8 Legal problems of pharming

8.1 Introduction

The regulatory framework of pharming is highly complex. As regards the sources of regulation, one must distinguish between European and national levels. The various phases of pharming, from the initial development to the authorization procedure to final manufacturing, are partly subject to different legal rules. In addition, the various regulatory issues at the relevant stages are addressed by different pieces of regulation. The following text is organized so as to follow the "life cycle" of pharming products. When appropriate, the phases are further divided into segments according to the regulatory issues arising and the type of regulation concerned. The following overview provides an initial orientation.

8.2 Development phase I: Protection from risks to the environment caused by the use and release of GM0s

As regards risks to the environment caused by the use and release of GMOs in the development phase, the fundamental question concerns the necessary safety requirements in order to prevent harm to the environment from the relevant transgenic plants or animals. Alternative strict safety requirements exist under the contained use regime established by the Directives 90/219 and 98/8 and the more liberal precautions under the release regime laid down by Directive 2001/18.

8.2.1 Sources of legal regulation and their scope of application

In this respect, two major EC directives[1] may be relevant:

- Directive 90/219 on the contained use of genetically modified microorganisms (contained use directive) as amended by Directive 98/81 (which has replaced almost entirely the former directive)[2],
- Directive 2001/18 on the deliberate release into the environment of genetically modified organisms (release directive).

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1 All the more recent EC directives and regulations can be accessed free of charge through www.eur-lex.europa.eu.

2 Except for articles 1 and 17. The original directive is published in O.J 1990 No. L 117:1.

Table 8.1: Overview of the legal regulations and institutions involved in pharming

1. Development phase	
Risks to the environment	**Animal welfare**
Directives 90/219 + 98/8 on contained use or Directive 2001/18 on release of GMOs, Part B and national law on biotechnology Waste: in addition Regulation 1774/2002 on disposal of animal parts and national law Commission guidelines (releases)	Directive 86/609 and national law on ani-ima1 protection
P/S: National authorities P: Commission (release in simplified procedure)	P/S: National authorities
Occupational safety and health	**Quality and safety of developmental product; risks from the environment;** ethical justification of clinical testing
Directives 90/219 + 98/8 on contained use or Directive 2001/18 on release of GMOs (conditions of permit) and national law on biotechnology Directive 2000/56 on biohazards and national law	Regulation 726/2004 + Directive 2001/83 on pharmaceuticals, Directive 2001/20 (ethical review) and national law on pharmaceuticals (production and clinical testing)
S: National authorities	P: National authorities (production and clinical testing); S: National authorities
2. Marketing authorization phase	
Quality, safety and effectiveness of medicinal product (including assurance of safety of production)	
Regulation 726/2004 + Directive 2001/83 on pharmaceuticals and national law (production) EMEA guidelines	
P: Commission/EMEA, National authorities (production)	
3. Production phase	
Risks to the environment	**Animal welfare**
Directives 901219 + 98/8 on contained use or Directive 2001/18 on release of GMOs, Part C and national law on biotechnology	National law
P: National authorities (contained use) or Commission/EFSA (cultivation in the open environment); S: National authorities	S: National authorities
Occupational safety and health	**Coexistence (impairment of economic interests through production)**
Directives 90/219 + 98/8 on contained use or Directive 2001/18 on release of GMOs (conditions of pernit) and nationallaw Directive 2000/56 on biohazards and national law	EC recommendation on coexistence National law (regulation, labelling and liability)
S: National authorities	S: National authorities
Quality and safety of medicinal product; risks from the environment	
Regulation 726/2004 + Directive 2001/83 on pharmaceuticals and national law (production) EMEA guidelines	
P: National authorities (production); S: National authorities	

P: permit/authorization; S: surveillance/inspections; for other abbreviations see list of abbreviations.

These directives need to be, and have been, implemented and partly supplemented by national law so that the relevant national laws[3] are applicable "on the ground". These are in:

- Germany: the Act on Biotechnology of 1990, consolidated in 1993, as last amended in 2008, and various regulations promulgated under the act, in particular the Regulation on Biotechnological Safety of 1990, consolidated in 1996, as amended (contained use) and the Regulation on Biotechnology Procedure of 1990, consolidated in 1996, as amended (contained use and releases);
- United Kingdom: the Environmental Protection Act 1990, part VI, the Genetically Modified Organisms (Contained Use) Regulations 2000 and the Genetically Modified Organisms (Deliberate Release) Regulations 2002;
- France: Code de l'environnement, Book V Title 3 (legislative and regulatory parts), in particular articles L532-1 to L532-6, R515-32 to R515-36, R532-1 to R532-l7 (contained use), articles L533-1 to L533-7, R533-1 to R533-48 (releases).

Directive 90/219 is an environmental directive and therefore only contains a minimum standard (article 176 EC Treaty, formerly article 130t EC Treaty). In contrast, Directive 2001/18 is based on the legislative competence of the Community to harmonize national law. A national deviation from such a directive is subject to severe restraints (article 95 [4], [5], formerly article 100a [4] EC Treaty). Since both directives are very detailed, the degree of divergence between the relevant national laws is not very large. Therefore, for reasons of convenience, the following analysis focuses on the two directives, and discusses national law implementing them only where suggested by particularities.

The scope of application of the two directives is essentially equal as regards the type of activities covered. They comprise the cultivation, keeping, propagation, storage, destruction, disposal, discharge, transport and other use or handling of GMOs. However, there are two differences. One is that Directive 90/219 only applies to genetically modified microorganisms (GMMs), while Directive 2001/18 comprises all genetically modified organisms. Microorganisms are defined as microbiological entities capable of replication or of transferring genetic material, including viruses, viroids,

[3] Unless the exact source is indicated, access to the national laws and regulations cited here is possible free of charge at the following internet addresses: Germany: www.bmu.de (July 2008) or www.gesetze-im-internet.de (July 2008); United Kingdom: www.opsi.gov.uk (July 2008); France: www.legifrance.gouv.fr. (July 2008); United States: www.law.cornell.edu/uscode (July 2008) or www.gpoaccess.gov/uscode/index.html (July 2008) and (as for regulations) www.gpoaccess.gov./ecfr (July 2008). Many member state texts can also be found in an English translation in: European Commission, Technical Regulations Information System (TRIS) at www.ec.europa.eu/enterprise/tris (July 2008).

and animal and plant cells in culture.[4] "Naked" DNA, r-plasmids and cell nuclei are not encompassed by the definition of both microorganism and organism. In the context of pharming, the distinction between microorganism and organism is not very important at the initial development stage, due to the frequent use of cell cultures as well as virus-based DNA sequences as promoters. However, the subsequent stages of development, especially the handling of GM plants and animals after genetic modification, are no longer covered by directive 90/219. Since the scope of application of the national laws and regulations on contained use extends to all GMOs, especially transgenic animals and plants, this restriction does not mean that there are no rules on contained use in place. The second and fundamental difference between the two directives concerns the kind of handling. While Directive 90/219 and implementing national laws apply to the contained use of GMMs, releases of GMOs into the environment, including placing them on the market, are covered by Directive 2001/18.

From an environmental perspective, the operator can in principle choose between the two regimes. Development with containment under Directive 90/219 and national laws on contained use can be carried out in order to secure an authorization for the finished pharmaceutical product under Regulation 726/2004. This is especially attractive in animal pharming because the number of animals needed for development is limited. Even in plant pharming, development with containment, for example in glass-houses, would make sense. Alternatively, the operator can start development operations without containment under the regime of the release directive, and then initiate the authorization procedure for the medicinal product derived from the transgenic plants or animals. Finally, the operator can divide the development process into two phases, first using the contained use directive and later on switching over to the release directive. The operator might consider it useful to gain experience with a release, especially if he/she wants to perform the later production in an open system under part C of Directive 2001/18, or wants to introduce the transgenic plant as seed (see section 8.7). Directive 2001/18 is based on the "step by step" principle of continuous generation of new knowledge, whereby containment of GMOs is gradually reduced and the scale of release increased if the evaluation of the earlier steps, in terms of human health and the environment, indicates that the next step can be taken (Directive 2001/18, recital 24).[5] Although the step-sequence concept is not strictly mandatory,[6] it may serve as a guideline for the interpretation of the directive. Therefore, it may appear reasonable to follow this line in devising the stages of the development process for pharming drugs.

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4 The definition intentionally goes beyond the common scientific understanding of a microorganism.

5 See Winter *et al.* 1993:49 *et seq.*

6 Administrative Court Berlin, in: Ebersbach/Lange/Ronellenfitsch 1995 vol. 4, § 16 GenTG No. 7.

However, Regulation 726/2004 in conjunction with Directive 2001/83 and the applicable requirements relating to the quality of development pharmaceuticals and the production process for such pharmaceuticals may limit these options. As will be discussed in more detail later (see section 8.5), in contrast to medicinal products that contain, or consist of, GMOs, medicinal products that are merely derived by using recombinant DNA techniques such as the normal pharming drugs need only to undergo the normal authorization procedure under Regulation 726/2004. An environmental risk assessment relating to a release is not required. From this perspective, a release would not be necessary but, of course, possible. However, under pharmaceuticals regulation the production process for pharmaceuticals under development ("developmental pharmaceuticals") requires a considerable degree of protection from risks from the environment in order to ensure a sufficient quality and safety of the product to be submitted for testing, especially clinical testing. This may limit or even exclude the use of the release regime, at least with respect to animal pharming (see sections 8.4, 8.5.3).

In the United States, from an environmental perspective the development of transgenic medicinal products can be performed either as a contained use or as a release of GMOs. Under the sectoral approach that the US follows in this field, contained uses and releases of GMOs are regulated according to products rather than processes. The Toxic Substances Control Act (TSCA; 15 U.S.C. §§ 2601–2692) only applies to genetically modified microorganisms, which are considered by the Environmental Protection Agency as "new substances" in the meaning of section 3 [2] [a] [i] TSCA. It is not applicable to transgenic plants and animals. The contained use and release of transgenic plants are regulated by the US Department of Agriculture under the Plant Protection Act (7 U.S.C. §§ 7701–7758) and implementing regulations (7 C.F.R part 340), provided the GMO constitutes a plant pest. A plant pest includes bacteria, fungi, viruses or similar organisms, as well as infectious agents or substances that may cause damage to plants (7 C.F.R § 340.1). Although the regulations assume that introduced genetic material that encodes products intended for pharmaceutical use may be covered (7 C.F.R § 340.3 [b] [4] [iii]), pharmaceutically active agents produced in pharming activities, for example vaccines or antibodies, as such are not encompassed by this definition. Rather, it is necessary that the donor or recipient organism, or the vector or vector organism constitutes a plant pest, which may be the case where gene fragments from pathogens, viruses or bacteria are used as promoters.[7] The regulatory activities of the US Department of Agriculture (Animal and Plant Health Inspection Service – APHIS) relating to GMOs focus on the release of transgenic plants used for the production of food and

[7] See USDA, 65 Fed. Reg. 53976 (2000); Anderson *et al.* 2001:3,4,15–24; Steines 2002:147.

feed. However, transgenic plants for pharmaceutical and industrial use are also regulated. There is as yet no parallel regulation of transgenic animals. However, powers to regulate exist under the Animal Health Protection Act (7 U.S.C. §§ 8301–8317), and the US Department of Agriculture is considering regulating transgenic animals in the future.[8] As in Europe, the regulation of medicinal products under the Federal Food, Drug and Cosmetic Act (21 U.S.C. §§ 301–399), administered by the Federal Food and Drug Administration (Center for Biologics Evaluation and Research – CBER – and Center for Veterinary Medicine – CVM), also addresses safety and quality issues of products under development derived from transgenic plants or animals. The agency is also competent to regulate risks to the environment that may be associated with the development process.

8.2.2 Development of recombinant medicinal products with containment

Directive 90/219, which may be applicable to the initial development of recombinant medicinal products with containment, aims for the protection of human health and the environment from risks arising from activities that engender the use of GMMs and hence also initial pharming operations. Although the formulation of the relevant article 1 of the directive, even after the fundamental reform of 1998, does not contain any language to the extent that it could be an expression of precautionary elements, the directive has to be interpreted in conformity with the precautionary principle laid down in article 174 [2] EC Treaty. This is not only suggested by the jurisprudence of the European Court of Justice,[9] but also by the recitals of the directive (recitals 1 and 3) and its article 5, which requires the member states to avoid adverse effects on human health and the environment which might arise from the contained use of GMMs. Moreover, as can be derived from the definition of accident, the directive aims to minimize the risk of escape of GMMs into the environment as well as exposure of workers. The definition of accident that has to be prevented refers to mere hazards to human health and the environment (article 2 [d]). In view of the uncertain nature of risks presented by GMMs and the resulting impossibility of a definitive risk assessment, this application of the precautionary principle is indispensable.

Directive 90/219 employs a system of four risk classifications (containment categories) ranging from no or negligible to high risks, which trigger containment measures of increasing stringency.[10] The attribution of a par-

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[8] Based on 7 U.S.C. § 8303; see 72 Fed. Reg. 69762-63 (2007). Animal cloning is already regulated; see 73 Fed. Reg. 2923 (2008).

[9] 1998 ECR I-2265 No. 90 – BSE; 2006 ECR I 53 No. 40 – Commission v. Germany; see also European Court of First Instance, 2002 ECR II-3305 Nos. 135 *et seq.* – Pfizer Animal Health.

[10] Based on American National Institute of Health guidelines; see Marx 1997:295 *et seq.*; OECD 1986:34 *et seq.*

ticular activity to one of the risk categories must be based on a risk assessment to be performed by the operator, using the criteria contained in annex III (article 5 [2], [3]), and notified to the competent authority. The factors to be considered concern the risk potential presented by the recipient organism, the genetically modified insertion, the vector, the donor organism and the resulting GMM, the characterization of the activity and the severity and likelihood of harm. Classification is the responsibility of the operator. As a safeguard against under-classification by the operator, the directive (article 4 [4]) provides that, in case of doubt, the more stringent category shall be applied unless sufficient evidence, in agreement with the competent authority, justifies the application of the less stringent measures. The competent authority has a margin of discretion in attributing a particular use to a risk class.[11]

The directive prescribes a consent procedure when premises are used for contained use of GMMs (maximum delay: 90 days; article 10). This requirement is limited to the risk classes 3 and 4. In other cases, a notification is sufficient. Articles 8 and 9, in conjunction with article 11 [2], [3] of the directive, mandate the member states to grant their authorities sufficient powers to review all notifications, the correctness of the risk assessment including the classification of the activity in question, and the suitability of the containment and protection measures proposed by the operator. The operator may also be obliged to set forth an emergency plan for the case of an escape of GMMs falling under the higher risk categories.

As stated, national law relating to contained use extends to all GMOs. It more clearly spells out the precautionary principle as a basic standard of protection, while following relatively closely the risk classification and duties of care established by the directive. In setting permit and notification requirements, Germany and the United Kingdom distinguish between the facility in which a contained use is to be carried out (facility accreditation) and the process as such (contained use). Moreover, the degree to which national law also adheres to the procedural design of the directive varies. The most liberal regime exists in Germany. Here, the construction and operation of a facility for use of classes 1 and 2 GMOs and the initial use of such GMOs are only subject to a notification procedure (coupled with alleviations regarding repeated uses). A facility and use permit is required for the higher risk categories. In the United Kingdom, facilities for the use of GMMs of all risk categories need to be notified. With respect to the use of class 1 GMMS, a further notification is not necessary. The initial use of all other risk classes requires a consent. A further differentiation between the relevant risk classes is made with respect to repeated uses. With respect to GMOs other than GMMs, the regulations provide that a notification and

[11] Administrative Court of Appeal Mannheim, Neue Zeitschrift für Verwaltungsrecht 2002:224.

consent are not required where the potential risk is equivalent to that of non-transgenic organisms. In France, initial and repeated uses of GMOs classified into all risk categories are subject to the requirement of a consent, while some procedural alleviations are provided for repeated uses. Normally, in all countries there are relatively short delays for reacting to a notification or granting a consent.

