information should be obtained, provided that this does not jeopardize the confinement measures. Especially analysis of non-target effects of exposure to the release site and environment should be measured. As knowledge about gene flow can be gained from equivalent non-transgenic lines and applied to the GM plant, gene dispersal aspects do not have to be studied in releases, and large isolation distances or other types of confinement can be applied to the field trial. The risk of commingling should be minimized, until risks have been thoroughly evaluated. Staff involved in pharming plant releases should be required to receive special training in how to minimize potential personal and environmental risks. More and longer monitoring should be a recommendation for both field trials and production fields. Monitoring should continue after termination of the release. In this way, experience can be accumulated on which better risk assessment and management can be built.

Extra strict confinement may, if technically possible, include the use of crops not used for food and feed. This confinement strategy will reduce the risk of both commingling and gene flow, especially if taxonomic relationships are weak between the pharming crop and food or feed crops and wild relatives in the area. Whether this non-food and non-feed strategy should apply only to the production of highly bioactive pharming products or should be a general precautionary measure for all pharming plants can be debated. Another confinement strategy may be zoning, an extreme variant of physical isolation by distance.

During deliberate pharming plant releases for development and regular production, extra high safety standards should be enforced including:

- education of personnel;
- extra strict confinement (for example zoning);
- total genetic containment in some cases;
- more and longer monitoring;
- research on the interaction between the pharming plant and the environment (where applicable).

The present guidelines for GMOs were not developed to apply to pharming but only to food and feed crops. As all containment or confinement measures may be leaky at some point, the authorization of experimental releases and regular production entails a decision on the acceptability of risks associated with pharming. Even where the competence for taking this decision is vested in the member state authorities, common guidelines are advisable to protect health and the environment because pharming presents novel problems of risk assessment and risk management. Guidelines could collate the scattered experiences with pharming and put them at the disposal of all relevant authorities as well as researchers and industry.

The guidelines should aim for minimum harmonization only, leaving the member state authorities an ample margin of discretion to take more stringent precautions.

Common guidelines for pharming plant experimental releases and regular cultivation should be developed, providing a harmonized basis for risk assessment at national and EU levels.

9.3.3.2 Coexistence

The potential economic harm that organic and conventional farmers in the vicinity of fields with transgenic crops, including pharming crops, may suffer due to gene spread and commingling does not differ whether they are exposed to an experimental release or to a permanent cultivation. Therefore the rules on coexistence, which presently only apply to permanent cultivation, should be extended so as to also cover experimental releases. Moreover, as with the risks to health and the environment associated with releases, common EU guidelines for ensuring coexistence between organic and conventional agriculture and pharming are advisable. However, member states should retain an ample margin of discretion for considering particularities of their country, such as soil and climatic conditions, agricultural practices and structure of land holdings, as well as for deciding on the appropriate level of protection of the economic interests involved.

Common EU guidelines for ensuring coexistence between organic and conventional agriculture and pharming are advisable.

9.3.4 Risks to animals in pharming

Risks to animals used in pharming can be divided into those that arise during the experimental phase, and those that arise during the production phase, where offspring are used to produce the protein for commercial use. Good laboratory practice in the experimental phase, and good farming practice throughout, are already legal requirements and include attention to species-adequate housing and management conditions, priority for non-invasive options for laboratory procedures, and trained personnel.

Nevertheless, and although this is not inevitable and not the intention, generating and using animals for pharming purposes potentially causes them to suffer. In view of the moral principle of avoiding animal suffering wherever possible, which is advocated in this book, emphasis should be placed on animal welfare risk assessment and management, and on the current lack of knowledge with regard to the effects of transgenesis on ani-

mal welfare. To gain more knowledge in the experimental phase, welfare parameters must be included in phenotyping protocols in order to carefully document unintended side-effects of transgenesis, including subtle dysfunctions. Continued epidemiological research (lasting into the production phase) is warranted in order to detect potential long-term consequences of transgenesis.

The risk assessment carried out before embarking on an animal pharming project should take into account not only potential welfare problems related to the experimental phase, but also those related to the envisaged production. In line with the above mentioned general principle of also considering the benefits, it should be noted that the legal status of cost-saving benefits in risk-benefit evaluation and the ethical review of animal trials and intervention in production animals is unclear. It should be clarified whether considerable cost savings for patients and collective social and private insurance institutions, as well as a speedier mass production of medicinal products, are factors that may be considered to be benefits in risk-benefit evaluations and the ethical review.

The current lack of knowledge with regard the effects of transgenesis on animal welfare should be taken into account in:

- precautionary measures, for example the animal welfare risk assessment carried out before an animal pharming project, which should also consider the potential welfare problems related to the production phase;
- facilitation of animal welfare research – including during the experimental and production phases – which is needed to fulfil even current animal protection legislation.

The production phase of animal pharming should be covered by the regulations on the keeping of animals used for agricultural purposes, because animal pharming is similar to the farming of animals for leather and fur and can therefore be defined as an agricultural activity.

Animal pharming in the production phase should be covered by the regulation on keeping of animals for agricultural purposes.

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Acknowledgement

The project “Pharming. Genetically Modified Plants and Animals as Future Production Site of Pharmaceuticals?” (“Pharming. Gentechnisch veränderte Pflanzen und Tiere als Arzneimittel-Produktionsstätten der Zukunft? Vergleich von Innovationshemmnissen und Durchsetzungschancen”) was supported by the Federal Ministry of Education and Research (Bundesministerium für Bildung und Forschung, Förderungskennzeichen 16|1547). In addition, the support of the Banco Bilbao Vizcaya Argentaria (BBVA) Foundation in Spain made the fieldwork of chapter 5 possible. The authors of this study are responsible for the content.

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