In practice, pharming activities are classified under the risk category 1. This is based on the assumption that the risk associated with the development operations is negligible. However, as recognized by annex III point A and B 4, risk is a function of hazard, probability of exposure and harm, and kind and extent of assumed harm. The requisite probability is relative to the kind and extent of harm. Therefore, one may put the generality of this classification practice into question, especially in view of possible accidents. One of the criteria, among others, that may be considered when assessing risk is the biological activity of the GMOs (see section 3.7). Directive 2001/18 seeks to phase out the use of antibiotic resistant marker genes (article 4 [2]). This is predicated on a normative judgement, whereby substances that have pharmaceutical properties associated with potential deleterious effects on the possibility of treating a disease should not enter the environment through release of GMOs, even if the probability of a (horizontal) gene transfer associated with the release is considered to be very low. Without an express political decision laid down in the contained use directive or national law, this phasing-out policy cannot be transferred to other areas and substances. However, it calls for a higher degree of caution.

With respect to activities of all categories, the directive (article 6 [1], annex IV Point 1) and implementing and supplementary national regulations[12] in the first place require a minimum of containment and protection measures of a general nature (so called principles, in Germany: basic obligations). In this connection it must be noted that, since the amendment of the directive in 1998, the notion of containment has become more fluid and its delimitation from mere confinement used under the release regime more difficult. Under the new article 1 [1] [c] of the directive, containment measures are not only physical barriers, they can also be a combination of physical barriers with chemical and/or biological barriers. The notion of containment requires that the relevant measures are capable of limiting the contact with, and providing a high level of safety for, the general population and the environment. Among others, the "principles" require that the environmental exposure must be kept to the lowest practicable level, control measures and equipment must be checked and maintained adequately, which includes

[12] Germany: Section 6 [2] Act on Biotechnology, section 8 [2], [5] Regulation on Biotechnological Safety; United Kingdom: Section 106 [4] Environmental Protection Act 1990, section 17 [1] Genetically Modified Organisms (Contained Use) Regulations 2002; France: Articles R532-1 to 532-17, R515-32 to 515-36 Code de l'environnement.

the prevention of accidents, and, when necessary, testing for the presence of viable process organisms outside the primary containment must be undertaken. It may be assumed that the interpretation of the broad legal terms "practicable" and "adequate" varies from country to country, in particular regarding the requirement of proportionality to risk and the degree to which costs incurred are considered.[13] In Germany, reduction of exposure even to the lowest possible level is required, which, however, does not rule out the application of the principle of proportionality.[14] In the United Kingdom, the concept of best available technology not entailing excessive costs is applied.

In addition, the directive provides for special measures whose stringency depends on the risk class. Regarding category 1 activities, very few mandatory special containment and protection measures are prescribed. Rather, annex IV lists some specific measures of an "optional" character, especially for activities in animal units and for activities outside glass-houses and animal units. These measures concern viable microorganisms, bulk culture fluids, possible spillage, air pollution and final discharges of waste. "Optional" means that the operator may apply these measures on a case by case basis, subject to the risk assessment. The practical legal consequence of this somewhat cryptic formulation is that, depending on the risk assessment, such measures may be mandatory by virtue of the general obligation of care set forth by article 6 [1] of the directive and specified by the general principles under annex IV point 1.

National law normally follows very closely the annex IV but extends it, as stated, to all GMOs. Sometimes, the safety standard has also been specified. This is, for instance, true in Germany with respect to the keeping of transgenic animals. It is permissible to keep them outside with double fencing where there is no risk of horizontal gene transfer, measures for preventing theft are taken and a warning system in case of escape is in place.[15] In contrast, it would seem that open air cultivation of transgenic plants is not possible under the contained use regime because the contact of GMOs with the environment cannot be excluded.

The basic competences for applying national law implementing the directive are vested in the member states. Institutional arrangements vary. In Germany, the regional authorities are competent, but have to consult a central expert body (Central Commission for Biosafety, Committee on Biotechnological Works). In the United Kingdom the Health and Safety Executive, and in France the Minister for the Environment is competent. In both countries, too, expert bodies have to be consulted (Health and Safety Commission, Commission de génie génétique). The expert bodies exert a con-

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[13] See Hughes *et al.* 2002:356.

[14] Federal Administrative Court, Entscheidungen des Bundesverwaltungsgerichts (BVerwGE) 119:329,333/34; Neue Zeitschrift für Verwaltungsrecht 1991:1187; 1997:497.

[15] Regulation on Biotechnological Safety, Annex V I.

siderable influence on the contents of the consent, which has been criticized as a disguised form of governance by expert bodies.[16] In Germany, the Act on Biotechnology (section 10 [7]) expressly requires that the opinion of the expert body must be considered and the grounds for deviating from it stated in writing. Nevertheless, from a legal point of view the ultimate responsibility is vested in the competent administrative authority.[17]

8.2.3 Development of recombinant medicinal products without containment

8.2.3.1 Scope of application and regulatory principles of Directive 2001/18

The development of transgenic medicinal products without containment is governed by Directive 2001/18. The directive in principle applies to the same type of activities as the contained use directive. It distinguishes between a release in the strict sense and the placing on the market (article 2 [3] and part B, article 2[4] and part C). A deliberate release of GMOs is an intentional introduction into the environment of GMOs for which no specific containment measures are used to limit their contact with people and the environment. A release which consists in making the GMOs, as such or in products, available to third persons is defined as placing on the market. However, a supply to contractors for the exclusive purpose of performing, or cooperating in the performance of, a simple release does not constitute a placing on the market (article 2 [4], 3rd indent).

Directive 2001/18 is designed to protect human health and the environment from risks associated with the release of GMOs. The standard of evaluating and controlling these risks is the precautionary principle.[18] In contrast to Directive 90/219, the applicability of the precautionary principle is expressly spelt out in the goals provision of article 1 and the fundamental obligation set forth in article 4 [1] of the directive. Recital 8 of the directive adds that the precautionary principle must be taken into account when implementing the directive. Likewise, the national laws and regulations that implement the directive adhere to the precautionary principle.[19] Despite this clear pronunciation of legislative intent, it remains to be seen whether, and to what extent, the precautionary principle really guides the application of the directive and national law implementing it.

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16 Reinhardt 2003:1446.

17 Administrative Court of Appeal Mannheim, Neue Zeitschrift für Verwaltungsrecht 2002:224.

18 See Christoforou 2004: 645; Boy 2002:9–13; Calliess and Korte 2006:11/12; with respect to the predecessor Directive 90/220: Hill 1994:180; Schenek 1995:182/83,199 *et seq*.

19 Germany: Sections 1 No. l, 16 [1] Act on Biotechnology; United Kingdom: Section 106 [4] Environmental Protection Act 1990; France: Articles L110 [2] No. 1, L531-3, L531-4 and L533-3 Code de l'environnement.

Transgenic animals can be kept with a minimum of containment, such as double fencing. An escape of these animals or an intrusion of other animals that then could disperse GMOs into the environment can normally be effectively prevented,[20] although an escape of small mammals or theft or sabotage, for example by members of animal rights groups, cannot entirely be ruled out. The more important potential adverse impacts of animal pharming relate to the transport of the transgenic crude bulk material to the manufacturing premises, if any, the disposal of urine and manure from the herd and the disposal of excess animals. Therefore, the focus of possible risks to the environment clearly is on transgenic plants, especially from the perspective of spread of genes that have pharmaceutical properties. The crucial question is what distinguishes plant pharming from the "normal" cultivation of transgenic crops, and whether the legal requirements relating to information and the risk assessment to be supplied and performed by the applicant and the prerequisites for granting the authorization adequately respond to these concerns.

8.2.3.2 Information requirements and risk assessment

The directive (article 6) and implementing national law[21] introduce an authorization procedure for releases of GMOs. Before starting a release, the operator must notify his intention to perform the release to the competent authority. The notification must be accompanied by documentation prescribed in article 6 and specified in annex III of the directive.

Article 6 [2] of the directive obliges the operator to supply information relating to the GMOs, the conditions of release and the receiving environment, the interactions between the GMOs and the environment, and control and remedial methods as well as monitoring, waste treatment and emergency response plans. Annex III distinguishes between genetically modified organisms other than higher plants, to which category also belong transgenic animals, and genetically modified higher plants. A number of human health and environmental problems raised by plant pharming activities, such as direct adverse effects on human and animal health and the consequences of possible gene spread, are addressed by items listed in annex III B as part of the requisite information. Adverse effects on human health caused by the genetic modification are covered. Moreover, annex III B lists a variety of ecological impacts or impacts on agriculture that are relevant to plant pharming. This is true of sexual compatibility of the transgenic plant with other cultivated or wild plant species, as well as the presence of such plants at or near the site of release, the ways and extent of dissemination, the

[20] Critical Schmitt 2004:30, from the perspective of risk from the environment.

[21] Germany: Section 14 [1], [5] Act on Biotechnology; United Kingdom: Sec. 111 EPA 1990 in conjunction with section 8 Genetically Modified Organisms (Deliberate Release) Regulations 2002; France: Article L533-3 Code de l'environnement.

proximity of officially recognized biotopes or protected areas which may be affected, methods for managing the release site, including cultivation practices and harvesting methods, and post release treatment methods.

Since Directive 2001/18, due to its specificity, considerably limits the discretion of the member states with respect to the information requirements, national law closely follows annex III.[22]

The applicant must also include in the notification the environmental risk assessment, which every operator has to carry out in accordance with annex II before commencing the release (article 4 [2]). The risk assessment identifies, describes and evaluates the possible effects on human health and the environment associated with the release and, if necessary, indicates measures for risk management. Annex II sets forth the general principles that govern the risk assessment. Commission Guidelines on environmental risk assessment published in 2002[23] specify these requirements. Although adopted in the legal form of a Commission decision which is in principle binding on the member states, the guidelines only claim to supplement Annex II of the directive and therefore cannot have more extensive legal effects than the directive itself.[24] There also is an EFSA Guidance document on the risk assessment of genetically modified plants and derived food and feed of 2004.[25] Although this document is limited to EFSA involvement in the placing on the market of GMOs, it will be considered already in the development process where a later authorization under part C of Directive 2001/18 is required.

Annex II prescribes, as part of the risk assessment, (1) the identification of inherent properties of the GMOs that may cause adverse effects, such as gene spread or transfer, genetic instability and interaction with other organisms, (2) an evaluation of the potential consequences of these adverse effects if they occur, to be classified, according to the guidelines, into 4 categories, (3) an evaluation of the likelihood of occurrence of such potential effects, (4) an estimation and classification of the risk posed by the each identified characteristic of the GMOs, (5) the definition of risk management measures and (6) a determination of overall risk taking into account these measures (annex II C. 2.). The guidelines specify these requirements and add to the estimation of the risk an element which is also important for plant pharming, namely that the operator must, in relation to the severity of the adverse effects to be expected, also identify, describe and evaluate the

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22 Germany: Section 15 [1] Act on Biotechnology, sections 5, 6 and Annex III Biotechnology Procedure Regulation; United Kingdom: Section 111 [4] EPA 1990, section 11 and Schedules 1 and 2 Genetically Modified Organisms (Deliberate Release) Regulations 2002; France: Article R533-3 Code de l'environnement.

23 Commission decision 2002/623, O.J. 2002 No. L 200:22.

24 Brand and Winter 2004:273/74.

25 Final edited version EFSA 2006a. EFSA is preparing a new guidance document on GMOs used for non-food or non-feed purposes; see EFSA 2008.

degree of uncertainty. National law once again closely follows annex II of the directive.[26]

The risk assessment prescribed under the directive is based on the example of chemical substances. Its transfer to GMOs is problematic in view of a lower quantification potential and a higher degree of uncertainty. However, this is a general reform problem of GMO regulation and not a pharming-specific one. Within these possible limitations, the risk assessment model of the directive is also capable of addressing potential adverse effects that are associated with plant pharming releases. Annex II D.2 lists a number of risk configurations that are also relevant to plant pharming. The most significant problem appears to be posed by the spread of genes having pharmaceutical properties from the transgenic, cultivated plants to sexually compatible, non-transgenic species of cultivated or wild plants. Thereby the GMOs might establish themselves in the natural environment and even enter into the feed/food chain. This type of potential risk is only partially addressed in annex II D.2. point 2 and 3. However, since annex II is not definitive, risk assessment is not limited to identifying, describing and evaluating gene spread from the perspective of selective advantage and disadvantage of the transgenic plants. Rather, the whole potential direct and indirect risks to human health and the environment presented by GMOs that have pharmacological properties must be identified, described and evaluated. Although not specific to plant pharming as far as the possible causation of gene spread as such is concerned, the evaluation of the risk associated with it may engender different implications due to the pharmaceutical characteristics of the GMOs. Moreover, adverse interactions with non-target organisms (annex II D.2. point 5) cannot be ruled out.

Another, probably less relevant aspect of plant pharming releases is possible indirect or delayed effects on health of people who come into contact with, or are in the vicinity of, the release (annex II D.2. point 6). The same is true of effects on animal health and the consequences for the feed/food chain resulting from consumption of the GMOs (annex D.2. point 7), since the transgenic plants used for pharming are not intended to be used as animal feed. However, in this situation there may be misuse and adventitious admixtures with conventional feed.

In the United States, a permit is required for releases of transgenic plants that may cause harm to plants (7 C.F.R. § 340.0, § 340.2). With respect to transgenic plants that are deemed to be associated with no or minor risks ("non-regulated status"), the applicable regulations only require a notification. This applies to about 90 percent of all releases. However, the reg-

[26] Germany: Section 15 [1] No. 4 in conjunction with section 6 (1) Act on Biotechnology, section 5 Biotechnology Procedure Regulation; United Kingdom: Section 108 [1] [a] Environmental Protection Act 1990, sections 6, 11 [1] [c] Genetically Modified Organisms (Deliberate Release) Regulations 2002; France: Article R533-3 No. 4 Code de l'environnement.

ulations exclude introduced genetic material which encodes products for pharmaceutical use from this procedural alleviation (7 C.F.R. § 340.3 [b] [4] [iii]). The operator is obliged to submit information which, by and large, resembles that needed in Europe, but is somewhat less specific regarding environmental impacts such as escape, dissemination and persistence in the environment (7 C.F.R. § 340.4). An environmental assessment may be prescribed where this appears necessary to evaluate the potential environmental effects of the release, for instance where a new genetic modification raises problems that cannot be addressed through normal safety measures (7 C.F.R. § 372 [d] [4]). Moreover, the assessment serves to determine whether the proposed action may significantly affect the quality of the environment and thereby be subject to an environmental impact assessment under the National Environmental Policy Act (7 C.F.R. Parts 1b and 272). The latter requires that the decision on the release is a major federal action, which is not normally considered to be the case with pharming development operations. The Department of Agriculture has recently published a guidance document relating to the relevant permit process which in particular applies to plant pharming development.[27] As stated, the development and manufacture of pharmaceuticals from transgenic plants and animals can also be regulated within the framework of pharmaceuticals regulation under the Federal Food, Drug and Cosmetic Act, especially as part of the pre-marketing permit procedure. Under the applicable regulations, an environmental assessment may also be needed (21 C.F.R § 25.21 and § 25.22).

8.2.3.3 Authorization prerequisites

Basic standard. Article 4 [1] of the directive establishes the basic standard for granting the authorization for a release. Direct or indirect adverse effects on human health and the environment which might arise from the release, in the case of plant pharming especially through the spread of genes having pharmaceutical properties, must be avoided. The decision on the application for an authorization is taken on a case by case basis considering the information and risk assessment provided by the operator, but also using other information that is available. This decision-making technique opens the process to political influence. This is most visible at EC level and perhaps less so at national levels. However, its advantage is a higher degree of flexibility and capability to adjust to novel configurations and achieve regulatory innovations. Moreover, it can be justified on grounds of political accountability and democratic legitimacy.[28]

Article 4 [1] of the directive has to be interpreted in the light of the precautionary principle, which also means that controversies relating to the

[27] USDA/APHIS 2008.

[28] To this extent European Court of First Instance 2002 ECR II 3305 No. 201 – Pfizer Animal Health; Christoforou 2004:679–682,695,705; see also Breyer and Heyvaert 2000:330–337.

interpretation of this principle may gain some importance. A clear Community standard of decision-making that would have to be uniformly implemented under national law and applied on the ground is not provided, although the annexes to the directive have been literally transposed into national law. This is in particular true of the questions as to which effects are insignificant and whether there are spatial and temporal limits to the scrutiny of a release.[29] The consequence is a certain degree of divergence in the statutory formulation of the authorization prerequisites in the member states as well as in the practice of the authorities that are responsible for applying the respective national laws.

For example, section 16 [1] of the German Act on Biotechnology establishes two major prerequisites for granting the authorization, namely that the operator must have taken all safety measures that are necessary, according to the state of science and technology, and that the release may not cause unacceptable adverse effects on human health and the environment. The relationship between these two prerequisites is controversial. In accordance with the German tradition of applying the precautionary principle and in view of the systematic structure of the provision, one should assume that the requisite safety measures have to be taken independent of concrete risks insofar as the measures are technically available and scientifically necessary as a precaution against, and proportionate to, potential risks presented by the release. By contrast, the second requirement of avoiding unacceptable adverse effects addresses risks presented in spite of such safety measures being taken.[30] Moreover, section 16[1] of the Act enlarges the authorization prerequisites by a risk-benefit analysis, whereby the acceptability of the risks presented by a release has to be determined in the light of the benefits conferred by it. Risk-benefit analysis is said to operate as an additional filter for eliminating low risks that are not justified by the benefits associated with the use of biotechnology. It is not meant to make higher risks acceptable in view of the benefits derived.[31] One can justify this as an extension of proportionality which governs the application of the precautionary principle.[32] The benefits of the release can be regarded as economic chances of placing transgenic products on the market; if these chances are foregone they are costs that have always to be considered in applying the precautionary principle. Nevertheless, it is

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[29] Lewidow *et al.* 1996:145,146; Ostertag 2006:339,340.

[30] In this sense Jörgensen and Winter 1996:296; Winter 1998:106 *et seq.*; Brand and Winter 2004:233; in the reverse sense Hirsch and Schmidt-Didczuhn 1991, § 16 No. 12; Dederer in: Ebersbach/Lange/Ronellenfitsch 2007 § 16 No. 70; Ostertag 2006:372. A matrix for structuring the decision using the criteria of likelihood, extent of possible harm, quality of the effects and degree of certainty is proposed by Winter 2006:459.

[31] Winter 2006:456,457/58; Brand and Winter 2004:251; in favour of the risk-benefit assessment also Ostertag 2006:373.

[32] COM 2001, 1 final:20.

clear that Directive 2001/18 does not provide for a risk-benefit analysis. Where Community law has opted for such an analysis, such as in the regulation of pharmaceuticals, plant protection products, biocides, and particularly hazardous chemicals for general use, it has expressly provided for it. Therefore, the insertion of a risk-benefit evaluation into the authorization prerequisites by German law raises some legal doubts relating to possible pre-emption,[33] although it is clearly desirable as a matter of policy. The risk-benefit evaluation does not play any role in the practice of the German permit authorities.

In the United Kingdom, the authorization prerequisites can be implied from the basic safety obligations of the operator under section 109 [4] Environmental Protection Act 1990. The operator shall not release the GMOs if it appears that, despite the precautions that can be taken, there is a risk of damage to the environment being caused as a result of the release; moreover, the operator has to apply the best available technology while not entailing excessive costs. It seems plausible that the relationship between precautionary measures and acceptability of remaining potential risk is the same as suggested for German law.[34] The possible benefits derived from the release are not considered.

Under French law, the decision on the application for an authorization to release GMOs is discretionary.[35] Article 533-3 Code de l'environnement does not contain any express authorization prerequisites. These can, at best, be derived from the statement in the law that the decision on the application for an authorization to release GMOs is taken after an investigation of the risks to human health and the environment. In any case, they are much less specific than in Germany or the United Kingdom.

In the United States, as can be concluded from the definition of plant pests and the information requirements of the Department of Agriculture regulations, the primary concern of the permit procedure for the release of GMOs is the prevention of risks to agricultural plants and also of risks presented to the environment, especially the environment beneficial to agricultural plants. The environmental perspective comes into play insofar as the competent agency performs an environmental assessment of the relevant releases of GMOs, which normally is the case with pharming development operations.[36]

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[33] See generally Christoforou 2004:671/72,677,682/83.

[34] See Macrory and Purdy 1998:69/70.

[35] See, with respect to marketing, Conseil d'État, Revue juridique de l'environnement 1999:561,563; confirmed by European Court of Justice 2000 ECR I 1676 No. 39 – Greenpeace; Brand 2004:148 *et seq.*

[36] See USDA 1986 Reg. 23302, 23313-19; USDA 2007 Reg. 14649; example of an environmental assessment of a trial release: USDA/APHIS, Environmental Assessment of 22 June 2007 (06-363-1035) concerning the use of sunflower as a pharming development platform.

Likelihood of effects. In keeping with the precautionary principle, under the directive also such possible adverse effects must be identified, evaluated and eventually controlled which cannot be excluded because, according to the present state of scientific knowledge, the possibility of future harm being caused can neither be positively determined nor ruled out, but there is reason to believe this may occur. The question as to the necessary degree of scientific substantiation of this "potential for concern" is controversial. The German Act on Biotechnology (section 16 [1] No. 3) requires that adverse effects that are expected must be excluded. The German administrative courts[37] go relatively far in assuming that, in the case of GMO releases, there are justified grounds for concern. In the United Kingdom, for denial of the authorization it is sufficient that it "appears" that a risk of damage is being caused (section 109 [4] Environmental Protection Act 1990). This suggests that reasonable grounds for concern are sufficient but also necessary. The European Court of First Instance, in two pharmaceutical cases that involved the withdrawal of a permit and in a more recent case regarding the listing of an active ingredient for a plant protection product,[38] has decided that a mere hypothetical risk does not permit precautionary action. Rather, there must be some scientific foundation for believing that adverse effects may occur (scientifically plausible grounds for concern), although the court does not necessarily require empirical findings and emphasizes the normative nature of the decision on tolerability of risk. These decisions are of general importance beyond the narrow field of pharmaceuticals law. They have been followed by the Commission of the European Union in its Communication on the precautionary principle.[39] Their reasoning is also shared by a number of commentators. Therefore, one may assume that the decisions set the future standard of precautionary analysis also in the context of national biotechnology law, insofar as it implements Directive 2001/18. As a matter of policy they make sense, even if one considers that the first two cases do not concern an initial authorization but the withdrawal of an authorization already granted where vested interests are at stake. In granting an initial permit the standard of scrutiny may be stricter. It is clear here that remaining uncertainties must be taken into account and evaluated as to the question of whether they are tolerable or not. However, the rule of law and the protection of economic fundamental rights militate against the prohibition of business activities by a denial of a permit, in case of uncertainty, that is

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[37] Administrative Court Gießen, Neue Zeitschrift für Verwaltungsrecht – Rechtsprechungs-Report 1993:534,537/38; Administrative Court Berlin, Neue Zeitschrift für Verwaltungsrecht – Rechtsprechungs-Report 1994:150,152; Zeitschrift für Umweltrecht 1996:146,147.

[38] 2002 ECR II-3305 Nos. 143–146,152 – Pfizer Animal Health; 2002 ECR II-4945 Nos. 181 *et seq.* – Artegodan; case T-229/04, judgement of 11 July 2007, Nos. 161,170 – Sweden/Commission (not yet published).

[39] COM 2001, 1 final:15–18.

merely based on speculative concerns. Post-event monitoring provides an additional safety net provided it is extensive and long-term.

The interpretation of the precautionary principle is particularly relevant with respect to horizontal gene transfer from transgenic plants to sexually non-compatible organisms, which quite a number of scientists would denote as purely speculative. However, the more immediate concern in plant pharming is gene spread from transgenic cultures to conventional ones, and the entrance of genes with pharmacological properties into the feed and food chain. The likelihood, frequency and extent of such gene spread or adventitious commingling, as well as the safety that can be provided for receiving cultivated plants by confinement and other management measures, are in principle amenable to scientific research although there are limits to the validity of the findings stemming from the long-term and systemic effects of the releases of GMOs.[40] Scientific uncertainty, of the kind which the precautionary principle is designed to address, comes in any case into play where one attempts to transfer empirical research results, gained from a particular crop and physical environment, to other crops and environments. Although this kind of transfer of findings is in principle scientifically accepted, and uncertainties are accommodated for by inserting "prudential" elements in the risk assessment process, drawing conclusions from studies relating to other crops and physical environments is scientifically problematic in the field of agricultural and ecological effects.

In the United States the precautionary principle is not accepted in the regulation of GMOs. Rather, the competent agency determines whether there is an unacceptable risk to agricultural plants and the environment. In case of uncertainty or ignorance the release will be permitted.[41] The decision on the application is taken on the basis of a classical risk assessment which is divided into four steps, namely hazard identification, risk assessment, risk evaluation including determination of risk management measures, and risk-risk comparison. A risk-benefit evaluation does not take place.[42]

Definition of adversity. Apart from the question of possible causation of effects on human health and the environment, the definition of harm or adversity of an effect is far from clear. Problems of interpretation of the directive, in this respect, are addressed in the case by case evaluation but deserve more fundamental discussion. The first starting point is the notion of environment, which encompasses all media and elements that constitute the environment as well as their interrelationship. The agricultural environment is included.[43] Furthermore, it is clear from the text of the direc-

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[40] See Breckling 2004:52–64,68,69–77; Sukopp 2004:100–113.

[41] Fisahn 2004:186.

[42] Anderson *et al.* 2001:18; Dederer 1998:281/282; Steines 2002:172.

[43] Annex III B section E 3., G 1. [a] Directive 2001/18; No. 3, 1st and 3rd indent Directive 2002/623 (Guidance on risk assessment of GMOs); Brand and Winter 2004:231; Ostertag 2006:275–379; Herdegen 2004:19.

tive (article 1 No. 8, article 4 and annex II D.2.5) that direct and indirect, immediate and delayed effects are covered. Finally, as adversity is a qualified effect and more than a simple alteration of the environment, a certain threshold of significance is inherent in the term. It is a fact, corroborated by spectacular incidents such as the Starlink case, that gene spread through pollen dispersal and seed dispersal and commingling cannot be entirely prevented. Consequently, the admission of biotechnology in agriculture by Directive 2001/18 (and its predecessor Directive 90/220) implies that simple alteration of the environment as such cannot be deemed to be unacceptable in principle.

In German practice, gene spread and transfer of genes, for example by out-crossing to sexually compatible agricultural plants or wild plant species, by volunteers of the transgenic plant or by commingling, are not yet considered as adverse effects.[44] This position is shared by section 107 [6] of the British Environmental Protection Act 1990 which requires an interference with, rather than a simple alteration of, the ecological system. The European Food Safety Authority (EFSA), which is involved in the risk assessment of commercial cultivation of transgenic crops, also seems to take the same position.[45] In German practice, an evaluation according to the standards of naturalness (equivalence to nature) and selective advantage is carried out. Effects of the same kind as occur in nature, or which can be caused by conventional breeding, are not considered as adverse or at least are considered as acceptable. In the absence of a new selective advantage, adversity is normally denied. While new properties can spread in the environment, one assumes that nature can adjust to them. However, a special evaluation is necessary when a release is associated with a novel process. New selective advantages, due to strong propagation potential and higher vitality, are relevant where they can lead to the establishment of a transgenic plant in the environment. These advantages must be evaluated regarding their kind and consequences for nature.[46] In British practice, too, only an additional risk is considered as relevant; factors such as the scale of the release, the genetic predictability of the organism, and the relationship of the size of the genetic change of the gene construct and its likely consequences for the affected environment are considered.[47] In France, one deems risks originating from a release to be acceptable if there is sufficient knowledge.

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[44] See Administrative Court Berlin, Zeitschrift für Umweltrecht 1996:146,147; Brand and Winter 2004:246; Fisahn 1998:38 *et seq.*; Fisahn himself is critical of this position and pleads for growth intervals (as they partly already exist in Denmark); see Fisahn 2004b:145.

[45] EFSA 2006b. The Commission has not yet granted the authorization but, rather, remanded the case to EFSA for further review.

[46] Fisahn 1998:186; Department of the Environment/ACRE, Guidance Note 1, The Regulation and Control of the Deliberate Release of GMOs, 1993, as amended 1995, Nos. 2.10,2.11. Under the 2002 regulations, there is no new guidance.

[47] Guidance Note, *supra* note 46, No. 2.9; Lewidow *et al.* 1996:145.

It is doubtful whether the concept of equivalence to nature sufficiently addresses, in view of the limited knowledge about the systemic, spatial and temporal interrelationships in nature, the dynamics and complexities of ecological systems. Therefore, it has been proposed to supplement it by recourse to natural variation of affected ecosystems and their development trends, as well as those of affected species.[48] However, this is not an issue that is specific to pharming.

The genetic modification of plants used for pharming does not normally entail a new selective advantage, since the genetic modification concerns other properties of the plant. Such an advantage could only be an unintended side effect of the genetic modification that aims to equip the plant with pharmaceutical properties. The more problematic aspect of pharming arises from these properties of GMOs. Notwithstanding the fact that plants may contain pharmaceutical properties, the kind of genetic modification that is generated by pharming – for example the introduction of pharmaceutical properties based on human or animal antibodies or vaccines into plants – is alien because it could not be brought about by conventional breeding. Therefore it constitutes a potentially adverse effect *per se*. This requires a case by case evaluation as to the effects on nature.

There is another reason why the appropriateness of the criteria of naturalness and selective advantage for determining adversity is limited. They are geared to structural effects on the environment, and do not necessarily address the protection of human and animal health. The same is true of eco-toxic effects, as the case of transgenic Bt-maize shows. In this field, certain properties of a transgenic plant as such may constitute a potential adverse effect. Pathogenic, toxic and allergenic effects presented by transgenic plants must, in principle, be classified as adverse, independent of whether they are directly associated with the inserted gene sequence or caused indirectly by a change in the metabolism of the plant. The same is true of eco-toxic effects. A qualification of this classification may ensue from considering significance (threshold concentrations) and exposure.[49] In the latter respect, the dispersal behaviour, the propagation patterns, the existence of sexually compatible food or feed plant or wild plant species as well as the selective advantage of the transgenic plant species, independent of the genetic modification, are most important. The analysis of naturalness and selective advantage of a transgenic plant is not relevant when exposure cannot be ruled out. Selective advantage may come into play, as an additional factor, in order to determine the kind and extent of exposure but is not essential.

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[48] Sachverständigenrat für Umweltfragen 1998:Nos. 813 *et seq.*; Breckling 2004:79–83.

[49] Administrative Court Berlin, Zeitschrift für Umweltrecht 1996:146,147; Hirsch and Schmidt-Didczuhn 1991:§ 16 No. 15; Dederer, in: Ebersbach/Lange/Ronellenfitsch 2007:§ 16 No. 100; Guidance Note, *supra* note 46, Nos. 2.9,2.10.

An adverse effect on human and animal health may also be constituted by compromise of prophylactic or therapeutic medical or veterinary treatments. The involuntary intake of GMOs in food or feed may cause resistance to pharmaceuticals. Such effects may occur either by gene spread and the resulting propagation of transgenic cultivated plants on neighbouring fields, or by adventitious commingling. Directive 2001/18 contains a phase-out programme for antibiotic resistant marker genes (article 4 [2] subparagraph 2). This implies that causation of resistance to treatment with antibiotics through gene transfer, or otherwise, may constitute an adverse effect. Moreover, annex II (C.2. point 2, 5th indent) generally includes the issue of causing resistance to pharmaceuticals in the risk assessment. Hence, under the directive adversity of such indirect effects on health cannot be questioned as a matter of principle.

Whether concrete pharmaceutical properties of transgenic plants used in pharming present such risks is a matter of individual assessment of the kind and extent of effect and likelihood of causation. From an initial perspective, apart from the properties of the host plant, including its transgene content and the state of the recipient environment, one might have to distinguish here between different kinds of pharmaceutical effects, in particular the degree of bioactivity (see section 3.7). In any case, the relevant risks are more difficult to trace and a determination that the risks presented are negligible appears problematic. In contrast to antibiotic resistant marker genes, where the probability of horizontal gene transfers to microorganisms that could cause such effects, according to the present state of knowledge, is very low, plant pharming arguably presents a higher potential risk because some gene spread, due to pollen or seed dispersal, is to be expected and commingling cannot be ruled out either.

In the United States, a variant of the concept of equivalence to nature and selective advantage is applied as well. In principle, one assumes that the risks presented by the release of GMOs do not fundamentally differ from those associated with traditional plant breeding, although their extent may be different. Apart from adverse effects on human health, persistence in the environment including the agricultural environment, development of weediness, and risks of commingling with non-transgenic seeds are the relevant factors that are considered.[50]

Risk management. Depending on the outcome of the risk assessment, a significant gene spread and commingling may have to be reasonably excluded. If this is not possible, the authorization must be denied. The measures to be imposed are governed by the principle of proportionality.[51] They largely

[50] USDA/APHIS, Environmental assessment of 22 June 2007, *supra* note 36; USDA/APHIS, Final Environmental Assessment of 28 June 2007, 05-354-015 concerning the use of tobacco as a production platform for a pharmaceutical; Anderson *et al.* 2001:18; Fisahn 2004:186.

[51] Christoforou 2004:706/07; Commission, *supra* note 32:20/21.

depend on a weighing of conflicting values and will also be influenced by public attitudes towards GMOs. Radical solutions would require a contained use, limiting the plant species that can be used for pharming to non-food/feed plant species, or prohibiting an expression of pharmaceutical properties in the pollen of the plant. This is, at least, plausible in the case of highly bioactive genes. In other cases using some form of confinement, establishing safety distances and employing good farming practices may be sufficient. The duties of care and rules of good professional practice, established under national law for avoiding adverse effects on human health and the environment and ensuring coexistence, can serve as a model, although not directly applicable because they are limited to cultivation and handling of transgenic products whose placing on the market has been authorized.[52]. For instance, section 16b German Act on Biotechnology contains a list of measures to prevent gene spread and commingling such as minimum distances, selection of suitable plant varieties, combating volunteers, use of pollen barriers, segregation in storage and transport and cleaning of containers. The necessary safety requirements can be imposed on the operator by a condition attached to the authorization.

Nature conservation areas. A special regime under nature conservation law is provided for releases of GMOs, especially transgenic plants, that may affect a protected habitat established under the Habitats Directive (Directive 92/43, as amended), more exactly under national law that implements the directive.[53] Although the risk assessment to be carried out by the operator under the release directive covers certain ecological effects, such as impacts on species and habitats affected by the release, Article 6 [3] of the directive and national law[54] require the performance of a habitat impact assessment whenever a release of GMOs, within or outside the protected area,[55] may considerably impair such an area. The habitat impact assessment is designed to determine whether the release is compatible with the conservation objectives established for the area. If it is not, an authorization for the release can only be granted where cogent reasons of paramount public interest justify the project and no other feasible alternative is available (article 6 [4] Habitats Directive). GMO regulation and habitats regula-

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[52] Section 14 [2] German Act on Biotechnology which declares sections 16a and 16b to be applicable to products governed by a special regime is limited to authorisations for the marketing of the product and does not cover mere releases. See also EFSA 2008:24–26.

[53] See Winter 2006:456; Palme and Schumacher 2007:16.

[54] Germany: Sections 32, 34 Protection of Nature Act; United Kingdom: Sections 18–21 Conservation (Natural Habitats) Regulations 1994, as amended; France: Articles L414-4, R214-19 to 23 Code de l'environnement.

[55] Germany had previously excluded releases outside the protected area but, following a judgement of the European Court of Justice (2006 ECR I 53 Nos. 39–45) that held this to be in violation of the directive, has extended its law to this type of release.

tion apply cumulatively, although in case of releases that concern a specific, defined area – in contrast to placing on the market – it is difficult to distinguish between the two kinds of risk assessment.

8.2.3.4 Special issues relating to animal pharming

The authorization procedure, the authorization prerequisites and the associated obligation of the operator to supply prescribed documentation and perform a risk assessment under Directive 2001/18 are also applicable to the creation of transgenic animals. Annex II D (risk assessment) and annex III A (information to be supplied) contain special requirements applicable to GMOs other than higher plants. This includes transgenic animals. The hazards presented by elements of the development procedure, such as viral vectors, and by the pharmaceutical properties expressed in the founder animal and the production herd must be identified and evaluated. Moreover, a possible gene spread through an escape of the transgenic animals, as well as an uptake of transgenic material by intruding animals and the ensuing possibility of survival and propagation, constitute a relevant potential risk that must be identified and evaluated. This is particularly true of small mammals. Other pathways of potential gene spread, such as discharge of urine and gaining and processing the crude bulk material such as milk derived from transgenic animals, are also relevant. However, it is safe to say that these risks can be reasonably excluded through confinement and other protection and control measures, in such a way that they do not create obstacles to the granting of the authorization.

8.2.3.5 Institutional arrangements

In contrast to placing GMOs on the market, the evaluation and authorization of releases is entrusted to the authorities of the member states (article 6 [1] Directive 2001/18). Community involvement in the procedure is, in principle, limited to information exchange, including an opportunity for the Commission and the other member states to present to the permit authority observations on the planned release and try to influence its decision (article 11). However, the permit authority is sovereign in its ultimate decision. In this information exchange, the Commission is supported by the European Food Safety Authority (EFSA) (article 28 [2] Directive 2001/18). An exception is possible where a member state authority intends to apply a simplified procedure; here the Commission can decide on the conditions of the release (article 7 Directive 2001/18). Moreover, it should be noted that "forum shopping" is easy. If a national authority denies a permit, the applicant can try again in another country.

National law attributes the competence for authorising releases to central authorities. In the decision-making process, expert bodies play an important role while public participation appears to be less influential. In Germany, the Federal Office for Consumer Protection and Food Safety

(Bundesanstalt für Verbraucherschutz und Lebensmittelsicherheit – BVL) is responsible. It decides after coordination with other federal agencies and consultation of the Central Commission for Biosafety (Committee on Releases and Marketing). In the United Kingdom, the Department of Environment, Food and Rural Affairs (DEFRA) is responsible. It normally has to consult the Administrative Commission on Releases to the Environment (ACRE) and, with respect to effects on human health, decides with the agreement of the Health and Safety Executive (HSE). In France, administrative competences are divided among the ministers or agencies responsible for the environment, health, agriculture and research depending on the kind of release; the agreement of the Minister for the Environment is always required. In the case of pharming, the Minister for Agriculture is competent. Before making the decision, an expert body (Commission de génie biomoléculaire – CGB) must be consulted.

As regards public participation and access to information, article 9 Directive 2001/18 requires that the public, including environmental groups, is consulted on the proposed release and mandates the member states to make available to the public information on all part B releases. The public must be given an opportunity to express an opinion. The directive also limits confidentiality of information. In particular, the general description of the GMO, the purpose of the release, the location of the release, the intended uses, monitoring and emergency plans and the risk assessment are not deemed to be confidential (article 25 [4]). These provisions have been implemented by the member states in a narrow and somewhat different way.[56] Germany and the United Kingdom require that the full dossier accompanying the application (except for confidential information) is made available for inspection. By contrast, France limits general access to information on the risk assessment to a mere summary, so that an interested person would have to take recourse to the provisions of the Code de l'environnement on environmental information (articles L124-1 to L124-8) in order to get full access. In all three countries public participation is in the form of individual comments which can be made during a limited period of time. There is no public hearing.

The attribution of administrative competences for the control of releases is based on a deliberate decision that is motivated by the principle of subsidiarity (article 5 [2] EC Treaty). It includes cases where the authorization for the end product is centralized. A certain variation in the national authorization practice is taken into account. It is mitigated by the consultation procedure set forth in article 11 Directive 2001/18. Therefore, the mere fact that

[56] Germany: Section 18 Act on Biotechnology, section 5 Biotechnology Procedure Regulation, Biotechnology Hearing Regulation of 1990, as amended in 1996; United Kingdom: Sections 11, 12, 33 and 34 Genetically Modified Organisms (Deliberate Release) Regulations 2002; France: Articles L 535-5, R533-5 and R533-10 Code de l'environnement.

recombinant medicinal products are subject to a centralized authorization procedure is not sufficient to require that the competences for the release of transgenic plants and animals used in the pharming process should also be transferred to the European level. While one could argue that the novel kind of risk involved justifies such a transfer, as long as decentralization does not prove to be clearly inadequate in the field of pharming the extension of Community powers should be renounced. Decentralized decision making offers better chances for social learning, and this is important in an area of high uncertainty. This does not exclude the establishment of EU guidelines that collect already-existing national experience and provide for minimum harmonization.

8.2.4 Coexistence between experimental cultivation of GM0s and organic and conventional agriculture

Adverse impacts of gene spread and commingling on the ability of farmers to maintain production and market their products according to their quality preferences are not considered as harmful and, hence, are neither a subject of the risk assessment nor of the authorization and conditions attached to it. Article 26a Directive 2001/18 and the Commission Recommendation on coexistence[57] conceive the problem of coexistence between pharming, including experimental releases of GMOs, and conventional and organic agriculture as a purely economic problem which may be addressed by the member states. This is based on the assumption that adverse effects on health and the environment, including the agricultural environment, that may be caused by gene spread and commingling during the development process are already practically avoided by confinement and other protection measures taken under the directive.

The problem of coexistence in agriculture mainly concerns large-scale cultivation of transgenic crops which occurs on the basis of a marketing authorization. If one stresses the very concept of coexistence between different methods of agriculture, it seems natural not to include trial releases of transgenic plants, the more so since such releases are normally performed subject to some form of confinement. However, seen under the perspective of the victim who suffers economic losses due to a release, the concept of coexistence could be understood in a broader sense. Article 26a [1] Directive 2001/18 generally empowers the member states to take action to prevent the adventitious presence of GMOs in other products. It is only from article 26a [2] of the directive that one could, at best, derive a limitation of the concept to coexistence between genetically modified, conventional and organic agriculture. The Commission Recommendation on coexistence[58] seems to interpret article 26a of the directive in this sense, although this conclusion

[57] Commission 2003:36.
[58] See note 57.

is not cogent. In national practice there is a clear focus on conflicts between different methods of agriculture. However, certain rules, such as the provisions relating to the location registry, cover experimental releases as well. Moreover, some states such as Germany have special liability rules with respect to authorized releases (section 23 Act on Biotechnology).

8.2.5 Waste disposal

In pharming, development processes generate different kinds of waste. In plant pharming, straw and other plant materials are generated from processing. Animal pharming is a source of urine, manure, excess animals and unusable animal parts that must be disposed of. This waste contains, or is at least likely to contain, the inserted genes or gene products. Therefore, special controls are necessary.

8.2.5.1 GMO-specific regulation

The legal regulation of GMO waste is primarily provided by Directive 90/219 on the contained use of genetically modified microorganisms (as amended by Directive 98/81) and Directive 2001/18 on the release of genetically modified organisms into the environment, as implemented and – in case of contained use – supplemented by national law. The applicability of the two regimes depends on whether the pharming operations are carried out with or without containment. The risks to human health and the environment, presented by GMM and GMO waste originating from pharming activities, constitute part of the risk assessment the operator has to perform (article 4 [2] Directive 90/219; article 4 [2], annex II Directive 2001/18) and the competent authority can subject the contained use or the release to conditions relating to waste disposal (article 11 [3] Directive 90/219; article 6 [7] Directive 2001/18). However, the two directives and national law implementing and supplementing them do not establish an exhaustive regime. Therefore, unless there are specific legal provisions or conditions attached to the authorization, reprocessing, incineration and disposal under general law are in principle possible. Whether pre-treatment is necessary depends on national law. Where GM plant material is processed as animal feed, a special authorization must be secured under Regulation 1829/2003.

Directive 90/219 sets forth some provisions on the treatment of waste produced by genetic activities with containment that have been implemented and supplemented under national law.[59] The applicable requirements are different according to the relevant safety level (containment level). As regards the safety level, 1 the directive sets forth relatively leni-

[59] Germany: Regulation on Biotechnological Safety; United Kingdom: Genetically Modified (Contained Use) Regulations 2000; France: Articles R532-1 to R532-17 Code de l'environnement.

ent and not very specific measures for waste disposal. The operator must include information about waste disposal (annex V part A) in the initial notification to be made under article 7 of the directive. According to the "General Principles" contained in annex IV, in laboratory activities inactivation of GMMs in contaminated material and waste is optional and only required as of safety level 2. As regards development activities using glasshouses and rooms for cell cultures, minimization of dissemination, including waste-related dissemination, of GMMs is prescribed. There are no specific waste-related requirements applicable to animals kept in laboratory units in level 1 facilities. With respect to activities other than laboratory activities, regarding safety level 1 activities Annex IV Table II requires the inactivation of GMMs in contaminated material and waste, including those in process effluent before final discharge, only where the results of the risk assessment suggest this in an individual case, and declares it to be generally mandatory only as of safety level 2. Assuming that developmental pharming will be classified as level 1 (no or negligible risk; see above 8.2.2), the requirements set forth in annex IV of the directive do not appear to be particularly stringent.

However, national law supplements EC regulation through more extensive (all GMOs) and more stringent requirements. In Germany, section 13 of the Regulation on Biotechnological Safety sets forth the general requirement of disposal of GM waste according to the state of science and technology; general waste law remains applicable. With respect to safety level 1, the regulation dispenses the operator from special pre-treatment of waste when animals or plants are used and where adverse effects to human health or the environment are not expected, or the waste is so slightly contaminated that the risk is negligible. Otherwise, inactivation of GMOs is prescribed. In the UK, there are no special duties of care relating to waste generated in the process; rather, under section 17 [1] of the Genetically Modified Organisms (Contained Use) Regulations, the general duty of minimising exposure and risk applies. Moreover, British law goes beyond the directive in generally prescribing inactivation of GMMs in waste also for class l activities (schedule 8 No. 16). France has literally transposed the relevant provisions of the directive.

In contrast, with respect to releases without containment Directive 2001/18 exclusively addresses the waste problem at the level of the environmental risk assessment. As regards GM animals, the applicant must include information about the type and amount of waste generated by the planned release (article 6 [2] [a], annex IIIA point III.V.C) in his/her notification. In plant pharming the operator must describe the post-release treatment methods (article 6 [2] [a], annex IIIB point G 3). Although not specifically mentioned, the waste problem must also be dealt with in the risk assessment to be performed by the applicant. Based on the risk assessment, the competent national authority can make the authorization subject to condi-

tions relating to waste disposal (article 6 [8]). In doing so, it may consider the requirements applicable to contained use under Directive 219/90.

The relevant provisions of Directive 2001/18 are implemented under national law. While the waste regime applicable to contained use is satisfactory, the concept of sole reliance on case by case assessment under the release directive appears problematic from a legal point of view, the more so since general law is not very demanding either. However, as in the case of contained use in practice one normally requires incineration of the waste which solves the relevant problems.

8.2.5.2 Regulation under general waste law

As regards general waste management law, the relevant EC directives do not contain special regulation on GMO waste. Directive 91/689 on hazardous waste, as amended by Directive 94/31 and Regulation 166/2006, theoretically applies to several categories of GMO waste as the European List of Hazardous Waste (Council Decision 94/904) includes animal tissues, animal urine and waste from milk processing, production of pharmaceuticals and research and development. However, the directive concentrates on hazards to human health and therefore only covers those categories of pharming waste that are toxic, or otherwise potentially harmful, to human health (for example cancerogenic or teratogenic), and provided the GMO substances contained exceed certain concentrations levels (Council Decision 94/904). Hazards to the environment are not included (see Directive 91/689, annex III). Therefore, even recourse to article 1 [3] 2nd indent of the directive, which empowers the member states to also classify unlisted waste as hazardous, is not available where environmental hazards are at issue. Nevertheless, the member states could enact more stringent national regulation that applies to such waste under article 176 EC Treaty. As far as can be seen, no member state has used these powers with respect to GMO waste as yet.

8.2.5.3 Disposal of excess animals and animal parts

As regards excess animals and animal parts, there is special, although not GM-specific regulation relating to the disposal of animal side products under EC Regulation 1774/2002 and national regulations specifying it.

Regulation 1774/2002 applies to all animal side products such as whole animals, animal parts, skins, wool und urine. As a reaction to animal pests and human diseases caused in the past by feeding reprocessed protein feeding stuff, the regulation is designed for the protection of human health, the health of animals and the environment against significant risks by controlling the relevant waste. The regulation classifies animal side products into different risk categories and attributes to them particular waste management options (articles 4–6). Category 1 comprises special risk material, including among others parts from experimental ani-

mals; here, incineration or pre-treatment in special facilities, before normal incineration or closed deposit on land, is required (article 4). Category 2 applies, among others, to animals slaughtered for purposes other than trading purposes. In this category, a variety of waste management methods is permitted such as incineration, pre-treatment for incineration or deposit on land, processing for the production of biogas, fertilizers, cosmetics, pharmaceuticals and medical equipment (article 5). This also applies to urine from animals which, unless there is a special risk of illness, can in addition be sprayed on land as fertilizer. Category 3 comprises low risk materials such as milk and wool. Milk can be processed as pet feed (article 6). The latter two provisions raise the question as to whether urine from pharming animals must be regarded as presenting a special risk of illness, and milk from transgenic herds can be treated just as any other milk. In view of the limited purpose of the regulation, one should arguably answer the question in the negative, since the kind of risk presented by GMO traces in the waste materials does not correspond to the kind of illness the regulation wants to counteract. However, it is safe to say that a new exposure of the environment to GMO traces is subject to case by case scrutiny under Directive 2001/18.

The regulation also contains detailed obligations for collecting and transporting category 1 and 2 animal waste (articles 4 [2] and 5 [2]), as well as provisions on the organization of collection, deposit and processing (articles 10–15, 17–19) which are supplemented by national law. It also sets forth rules relating to the placing on the market of certain recycling products such as animal pet food, dog chews, certain technical products and organic fertilizers. As the regulation in general, these provisions aim to prevent animal pests and hygienic problems associated with recycling of animal side products, and are not geared to the specific problem presented by GMOs contained in the recycling products. However, it should be noted that products manufactured from transgenic animal side products are also subject to GMO-specific controls. With respect to products such as pet food, soap or wool, an authorization for placing on the market would be required under article 6 [9] of Directive 2001/18, even if the end product no longer contains GMOs (see below 8.7). Moreover, national product regulation may apply. Therefore, in this respect the regulation is, by and large, sufficiently protective of human health and the environment.

8.3 Development phase II: Animal protection

Development activities for the generation of transgenic animals to be used as production platforms for pharmaceuticals invariably involve animal trials, at least in the initial stages of development. Therefore, the question arises as to what extent the existing regulation on animal protection might present obstacles and limitations to pharming development.

8.3.1 Sources of regulation

There are a variety of legal sources of regulation in the field of animal protection and welfare. Three levels must be distinguished. Pan-European conventions, EC directives and national laws and regulations may be relevant for the protection of animals in the course of development activities in the field of pharming:

- European Convention for the protection of vertebrate animals used for experiments and other scientific purposes of 1986, as amended by the Protocol of 1998 (in force since 2 December 2005),
- European Convention for the protection of animals kept for farming purposes of 1976, as amended by the Protocol of 1992 (not yet in force),
- Protocol on protection and welfare of animals, annexed to the Treaty of Amsterdam amending the EU Treaty and the EC Treaty of 1997,
- EC Directive 86/609 on animal trials as amended by Directive 2003/65,
- EC Directive 98/58 concerning the protection of animals kept for farming purposes,
- national laws on animal protection and welfare in general and protection of animals used for experiments and other scientific purposes, such as the German Animal Protection Act of 2006 and the Regulation on the Keeping of Useful Animals of 2006, the British Animal Welfare Act 2006 and the Animals (Scientific Procedures) Act 1986, and articles R214-1 *et seq.* of the French Code rural on the protection of animals (codified in 2000).

The scope of application of these legislative texts is quite different. One category comprises the regulation of animal trials. These texts may be relevant in the development phase of pharming. However, it will be seen that the delimitation between an animal trial and production is not easy to draw.

A second category deals with the keeping of animals, either specifically or as part of more general rules. Theoretically, these texts could be applicable to the protection of animals during part of the pharming development and, which will be discussed later, the whole production process. However, subject to some qualifications such as the German Animal Protection Act, as a rule there is no comprehensive regulation that covers all pharming production operations during the development and later manufacturing stages.[60]

8.3.2 Animal trials: Scope of application of the relevant laws

The most extensive regulation exists in the field of animal trials, especially relating to vertebrates, and yet their relevance to pharming activities is open to some doubt. The reason for this is that the protection of experimen-

[60] The reason is that pharming animals are not considered as being used for farming purposes.

tal animals is limited to experiments using animals and does not extend to production activities. This raises the fundamental question as to whether and to what extent the various steps to be taken in developing medicinal products from transgenic animals can be considered as experiments or as normal development, breeding and manufacturing activities.

The conventional distinction between animal trials, on the one hand, and normal breeding and production activities, on the other, is that a trial is designed to generate new knowledge, while activities that focus on breeding or production belong to the production stage. However, in the case of pharming this distinction is difficult to make, the more so since all definitions provided in the legal texts are more or less circular. The European Convention on animal trials defines trials (called animal procedures) as "any experimental or other scientific use of an animal which may cause it pain, suffering, distress or lasting harm", starting with the preparation of the animal and the time when no further observations are made for that procedure (article 1 [2] [c]). This definition is resumed in article 2 of Directive 86/609. Conversely, Directive 98/58, relating to the protection of animals kept for farming purposes, excludes experiments on laboratory animals from its scope of application (article 1 [1] [c]). Similar descriptions of the scope of application of animal welfare laws can be found in national law.

In the specific context of pharming, one could sustain that the activities aimed at the mating of donor animals and insertion of the gene construction into the fertilized eggs of these animals, as well as their transfer to recipient females (foster animals), are based on known procedures and, as such, do not constitute experiments but rather are essentially breeding and production activities. The following stages of selecting the individual or individuals from the offspring that are a copy of the donor animal's transgenic eggs and express the inserted gene sequence (founder animals), as well as the propagation of the founder animals, could be regarded as resembling so very closely normal breeding procedures that they cannot be classified as a process whose focus is the generation of new knowledge. Furthermore, the initial generation of crude bulk material, and its processing for manufacturing a developmental medicinal product, could be denoted as a normal production process. It is clear that the final production of vaccines and antibodies from transgenic animals following the authorization of the medicinal product is a production process, even if associated with interventions in the animals.[61] However, one must make a clear distinction between the development and production stages of pharming. As expressly spelt out in French law (article R214-87 Code rural), applied research constitutes a part of research. There are a number of uncertain-

[61] Bundesministerium für Landwirtschaft, Ernährung und Forsten 2001:87; Caspar 1999:436; Goetschel, in Kluge 2002:§ 10a Nos. 2–4; Lorz and Metzger 1999:§ 10a No. 6.

ties associated with creating transgenic animals and developing their offspring to the stage of production. Even if the methods of transfer of the relevant gene sequences into fertilized eggs of the donor animals and their transfer to recipient females (foster animals) are known, there are no standardized methods. There is limited knowledge on the expression of the relevant gene constructs in founder animals. The outcome of the process is uncertain (see section 2.3). Therefore, the development process entails a fair degree of applied research. This is true of the gene transfer to the eggs of the donor animal as well as their reproduction in a suitable founder animal and in the latter's direct offspring. Therefore, good arguments militate for the proposition that the development stage can still be considered to constitute a series of animal trials. This seems to be the position of German and British practice, which treats the creation of transgenic animals up to the second generation of offspring (founder animal and two generations of progeny) as animal trials.[62]

8.3.3 The European Convention and Directive 86/609

The existing regulatory texts on the protection of animal trials can be classified into two different categories, namely the first and second generation of animal protection laws.

The European Convention of 1986, as amended in 1998 (in force since 2005), already sets forth the principle of justification when deciding whether an animal trial has to be performed. Moreover, at least in essence it establishes the so called 3-R concept (replacement, reduction, refinement)[63], to be used when deciding on how a trial will be carried out. Justification means that only certain purposes are admissible for vertebrate animal trials, and that the trial must be indispensable in order to achieve this purpose.

Directive 86/609 (as slightly modified by Directive 2003/65), among others, was adopted for implementing the European Convention. More demanding than the European Convention, the directive does not only require that animal trials entailing serious pain and suffering be specially justified. It further limits animal trials under these circumstances by prescribing a rudimentary risk-benefit evaluation, whereby the trial must be sufficiently important for the fundamental needs of man or animals (article 21 [2]). Recently, the Commission has published detailed guidelines for the accommodation and care of animals used for experiments and other scientific purposes.[64] Although the directive is based on the harmonization competence under former article 100 EC Treaty (now article 95 EC Treaty), it

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[62] Bundesministerium für Landwirtschaft, Ernährung und Forsten 1997:110; Goetschel, in Kluge 2002:§7 No. 8,22,28; Müller-Terpitz 2007:84; AEBC 2002:56 (minimum of two generations of offpsring); see also House of Lords Select Committee 2002:16/17.

[63] Russel and Burch 1959.

[64] Recommendation of 18 June 2007 (2007/526).

only aims for minimum harmonization. The maintenance or introduction of more stringent member state law is permissible. This explains why, under the umbrella of the directive, a second generation of national laws for the protection of trial animals could develop. A negative – at least partly negative – effect of minimum harmonization is that there have not been strong pressures for the modernization of the directive.

8.3.4 National law

National law, insofar as it is more stringent, is neither pre-empted by the European Convention nor, as stated, by Directive 86/609. It embodies, in many respects, more modern concepts of animal welfare. However, it should be noted that the focus of animal welfare law is on animal trials for the testing of chemical substances. Pharming activities are not of central importance, and there has been practically no regulatory experience in this field.

Germany. In Germany, animal protection and welfare has a general constitutional status. Article 20a Federal Constitution ("Grundgesetz") declares the protection of animals to be a task of the state. This ethical imperative is addressed to all state powers, in particular the legislature, although it does not establish subjective rights. A major legal effect of the state obligation to protect the animals consists of an enrichment of broad statutory terms, the performance of prescribed weighing of conflicting concerns and other exercise of discretion granted to the authorities. However, it is important to note that article 20a Federal Constitution does not afford absolute protection but, rather, only requires responsible treatment of animals.[65]

The German Animal Protection Act in its new version of 2006 describes the purpose of the law, in ethical terms, to protect life and welfare of animals in "responsibility of man for the animals in their capacity as co-creatures", but, in an anthropocentric stance, goes on to prohibit the infliction of pain, suffering or harm to animals without a reasonable cause (section 1).[66] Sections 7–9 of the law contain more specific provisions on animal trials, so that the general justification requirement under section 1 is not relevant here.

The notion of animal trial, and in particular trial on vertebrates, under the act is not limited to live animals but also comprises genetic material. It is defined so as to include interventions in, and treatment of, animals or genetic material for trial purposes which are associated with pain, suffering and harm to these animals or, in the case of genetic material, pain, suf-

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[65] Federal Administrative Court, BVerwGE 101:l,37; Administrative Court of Appeal Mannheim, Natur und Recht 2006:111; as to the concept of dignity of animals see Richter 2007:321 *et seq.*; Teutsch 1995.

[66] Pain and suffering does not include mere discomfort; Federal Administrative Court, in: Buchholz 2000, Entscheidungssammlung des Bundesverwaltungsgerichts, 418.9 Tierschutzgesetz No. 11; Federal Supreme Court, Neue Juristische Wochenschrift 1987:1833,1834.

fering or harm to the genetically modified animals or their founder animals (section 7 [1]). In the case of genetically modified animals, breeding up to the second generation after the founder animal is considered an animal trial.[67] Animal trials need to be justified by a variety of particular purposes described in the law, among others the prevention, determination or treatment of disease, suffering, physiological harm and distress, the testing of substances and fundamental research. The performance of an animal trial needs to be indispensable for achieving this purpose. In deciding whether this is the case, the state of scientific knowledge must be considered and it must be ascertained whether the purpose cannot be reached by using non-animal methods (section 7 [2]). Apart from this general justification requirement, the law prescribes an ethical justification whenever the trial is to be performed on vertebrates. This goes beyond Directive 86/609. Vertebrate animal trials may only be carried out when the expected pain, suffering or harm caused to the animals is ethically justifiable in relation to the purpose of the trial. Where such animal trials lead to longer lasting or repetitive considerable pain, suffering or harm, the review standard is strengthened. There must be reason to believe that the envisaged results will be of outstanding importance for the essential needs of humans or animals, including the solution of scientific problems (section 7 [3]). This is a severe restriction of animal trials, because it practically limits such animal trials to the prevention, determination and treatment of serious diseases.[68] However, as a rule, it does not concern pharming operations as they are not normally associated with the degree of pain, suffering or harm that the law has in mind.

Other restrictions on animal trials are formulated as requirements relating to the operative performance of animal trials, especially those on vertebrates. In keeping with the 3-R concept, such trials must be limited as much as possible and the state of scientific knowledge respected. Vertebrate animal trials are only permissible where trials on other animals are not sufficient for the envisaged purpose, the minimal number of animals is used and pain, suffering and harm are only inflicted on the animals insofar as this is indispensable for the purpose of the trial (section 9 [2]).

The requirement of ethical justification engenders a balancing process between the "costs" incurred by the animal trial, in terms of pain, suffering and harm caused to the animals, and the expected benefit to be derived from the trial. Relevant cost factors are also the high mortality of trial animals and the generation of "excess" animals in the trial that have to be killed, especially when using micro-injection methods. The exact contents of the balancing process are controversial[69] and the criteria for deciding on

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[67] See *supra* note 62.
[68] See Goetschel, in Kluge 2002, § 7 No. 45.
[69] Goetschel, in Kluge 2002:§ 7 Nos. 48 *et seq.*, 43; Kloepfer 2004:§ 11 Nos. 313,343.

the right balance are uncertain. In this respect, some authors refer to the "social morality" of the population[70] which provides a conduit for public attitudes about animal welfare, although, in contrast to section 5 [c] of the Norwegian Animal Welfare Act, ethical reactions of the public alone do not justify a prohibition of an animal trial. Besides, for making the necessary value judgement on admission or prohibition of an animal trial operative, one uses tables that classify the costs and benefits into three different categories ranging from low to medium to high, and attribute to them negative or positive decisions.[71]

Table 8.2: Illustration of classification of costs and benefits

	Cost (impairment of animals)		
Benefit	low	medium	high
low	-	-	-
medium	+	-	-
high	+	+	+/-

+ = permissible - = prohibited +/- = controversial[72]

However, the heuristic value of such classifications seems to be limited.

It is clear from the text of the German Animal Protection Act, especially its inclusion of interventions into genetic material in the definition of animal trial, that the provisions relating to justification, ethical review and the 3-R concept also apply to animal trials in the course of generating and propagating transgenic animals for the production of pharmaceuticals. One also sustains that from a policy point of view, the existing law is sufficient.[73]

An important issue is whether, and to what extent, cost savings ultimately expected from the results of an animal trial can be listed on the positive side of the balance. Section 9 [2] No. 3 of the German Animal Protection Act expressly excludes any cost argument with respect to the performance of an animal trial as an element of the evaluation of indispensability for the intended purpose. Pain, suffering and harm may not be inflicted on an animal in order to achieve savings in work, time or costs. From the systematic position of this provision in the act, one might conclude that it only relates to the question as to how an animal trial is performed and not to the ethical review that scrutinizes the question as to whether an animal trial may be permissible at all, in other words that it only concerns trial costs

[70] Kluge 1994:871.

[71] See Bundesamt für Veterinärwesen 1994; Goetschel, in: Kluge 2002, § 7 No. 60; Maisack 2007:197, 2002.

[72] In favour of a differentiation within this category Scharmann and Teutsch 1994:191; De Cock Buning & Theune 1994:107.

[73] Lorz and Metzger 1999:§ 7 Nos. 14 *et seq.*; Gruber and Kolar 1997:373 *et seq.*; Gruber 1995:239.

rather than cost savings achieved by exploiting the results of the trial. However, there is some authority to the contrary, although relating to the general justification clause set forth in sections 1 and 2 of the act.[74] Even if one adhered to this broad interpretation, this would only exclude the consideration of individual cost savings of the operators, not economic cost savings of society as a whole. In the market for medicinal products, rapid availability of new products and a cheap supply to social health care systems are, in particular in societies with an aging population, important and legitimate factors on the positive side of the cost-benefit balance that should not come under the verdict of mere costs savings for the operator.[75] Moreover, it does not appear permissible to look at the "purpose behind the purpose" when deciding on indispensability. Innovation and competition in the market, through the development of new pharmaceuticals, is considered as legitimate purposes. The question as to whether a new pharmaceutical, whose development requires animal testing, is needed on the market is not a relevant question in this context, even if this development "only" serves the ultimate purpose of saving costs (nor is it under pharmaceuticals regulation; see section 8.5.3). In order to establish an animal production platform, animal trials are indispensable. Therefore, there is no cogent reason to deal with this production method in a way that is fundamentally different from normal development operations. At best, the broader perspective – the purpose behind the purpose – can be considered in the ethical review process, and here the considerations relating to societal costs appear entirely legitimate. Of course, based on a need analysis, the legislature could ban animal trials in the development process entirely – as has been done with respect to cosmetics. However, such a fundamental decision should not be taken by the executive and the courts through the interpretation of existing law but rather politically, and it could not be confined just to pharming products.

Another open question relates to the relevance of animal welfare risk analysis. The definition of animal trial (section 7 [1] German Animal Protection Act) refers to the mere possibility that a trial may be associated with pain, suffering or harm to the animal. However, in the framework of ethical review, Section 7 [3] of the act partly refers to "expected" pain, suffering and harm, and partly seems to require certainty about the future causation of pain, suffering and harm by an animal trial. If one considers the latter formulation which concerns trials on vertebrate animals which cause

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[74] District Court Hamburg, 313 O 565/00, not published (a case based on the law of unfair competition that, due to an amendment of the Act on Unfair Competition in 2004 [section 4 No. 11], could no longer be brought to such a court); in the same sense Goetschel, in Kluge 2002, § 10a No. 7; Maisack 2007:176–179,221/2,234; Caspar 1999:455; Müller-Terpitz 2007:78/79,83 (who, however, suggests an exception in case of prohibitively high costs for patients); contra Lübbe 1994:472.

[75] District Court Düsseldorf, Recht der Landwirtschaft 1980:189,191; contra Maisack 2007:222 with respect to food.

longer lasting or repetitive pain or suffering as inaccurate, as suggested by the context of the clause, the standard of knowledge is that of "danger" in the conventional German categorization of risk.[76] This means that, while certainty is not necessary, there must be sufficient probability, based on past experience or other reliable evidence, that the trial will be associated with pain, suffering or harm. The precautionary principle does not apply. In view of wide-spread uncertainty about adverse effects caused by animal trials, including those that are inflicted in pharming development, for example uncertainties about harmful effects of insertion and transgene expression, this limitation of ethical review that excludes uncertain, but plausible future harm short of sufficient probability appears questionable.

The Act establishes a general requirement of a project authorization for any trial involving vertebrate animals (section 8). The authorization may only be granted under certain prerequisites, among which the following are the most important ones: The applicant must have demonstrated in a scientific manner that the prerequisites of indispensability and ethical justification are fulfilled and that the envisaged results of the trial are not sufficiently known despite exhaustion of accessible means of information or need to be reviewed, and it can be expected that when performing the trial the 3-R concept is complied with (section 8 [3]). The burden of proof and proffering evidence is placed on the applicant in a differentiated, somewhat confusing way ranging from full proof to mere demonstration (section 8 [2]). Demonstrate in this context means that the applicant must give substantiated and plausible information to support the application.[77] The differentiation made by the Act reflects both the knowledge available at the time of submitting the application, and the necessary knowledge base for proof of the authorization prerequisites (section 8 [2]).

Apart from the role of the applicant, it is also doubtful what degree of scrutiny – plausibility control vs. in-depth review – has to be employed by the competent authority in processing the application. Even within the judicature, there is no uniform opinion. It has often been sustained that the authority may only carry out a qualified plausibility control, but may not substitute its judgement for that of the scientists who perform the animal trial.[78] Others plead for a more extensive review of the application, in which plausibility review is limited to the purpose of the trial while all other authorization prerequisites are fully reviewed.[79] Still others take the view that at least after the insertion of animal protection in article 20a Federal

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[76] In this sense Kloepfer 2004:§ 11 No. 332.

[77] Lorz and Metzger 1999:§ 8 No. 12.

[78] Federal Constitutional Court, Neue Juristische Wochenschrift 1994:869; Administrative Court Berlin 1995 Zeitschrift für Umweltrecht:201; Kloepfer 2004, § 11 No. 130.

[79] Federal Administrative Court, Entscheidungen des Bundesverwaltungsgerichts (BVerwGE) 105:73,82; Caspar 1999:460/61; Kluge 1994:870.

Constitution, full scrutiny of the authorization prerequisites, including the purpose of the trial, is warranted.[80] A decision of this controversy is not easy. German administrative procedure law is based on the principle of full agency review of the prerequisites for an authorization, unless a statute prescribes another standard. However, this seems exactly to be the case under the act, insofar as section 8 [3] only requires the applicant to demonstrate the fulfilment of certain authorization prerequisites, especially those that involve scientific judgement or a prediction of future behaviour. Article 20a Federal Constitution protects animal welfare only subject to legislation. In a more recent law relating to stem cell research, the legislature has expressly provided for a mere plausibility control. There is no cogent reason to reinterpret the Animal Protection Act in the light of the Constitution.

The law also mandates the nomination of one or more officers for animal protection in all facilities where animal trials on vertebrates are performed (section 8b [1], [2]). The officer for animal protection is obliged to pay attention to compliance, advise staff responsible for performing animal trials and keeping trial animals, comment on applications for the authorization of such trials, and promote the introduction of non-animal trial methods (section 8b [3]). The establishment of internal ethical commissions is not prescribed, except for public research facilities such as universities where state law or internal regulations provide that such commissions must be established. Ethical review is, in principle, considered a matter of administrative control rather than self-regulation. Section 15 [1] subparagraphs 2, 3 provide for the establishment of animal protection commissions inside the administration, whose task is to advise the state agencies on decisions on applications for authorizations. Apart from requirements as to qualification of the members of these commissions, the law mandates a fairly high representation of animal protection interests.

In the development phase of pharming, the breeding prohibitions set forth by section 11b Animal Protection Act may also be relevant. The modification, by bio-technological or biological means, is prohibited where it must be expected that the animals or, for genetic causes, their offspring lack parts or organs for proper functioning or these parts or organs are unsuitable or modified in such a way that pain, suffering or harm occurs. The same is true where, in the offspring for genetic causes, behavioural disturbances occur that are associated with suffering. In these cases, the competent authority can order sterilization of the animals. In pharming, these prohibitions may become relevant, especially with respect to the propagation of the donor animal.

United Kingdom. In the United Kingdom, the Animal (Scientific Procedures) Act 1986 is largely based on the European Convention, but contains

[80] Administrative Court Gießen 2004, Natur und Recht:64; Goetschel, in Kluge 2002, § 7, No. 32a; § 8 Nos. 9 *et seq.*; Maisack 2007:168–170,357.

a number of innovative elements. The definition of animal trial (section 5 [3]) follows the definition given by the convention. At the core of the act, as part of the prescribed authorization procedure, is a cost-benefit analysis whereby the competent authorities, when deciding whether and on what terms to authorize the project, weigh the likely adverse effects on the animals concerned against the benefits likely to accrue as a result of the programme (section 5 [4]). Furthermore, the 3-R concept is laid down in the law. An animal trial is only permissible where its purpose cannot be achieved satisfactorily by other reasonably practicable methods not entailing animal trials (section 5 [5] [a]). In performing the trial a method must be employed that uses minimum numbers of animals and uses vertebrates with the lowest degree of neuro-physiological sensitivity, causes the least pain, distress or lasting harm and is most likely to produce satisfactory results (section 5 [5] [b]).[81]

The act requires a project authorization for every animal trial (section 3). The restrictions on animal trials as described are prerequisites for granting the authorization for a project, and must be dealt with in the documentation accompanying the application. The burden of proffering evidence is described by the Home Office Guidance on the Operation of the Animals (Scientific Procedures) Act of 2000[82] as the need for the applicant to "demonstrate" fulfilment of the permit requirements. As in Germany, this means that the applicant must provide substantiated and plausible information to support the application. In making the decision on the application, the competent authority, the British Home Office and its Inspectorate, has a wide margin of discretion. According to the British practice, not only the cost-benefit evaluation but also the application of the 3-R concept entails a weighing of conflicting concerns. The transparency of the weighing process and the predictability of its outcome have been criticized as being low.[83]

The guidance document[84] interprets the cost-benefit analysis as an optimization process, whereby the benefits must be maximized and the (social or external) costs minimized. The likely benefit is derived from the utility of the data or products to result from the programme of work. It relates to the progress likely to result directly from the programme. The guidelines do not give any indication that efficiency of the end production could be a relevant beneficial factor. Rather, in relation to safety testing, they specifically rule out that the utility or benefit of the end product could be taken into consideration. However, it is difficult to see how the utility of the data generated can be assessed if one ignores the benefits to be derived from

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81 Radford 2001:297; House of Lords Select Committee 2002:37/38; AEBC 2002:34 *et seq.*

82 23 March 2000 Appendix I:10/11.

83 House of Lords Select Committee 2002:30.

84 Sections 2.44, 2.45 and Appendix I:10/11; see also Animal Procedures Committee 1997 Appendix F, chapter 2.

their use. Moreover, it is not clear whether the objective of creating a transgenic animal would be questioned at all, or constitutes the frame within which the cost-benefit evaluation operates. Consequently, the application of the British law on animal trials is confronted with the same kind of problem addressed in the context of German law. This means that, in principle, savings of individual costs at the level of the firm do not justify an animal trial,[85] and even cost savings within the social insurance system may be irrelevant.

In the context of the cost-benefit evaluation, cost is equivalent to social (external) cost. It is considered as the immediate or delayed adverse welfare effects (pain, suffering, distress or lasting harm) likely to be experienced by the animals used, as the consequence of the trial or the result of the care and handling systems. A better expression would be harm-benefit analysis.[86] Cost-benefit analysis is not to be performed by mathematical calculations in the sense of monetization; rather, it is conceived as a qualitative assessment.

Apart from the project license, the Animals (Scientific Procedures) Act 1986 also requires a personal license, which relates to the qualification of staff that takes part in animal trials. The keeping of trial animals is subject to the requirement of having appropriate animal accommodation and veterinary facilities which is confirmed by a certificate of designation (section 6). Moreover, every operator must, by virtue of a standard condition, appoint one or more animal care and welfare officers whose task is to ensure proper husbandry, care and welfare of the animals (section 10 [6B], Guidelines 4.48, 4.55–4.58). Codes of practice regulate the details.

Besides the statutory controls, especially the requisite cost-benefit analysis and the 3-R concept, since 1999 the regulation of animal trials in Britain also operates through controlled self-regulation based on a local ethical review process. This procedure is not set forth by law. Rather, it has been introduced as a standard condition under section 10 [1] of the act. All operators that carry out animal trials must establish an ethical review committee, which may be composed of staff members but normally contains outsiders. The objective of the ethical review process is to provide ethical advice to the operator, promote the use of ethical analysis, increase awareness of animal welfare issues and develop initiatives for the widest possible application of the 3-R concept.[87] This includes the encouragement of non-animal alternatives for a projected license and consideration of the care and accommodation standards for trial animals. In practice, the ethical review process has developed into the second core element of animal protection in the field of research and development.

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[85] Board on Agriculture and Natural Resources 2002:51 *et seq.*; Boyd Group 1999; see also ECVAM 1898:21 *et seq.*

[86] In this sense House of Lords Select Committee 2002:30.

[87] Guidance document, *supra* note 81, appendix J No. 3.

In contrast to Germany, the United Kingdom relies somewhat less on administrative regulation. While ethical review is a part of the authorization procedure in Germany, it is based on self-regulation in the United Kingdom. However, in assessing the differences between the two countries, one must also consider that the cost-benefit analysis prescribed in the United Kingdom is part of what German law understands by an ethical review process. In a way, cost-benefit analysis and ethical review overlap, which has been criticized.[88]By and large, the actual authorization practice seems to be strict and rather bureaucratic. In particular, the 3-R concept is pursued strictly.[89] Whether the often made claim, that the United Kingdom has the most stringent system of animal protection in the world,[90] is justified could only be verified by an empirical investigation.

France. In France, articles R 214-1 *et seq.* of the Code rural regulates animal protection in the course of animal trials. This is the former Regulation 87-848, as amended by the Regulation 2001-464, which has been codified in the regulatory part of the Code rural.[91]

Following the European Convention, article R214-87 permits animal trials for a variety of purposes. The prerequisites for admissibility of animal trials are formulated without a clear distinction between obligations of the operator or authorization prerequisites and required information to be supplied by the operator. Every project that involves an animal trial requires an authorization (article R214-93). In performing an animal trial, the number of animals must be kept to a strict minimum and the proposed trial be justified in the application for an authorization. Where the trial entails intensive or prolonged pain or suffering, or the risk of such pain or suffering, this must be expressly declared and justified (article R214-91 [2]).

The application must be accompanied by a dossier with prescribed items. These items reflect the 3-R concept. However, an ethical justification in the strict sense is not provided. The applicant must justify the choice of the animals used for trial. He/she must establish that there is no alternative method available which could be substituted for the animal trial, and that the animals are the most suitable for the type of envisaged research (article R214-99 [2] No. 1). The justification requirements relate to the kind and the manner of the trial. The choice must be guided by the objective to minimize the number of animals, selecting the least sensitive from a neurophysiological point of view as well as selecting animals that present the best chances of deriving satisfactory results from the trial (article R214-99 [2] No. 2). However, in practice, the applicant must state the reasons for the use of the animals only in very broad terms.

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88 House Select Committee 2002:34.
89 Radford 2001:298/99; House of Lords Select Committee 2002:34/35, 37/38.
90 See House of Lords Select Committee 2002:12.
91 See Ziani 2006:425–441.

Although the law does not state this expressly, the prescribed contents of the application also serve as prerequisites for granting the authorization. The decision on the application is discretionary and can be restricted or granted subject to conditions (article R214-100). Therefore, the competent authority, namely the prefect of the department and its veterinary inspector, has the power to decide on the application, relying on a cost-benefit analysis or an ethical review even if this is not formally provided, and the applicant is not required to specifically demonstrate costs and benefits of the trial. Besides the project authorization, the law also requires a personal authorization which, in practice, contains elements of a project authorization (article R214-93). It is sustained in legal literature that the administration is not very sensitive to the concerns of the public about animal trials and, by and large, decides in favour of the applicants from industry and research institutions.[92] The degree of controls seems to be low.

The facilities where the trial shall be performed need a certification (agrément) (article R214-100 to 103). Breeding facilities must be notified to the prefect and also require a recognition (article R214-107). The keeping of the animals is subject to a general duty of care (article R214-17).

Finally, the law establishes two national commissions in the field. One is the National Commission on Animal Trials (article R214-116), and the other is the National Committee for Ethical Reflection on Animal Trials which forms a part of the former commission (article R214-122). Both are consultation bodies of the competent Ministry.

United States. In the United States, animal trials are covered by the Animal Welfare Act of 1966, as amended (7 U.S.C. §§ 2131–2159) and Department of Agriculture regulations (9 C.F.R. parts 1 and 2).[93] Moreover, most large companies receive accreditation from, and are inspected by, the private Association for Assessment and Accreditation of Laboratory Animal Care (AALAC),[94] which, however, focuses on animals used for the testing of hazardous substances. Apart from the requirement of a facility license, American law is dominated by the concept of controlled self-regulation. The Animal Welfare Act (7 U.S.C. § 2143 [b)[1]) prescribes that all research facilities (including industry) establish an Institutional Animal Care and Use Committee, composed of people selected on the basis of their experience and expertise, including outsiders. In its capacity as an agent of the firm, the committee must regularly review the animal welfare practice of the enterprise and needs to approve any animal experiment

92 Ziani 2006, *supra* note 91.

93 To the extent that research is government-funded, the Policy on Humane Care and use of Laboratory Animals of the Public Health Service under the Health Research Extension Act may apply in addition; see House of Lords Select Committee 2002:12/13.

94 House of Lords Select Committee 2002:13.

(9 C.F.R. § 2.31 [8] [d]. Compared with European standards, the prerequisites for approval are couched in rather weak terms. The Animal Welfare Act only refers to scientific necessity (7 U.S.C. § 2143 [a] [3] [D]). The regulations require avoidance or minimization of discomfort, distress and pain, the mere consideration of non-animal alternatives and written demonstration that they are not available, and the avoidance of duplications of animal trials. An ethical review process or cost-benefit analysis is not provided, and the implementation of the requirements within the enterprises seems to be lenient.

8.4 Development phase III: Protection of occupational safety and health in the development of recombinant medicinal products

Since the development of pharming products will normally be carried out within an enterprise or a research facility by the staff, it also raises problems of occupational safety and health. The relevant problems are in general addressed by the two major Community regulatory texts on GMOs, namely Directive 90/219, as amended by Directive 98/81 (containment) and Directive 2001/18 (release without containment) as well as national law implementing these directives.

8.4.1 Contained use

Directive 90/219 is designed to protect human health and the environment (article 1). As must be concluded from the general principles of containment and other protective measures set forth in the annex IV, this notion includes the protection of occupational safety and health. The annex contains a variety of measures for good occupational safety and hygiene. As regards concrete measures in the field of occupational safety and health, one can distinguish between information and operational obligations.

The obligation of the operator to perform a risk assessment in order to determine the kind and magnitude of risks associated with the activity, and to classify it into one of the four risk levels (article 5 [2]), is also designed to protect occupational safety and health. A summary of this risk assessment must be communicated to the competent national authorities as part of the notification required for starting operations under article 7 Directive 90/219. With respect to category l activities the directive does not require more specific information on occupational safety and health. In contrast, the envisaged containment and other protection measures must be described in detail for the following safety categories (annex V). Pursuant to national law, the competent authorities can impose upon the operator of category 1 activities concrete obligations for the protection of workers (cf. article 5 [1]).

Apart from that, Directive 90/219 contains general and specific requirements for the protection of human health that in particular concern occupational health. For all activities involving GMMs, according to annex IV the principles of good microbiological practice and specified principles of good occupational safety and hygiene apply. Among others, the operator must minimize exposure to GMMs to the lowest practicable level, perform engineering control measures at the source of risk, provide protective clothing and equipment, test and maintain control measures, provide appropriate training, instructions and warnings, and formulate and implement local codes of practice. This catalogue of general obligations is specified by particular measures, which vary according to the relevant risk category. As regards Category 1 activities, there are only very few additional optional requirements which must be evaluated in the risk assessment (annex IV, General principles, No. 2). It is only beginning with category 2 that the Directive sets forth more demanding requirements.

National law by and large has transposed the provisions of the directive relating to occupational safety and health literally but extended them to all GMOs. Apart from this important extension and from providing specific agency powers, it does not add much to it in terms of protection.

8.4.2 Release without containment

By contrast, Directive 2001/18 and national law implementing the directive are almost silent about risks to occupational safety and health presented by releases of GMOs without containment. This does not mean that occupational safety and health are not subjects of protection at all. Rather, as in the case of Directive 90/219, the notion of health (articles 1, 4 [1] and [3]) includes occupational safety and health. This interpretation is confirmed by the notification requirements set out in annex IIIA that applies to animals. The applicant must, among others, include in the risk assessment effects on human health resulting from direct or indirect contact of persons working with the GMOs (annex II D.1 point 6) and provide information about workers' protection measures to be taken during the release (annex IIIA point III A 8). As regards higher plants, the risk assessment also comprises occupational health (annex II D.2 point 6), while the applicable annex IIIB does not require supplying information on occupational safety and health. This gap may be explained by the assumption of the drafters of the directive that the problem is less relevant for the release of higher plants. However, when the competent authority has reason to believe that there might be a problem of workers' protection in the case of release of transgenic higher plants in the course of pharming activities, it can request additional information (article 6 [7]). As can be concluded from article 4 [2] of the directive which describes the content of annex III as information that may be necessary to carry out the requisite risk assessment, annex III is not definitive.

Insofar as the competent national authority, on the basis of information supplied by the applicant on his/her own or upon its request, sees a particular workers' protection problem being presented by a release, which in particular may arise in case of consecutive releases (article 6 [9]), it can grant the authorization subject to conditions (article 6 [8]). In doing so, it may use the requirements set forth by Directive 90/219 as guidance. However, at least as regards pharming, more explicit language would be appropriate.

8.4.3 General regulation of occupational safety and health

In addition, the general regulation of occupational safety and health established by Directive 2000/54 on the protection of workers against hazards by biological substances at work and implementing national regulations may apply, both with respect to development under containment and release without containment. This directive is a daughter directive under the umbrella of Directive 89/391 for the improvement of the safety of workers and protection of the health of workers at work. It also covers transgenic microorganisms but not all GMOs (article 2 [1]). Directive 2000/54 is merely supplementary. Equivalent or more stringent regulation set forth by directives 90/219 and 2001/18 directives is paramount (article 1 [3]). It may be assumed that the primacy of specific GMO regulation includes conditions attached to an authorization granted under the two directives.

Apart from this, Directive 2000/54 is not of major relevance for typical potential health risks presented by GMM releases in the course of initial pharming development activities. The reason for this is that the system of risk classification established by Directive 2000/54 (article 2) is confined to the risk of infection from biological substances at work. In practice, one could think of the potential exposure of workers to pathogens contained in the cell cultures or viral vectors used in the process. However, this appears to be a marginal problem.

8.5 Development phase IV: Regulation of development medicinal products

During the development stage, the operator also has to comply with the substantive and procedural requirements applicable to medicinal development products. These are set forth – by way of reference – by Directive 2001/83, as amended in particular by Directives 2003/47 und 2004/63, and various guidelines in the field[95] as well as national pharmaceuticals law. The reason for this overlap between GMO and pharmaceuticals regulation of "upstream processing" is, on the one hand, that the marketing authorization

[95] For example with respect to the product: EMEA 2000; ICH 1998a and other ICH guidelines such as: ICH 1998a; ICH 1997; ICH 1995; with respect to production: guidelines on good manufacturing practice (GMP); see also Schmitt 2004:33/34 and 47/48.

for medicinal products requires the submission of the results of previous analytical, toxicological and clinical testing.[96] The developmental product needs to have an appropriate quality and stability and the production process must be carried out in certified facilities and comply with good manufacturing or agricultural practice (GMP or GAP) in order to generate test results that are valid also for the final product. On the other hand, ethical considerations play a role in deciding whether the development product can be subjected to clinical testing. The product must have a sufficient degree of biosafety and the testing operations must comply with good clinical practice (GCP). The commencement of clinical testing requires an authorization (article 9 [4] and [7] Directive 2001/20). This is granted, after consultation of a regional or national ethics committee, under national law by the central authorities of the member states that are responsible for pharmaceutical safety. Similar requirements apply in the United States.

With respect to pharming development, the regulatory problem is not the protection of the environment against risks associated with the release of GMOs, but rather the protection of the production process and the product against risks originating from the environment, such as infectious and viral agents that may spread to the production premises from the outside. This is especially true of animal pharming. However, the required safety measures are not necessarily such that options for development operations that are available under GMO regulation, especially an open release or even a contained use for class 1 GMOs with double fencing, cannot be used in practice. They affect more the safety and control measures to be taken regarding the gaining and processing of the crude bulk material and the manufacturing of the developmental preparation.

Since the requirements to be observed are, by and large, similar or closely related to those relevant for securing the marketing authorization, they shall be addressed under 8.6.

8.6 Market authorization phase

8.6.1 Regulation 726/2004: Objectives and scope of application

Placing recombinant pharmaceuticals on the market is regulated by EC Regulation 726/2004 laying down a Community procedure for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Medicinal Agency. Regulation 126/2004 refers

[96] Biomedical testing of the development medicinal product does not normally entail a release of GMOs because the finished product no longer contains, or consists of, GMOs. These have been removed from the bulk material during the manufacturing process. It is only in rare cases that the finished product generated in pharming would contain, or consist of, GMOs. This aspect of pharming can be neglected.

to Directive 2001/83, as amended in particular by Directives 2003/63 and 2004/27, with respect to quite a number of questions such as definitions, the documentation to be supplied with the application, labelling and the production process.[97] National law plays a major role in the production process for medicinal products.

The purpose of the authorization procedure is to protect human health and the health of animals as well as the environment (article 6 [2] subparagraph 2). As evidenced by the prerequisites for granting the authorization and recital 7 of the Directive 2001/83 which refers to potential risks, the regulation is guided by the precautionary principle. The quality, safety and effectiveness of the medicinal product must be cumulatively proven in a proper and sufficient manner. The burden of proof is placed on the applicant (article 12).[98]

Regulation 726/2004 applies to a limited number of categories of pharmaceuticals contained in the annex to the regulation (article 3 [1]). All medicinal products developed by recombinant DNA techniques, controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes including mammalian cells, and hybridoma and monoclonal antibody methods are listed in the annex and hence are subject to the centralized authorization procedure. These products are defined by the manufacturing process. The recombinant DNA is not required to still be present in the finished preparation. All techniques presently used in pharming operations are encompassed.

8.6.2 Special regime for recombinant pharmaceuticals?

The inclusion of pharmaceuticals developed by means of biotechnological processes in the centralized authorization procedure suggests that such products should be subject to a special procedure designed to ensure the control of typical risks associated with this process. Indeed, the regulation establishes a special regime for medicinal products that contain or consist of GMOs. In an application for authorising such a medicinal product, the consent to the deliberate release for research and development purposes under part B of Directive 2001/18, the complete technical dossier under annexes III and IV, and the environmental risk assessment performed in accordance with the principles set out in annex II, must be provided (article 6 [2]). The environmental safety requirements laid down by Directive 2001/18 must be respected in the evaluation of the application (article 6 [3] subparagraph 4). However, in contrast to the regulation of food and feed (Regulation 1829/2003), the special regime does not apply when the pharmaceutical is merely produced by a biotechnological procedure (or from GMOs) but

[97] Thereby the directive has the legal status of a regulation.

[98] European Court of First Instance 2002 ECR II 3305 Nos. 114,135 *et seq.* – Pfizer Animal Health; 2002 ECR II 4945 Nos. 181 *et seq.* – Artegodan; Blattner 2002:281/282; Lorenz 2006:167.

does not contain, or consist of, GMOs. Rather, these products are subject to the normal central authorization procedure in the framework of which special problems regarding safety and quality that may be associated with the manufacturing method have to be addressed.[99]

In the case of pharming, the crude bulk material gained from the transgenic herd is purified so that the finished active substance, and hence the preparation, no longer contains any organisms that are able to replicate or transfer genetic material (see the definition of organism in article 2 [1] Directive 2001/18). An extensive interpretation of article 6 [2] of the regulation is not warranted since, as will be shown, the possible effects of the biotechnological procedure of deriving the active substance such as impurities, contamination with host cell contaminants or risks of viral infection can be addressed in the normal authorization procedure.

There are guidelines on recombinant pharmaceuticals issued by the European Medicines Agency (EMEA) in 1995[100]. As they are outdated in view of new scientific knowledge about possible quality problems and adverse effects, EMEA is preparing new guidelines.[101] The lack of up-to-date guidelines means that the producer needs to use informal contacts to EMEA in order to receive sufficient and reliable information about the pertinent requirements, especially as regards the requisite product safety and quality of the medicinal product and the clinical trial programme. Pre-submission meetings with EMEA are common practice.[102] While problematic from the point of view of legal certainty, this procedure has the advantage that hand-tailored solutions can be devised for the development of a particular pharming product and for preparing the submission of an application for that product.

In the United States, medicinal products derived by recombinant DNA technology are in principle treated like conventional biological pharmaceuticals. The Federal Food and Drug Administration (FDA) is of the opinion that specific differences as to safety and quality can be addressed in the framework of existing regulation.[103] Transgenic pharmaceuticals have to be authorized as biologics under part V of the Federal Food, Drug and Cosmetic Act and implementing regulations (21 C.F.R. parts 58, 210, 211, 600 and 680). There are FDA guidelines relating to the manufacture and testing of pharmaceuticals derived from transgenic animals[104] which are outdated and presently under consideration. Where the medicinal product contains, or consists of, GMOs, an environmental impact assessment under

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[99] See EMEA 2007.

[100] Production and Quality Control of Medicinal Products Derived by Recombinant DNA Techniques, Guidance document 3AB1a, 1995; Use of Transgenic Animals in the Manufacture of Biological Medicinal Products for Human Use, Guidance document 3AB7a, 1995; see Schmitt 2004:51.

[101] As a first step not relevant here see EMEA, *supra* note 99.

[102] Schmitt 2004:35,39,48,51; Schneider 2003:96 *et seq.*

[103] FDA 1986.

[104] FDA 1995; FDA 1996.

the National Environmental Policy Act must be performed (21 C.F.R. part 25).[105] However, this is not relevant with respect to the normal medicinal products derived from transgenic plants or animals.

8.6.3 Authorization prerequisites and procedure

The basic prerequisite for securing an authorization for pharmaceuticals derived from DNA technology is that the applicant must prove in a proper and sufficient manner the quality (consistency and purity), safety and effectiveness of the product (article 12 [1] Regulation 726/2004). According to general opinion, this entails a risk-benefit evaluation and a corresponding weighing, whereby certain risks to human health or uncertainties as to such risks presented by the new product can be compensated for by the therapeutic value of the product and the expected benefits from using it, taking into account the kind and extent of undesirable side effects, the severity of the illness to be combated, and the therapeutic alternatives.[106] The wording of the provision does not support this interpretation. However, recital 14 of the regulation refers to a risk-benefit evaluation. Moreover, arguments based on consistency militate for such an interpretation. The parallel Directive 2001/83 which regulates the decentralized procedure for medicinal products for human use[107] expressly provides for a risk-benefit evaluation (article 1 Nos. 1, 28a, article 26 [1] [a]). It would be odd that pharmaceuticals should be treated differently depending on the attribution of competences either to the member state authorities or the Commission. Finally, even more cogently, the requirement of a risk-benefit evaluation must be derived from article 16 [2] subparagraphs 2 and 3 of the regulation. This provision sets forth obligations of the holder of the authorization to provide information with respect to new knowledge that might influence the evaluation of the risks and benefits of the product. Furthermore, it empowers EMEA to ask the holder of the authorization to forward any new data demonstrating that the risk-benefit balance of the new drug remains favourable. This provision would not make sense if the decision on the original authorization were not based on a risk-benefit evaluation.

The Commission and the expert bodies preparing the decision have a wide margin of discretion when determining whether the authorization prerequisites are fulfilled, in particular when performing the risk-benefit evaluation, in view of the scientific complexities that have to be addressed.[108]

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[105] Example: the authorization of a transgenic variant of the hormone BST, 58 Fed. Reg. 59946 (1993).

[106] Lorenz 2006:167/168.

[107] Directive 2003/82 relating to medicinal products for veterinary use will not be considered as the regulation essentially equals that on pharmaceuticals for human use.

[108] European Court of Justice 1999 ECR I-223 No. 34 – Upjohn; European Court of First Instance, 2002 ECR II-4945 No. 201 – Artegodan; Lorenz 2006:169.

However, an evaluation of the need for a particular new medicinal product is not required and not even permissible.[109] Although perhaps desirable as a matter of policy, article 12 Regulation 726/2004 contains no language from which one could seriously conclude that something like a need analysis could be added to the considerations that the competent agency must perform in the authorization process. This is also true of the consideration of therapeutic value, which does not allow a comparison with products that are already on the market. The only legal basis for such an analysis would be the discretion afforded the Commission by article 12 of the regulation. However, this discretion must be exercised in coping with the objectives of article 12, which does not indicate that beyond quality, safety and effectiveness other factors, such as the need for the medicinal product, could be relevant. The rejection of a need analysis under existing law also concerns the production method. The Commission cannot deny an application for a marketing authorization for a pharming product because it feels that, in view of existing conventional production alternatives, there is no need for such products. The member states could try and refuse to reimburse prescriptions of the pharmaceutical by their social security systems, but this is not very probable if one accepts the basic premise of pharming that it generates cheaper products.

Under regulation 726/2004, the application must be accompanied by information and documentation as required under Directive 2001/83, as amended in particular by Directives 2003/63 and 2004/27, applicable to the decentralized authorization procedure, namely articles 8 (3), 10, 10a, 10b, 11 and annex I Directive 2004/27. This mainly concerns manufacturing methods, control methods and results of physical-chemical, biological or microbiological, toxicological, pharmaceutical, and clinical testing. Moreover, the application must contain information about, and an assessment of, potential environmental risks associated with the use of the medicinal product (article 8 [3] [ca] and [g] Directive 2004/27). However, environmental effects are not considered in the risk-benefit analysis (recital 28 Directive 2004/27); they can only give rise to conditions for using the product.[110]

Directive 2003/63 contains modifications to the dossier which accompanies applications for various categories of biological pharmaceuticals such as human vaccines, insulin, herbal pharmaceuticals and gene therapeu-

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[109] Recital 34 Regulation 726/2004; Commission, Draft regulation, COM 2002, 735 final:13/14,27; Lorenz 2006:172/73; Kwizda 1998:66.

[110] It is doubtful whether a refusal of the permit is (in contrast to medicinal products for human use) possible with respect to pharmaceuticals for animal use. Article 1 Nos. 19 and 20 Directive 2004/28 expressly includes risks to the environment in the definition of the requisite risk-benefit analysis. However, article 37 Regulation 726/2004 which sets forth the prerequisites for granting the permit only speaks of "safety" of the product and recital 23 of Directive 2004/27 seems to limit the legal consequences of the environmental assessment to special requirements for limiting releases of active ingredients into the environment.

tics. Moreover, it generally regulates the requisite information on biological pharmaceuticals which are essentially equal to medicinal products already authorized (biogenerics) by reducing the dossier requirements (annex I part 1). However, medicinal products generated by pharming cannot be considered as essentially equal to conventional medicinal biologics already authorized since equivalence is defined both by product and process (article 10 [1] [a] [ii] Directive 2001/83).[111] Genetic modification constitutes a new process and therefore the applicant cannot claim any procedural alleviations.[112] Of course, equivalence may be established in appropriate cases between existing and new transgenic pharmaceuticals.[113]

Whether the normal authorization prerequisites and procedures adequately respond to the specific problems presented by pharming drugs may be questioned. The genetic modification of the relevant animals, especially the generation of recombinant protein, as such is tackled practically by purification of the crude bulk material. However, the generation of transgenic animals may lead to instability of the gene construct and alterations in the metabolism of these animals; the recombinant protein may have impurities and be contaminated with host cell contaminants and infectious viruses. An example in this respect is presented by the authorization procedure relating to the transgenic drug ATryn®, which was concluded in August 2006 with a positive decision.[114] In this case, concerns were raised that altered glycosylation patterns in recombinant proteins produced from animals could alter pharmaceutical properties and that there was a potential of immunogenicity. However, it would seem that such problems can, as this first case of a regulatory procedure relating to a pharming drug shows, be addressed in the normal authorization procedure.

The safety of the active substance and the preparation can in particular be documented by the results of the toxicological, pharmaceutical and clinical tests. In order to submit the developmental medicinal product to such tests, certain requirements relating to safety and quality must be observed in order to ensure the transferability of the tests and compliance with good clinical practice, including the ethical justification for exposing trial persons to clinical testing. In this respect, besides Directive 2001/83, as amended by Directive 2004/27, Directive 2001/20 and implementing national laws apply.[115]

Although fundamental differences between conventional and pharming drugs do not exist with respect to safety, certain problems have been identified in the literature that are specific to animal pharming, such as the risk of

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[111] See also EMEA 2005:point 4.
[112] Schmitt 2004:35,38/39.
[113] See EMEA, *supra* note 111.
[114] EMEA, Press Release of 2 June 2006, EMEA/203163; EMEA/CHMP, Report of the Plenary Meeting, May 2006; see also Schmitt 2004:48.
[115] See *supra* 8.5; Schmitt 2004:33/34,35,47/48.

novel infectious diseases and immunogenicity.[116] Moreover, the assurance and maintenance of the quality of the medicinal product raises pharming-specific problems. The quality of the medicinal product is an authorization prerequisite (article 6 [2] Regulation 726/2004) that is closely linked both to efficacy and safety. Article 8 [3] [c] and annex I part 2A Directive 2001/83 require the description of the composition of the product according to kind and quantity of all components. The applicant must also provide, together with the application, information about the methods of manufacture and control (article 8 [3] [d] and [h] and annex 1 part 2B Directive 2001/83). There are various guidelines issued by EMEA in this field.[117]

The stability of the gene construct, the purity of the recombinant protein, as well as the homogeneity of the active substance are important factors in the quality assessment. Various guidelines issued by the International Conference on Harmonization (ICH) and EMEA guidelines are applicable in this area. The stability of the gene construct must be investigated and demonstrated over several generations; variation must be within an acceptable limit. As regards purity, EMEA requires in particular sterility of the product. The producer must demonstrate the absence of non-viral and viral adventitious agents as well as Transmissible Spongioform Encephalopathy (TSE). He/she must also ensure the removal of unnecessary source protein and DNA. In the case of continuous production, the homogeneity of the active substance must be ensured to a sufficient degree. EMEA, in principle, requires in this respect batch-to-batch consistency[118] which is difficult to achieve in drug manufacture based on animals, especially in the case of antibodies. The producer must also be able to detect quality failures during the whole production process. The head of pharmaceutical production is obliged to comply with the requirements and principles of good manufacturing practice for pharmaceuticals established under Community law, including GMP and GAP guidelines (articles 46 [f], 47 Directive 2001/83). There are various guidelines on GMP and GAP of international origin such as ICH and WHO guidelines which the EC has partly incorporated into its own guidelines (Directive 2005/62).[119]

The general regulatory problem in this respect, especially in animal pharming, is the assurance of product consistency and protection of the production process and the product against risks originating from the environment, such as infectious and viral agents and TSE that may spread by intrusion of animals into the production premises from the outside. EMEA guidance is urgently needed regarding this matter. The required measures are not necessarily such that options for cost efficient mass production available under GMO regulation, especially keeping the production herd outside with double fencing or cultivation of transgenic plants in open

[116] See Schmitt 2004:26–29,46/47.
[117] EMEA 1995a (under revision).
[118] EMEA 1995a:No. 8.
[119] As to the various ICH guidelines see Schmitt 2004:25,34–36.

fields, cannot be used in practice. There may be particular cases of highly vulnerable production animals or plants, or perhaps also very risky uses of the end product, where biosecure facilities may be needed already with respect to the keeping of the production herd and the cultivation of the transgenic plants.[120] However, it would seem that normally the operator can also put the emphasis on safety and control measures relating to the gaining and processing of the crude bulk material and the manufacturing of the preparation.[121] What counts is that the medicinal protein is within the defined range and free of non-viral and viral pathogens and TSE.

The environmental assessment required by article 6 Regulation 726/2004 in conjunction with article 8 [3] [ca] and [g] Directive 2001/83 and the relevant EMEA guidelines[122] does not give rise to additional problems, since the kind of pharmaceuticals that are presently produced by pharming are not normally associated with new adverse environmental effects. However, this statement cannot be generalized. For example, if hormones were produced by recombinant DNA technology, the potential environmental effects would require careful assessment and consideration.

Finally, by reference to articles 40-53 Directive 2001/83, article 6 [1] Regulation 726/2004 requires that the production of medicinal products must be subject to a production (facility and personal) license whose prerequisites are regulated by national law. They include availability of suitable and sufficient premises, technical equipment and control, and existence of qualified and sufficient staff.

In the United States, under section 505 [a] Federal Food, Drug and Cosmetic Act the central authorization prerequisite for pharmaceuticals is that they are safe for use and effective in their application. This provision is based on a precautionary approach. The authorization is denied if there is insufficient information to determine safety or there is no substantial evidence on effectiveness (section 505 [d]). The guidelines on recombinant DNA derived pharmaceuticals of 1996[123] address a number of typical safety and quality issues in this field, but are outdated. The applicant has to supply detailed information to support the application in a way similar to European law. The application is processed by the Center for Biologics Evaluation and Research (CBER) of the FDA in a tiered system of pre-manufacture review, preliminary procedure and main procedure involving close contacts between the applicant and the authority. Moreover, a manufacturing authorization (license for the establishment) is required although pharmaceuticals based on DNA plasmids, certain peptides and monoclonal antibodies are exempt (21 C.F.R § 314.70 [b], [c], 61 Fed. Reg. 24227, 24231 [1996]).

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[120] As to xenotransplantation and cell therapy see EMEA 2003:No. 2.2; FDA 2003:point D 1.
[121] EMEA 2006b.
[122] EMEA 2006a.
[123] FDA 1996.

8.6.4 Labelling

A further authorization requirement is proper labelling of the medicinal product. In this field once again Regulation 726/2004 (Art. 12 [1] subparagraph 2) refers to Directive 2001/83. The authorization must be denied when the labelling proposal does not comply with the provisions about risk communication. Labelling requirements are limited to information about active ingredients, the area of application, possible adverse side effects and the kind and duration of recommended intake. Under existing law, consumer sovereignty is not a primary concern in the labelling of pharmaceuticals. Rather, supplementary to regulation on product safety, labelling serves to provide adequate safety of use, in particular by preventing inappropriate prescriptions and wrong dosage.[124] The pharmaceuticals in question do not contain active transgenic ingredients. In contrast to food and feed (Regulation 1829/2003), the production process does not need to be communicated.

However, one cannot rule out, at least as a matter of policy, that the information to be provided about active substances should also need to include information about their transgenic origin.[125] The case for increasing product safety through extended labelling appears weak. Although pharmaceuticals derived by recombinant DNA technology may be associated with specific quality and safety problems, these problems have already been addressed in the authorization procedure. The possibility of unexpected health effects is not greater than with any other animal-based production method, which under present law does not need to be labelled. On the other hand, arguments of consumer sovereignty and patient autonomy, as well as regulatory consistency, militate in favour of information about the transgenic production method. In this respect, a real difference between food and feed, where labelling is required, on the one hand, and pharmaceuticals, where it is not, on the other, does not exist. The interposition of medical doctors as proxies does not justify a differentiation; for complex issues it is common to rely on information agents such as medical doctors and address information to them although the need for information is determined from the perspective of the ultimate beneficiary. In order to avoid overregulation and gain experience with extended labelling, one should begin with a voluntary system whereby special labelling is permissible. In addition, one should introduce an individual right of access to information about the production method at the patient's request.

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[124] Lorenz 2006:171.

[125] See as to the fundamental issues in the general context of labelling transgenic food Cranor 2007:201–221; McGarity 2007:128–150; Streiffer and Rubel 2007:63–87, who are in favour of labelling, and Markie 2007:88–105; Peters and Lambert 2007:151–177; Wolf 2007:178–200, who are against (all in Weirich 2007).

8.6.5 Institutional design

Regulation 726/2004 provides that the application is processed by the Committee on Human Medicinal Products (CHMP) established as a part of the European Medicines Agency (EMEA; articles 5 and 7 Regulation 726/2004).[126] The formal decision is taken by the Commission in the administrative procedure (article 10 [1] Regulation 726/2004). The Commission is not bound by the expert opinion of CHMP.[127] However, it is under an obligation to motivate any deviation from the expert opinion (article 10 [1] subparagraph 3 Regulation 726/2004). Normally it follows the CHMP. This configuration raises questions that have been widely discussed under the perspectives of political accountability, delegation and institutionalized scientific expertise.[128] The institutional arrangements in the field of evaluation and authorization of medicinal products manufactured by pharming do not show major particularities.

EMEA is exclusively responsible for the evaluation of most medicinal products, including pharmaceuticals derived by recombinant DNA technology. EFSA and the member state authorities only play a role in the special procedure relating to medicinal products containing, or consisting of, GMOs under article 6 [2] and [3] of Regulation 726/2004. As regards developmental medicinal products and more generally the development process for such products, national central authorities competent for medicinal products have major responsibilities.

Regulation 726/2004 does not contain rules on public participation relating to applications. The decision-making process is essentially of a technocratic nature. Access to information is ensured, subject to exceptions predicated on confidentiality, by Regulation 1049/2001 as amended by Regulation 1367/2006 on public access to information held by Community institutions and bodies. Moreover, in order to meet growing demands and criticism in this direction, EMEA in 2006 adopted a policy of greater transparency that includes the publication of its meeting agendas and minutes as well as rules for strengthening impartiality and independence of its expert bodies.[129]

8.7 Production phase

After having secured an authorization for the medicinal product, the production can commence. It consists of cultivating transgenic plants or keeping a transgenic production herd, gaining transgenic crude bulk material

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[126] For details see Lorenz 2006:266 *et seq.*

[127] European Court of First Instance, 2003 ECR II 6053 Nos. 52/53 – Nancy Fern Olivier; see also 2002 ECR II 3305 Nos. 188 *et seq.* – Pfizer Animal Health; 2002 ECR II 3395 Nos. 195 *et seq.* – Artegodan.

[128] See, e.g., the contributions in Joerges *et al.* 1997.

[129] EMEA Press release of 12 June 2006, EMEA/216787/2006.

from the plants or animals, purifying and processing it and manufacturing the medicinal product ("downstream production"). The regulatory problems that arise in this stage are not fundamentally different from those typical for the previous stages. However, additional factors to be considered are the larger scale of the relevant operations and greater access to the environment.

8.7.1 Protection against risks to the environment by use and release of GMOs

The production entails an ongoing use or release of GMOs which is not expressly regulated. As a matter of policy, since the authorization of the medicinal product does not cover the manufacturing process except for product quality, it seems clear that GMO-specific regulation must apply to the production process, either Directive 2001/18 or national law on contained use based on Directive 90/219.

However, as far as production without containment is concerned, it is unclear which regime of Directive 2001/18 governs the production process. Both the regime concerning releases (part B) and placing on the market (part C) have to be considered. Directive 2001/18 in its recitals seems to reserve the release regime to development releases (recitals 23, 25). Likewise, article 6 [2] Regulation 726/2004 with respect to pharmaceuticals that contain, or consist of, GMOs only refers to such activities.[130] One could conclude – and this seems to be the common understanding of the release regime – that releases that engender ongoing production activities are not covered by it. Although the notion of release as defined in Directive 2001/18 does not contain this restriction – release is any introduction into the environment unless it entails making the GMO available to third persons – this interpretation is suggested by the express provision of article 6 [9] of Directive 2001/18.[131] According to this provision, material derived from GMOs which are deliberately released in accordance with part B may only be placed on the market if authorized by a part C permit. The directive does not require this material to contain GMOs. As a matter of policy, the regime relating to the placing on the market also appears to be more appropriate because, beyond the marketing in the strict sense, it includes the permanent and wide-spread cultivation of transgenic crops and keeping and propagation of transgenic animals (see articles 19 [3] [c], 20, 23 [1] Directive 2001/18). That the rules relating to coexistence are connected to marketing must also be considered.

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[130] Article 5 [1] of directive 2002/18 which rules out, under certain conditions, the application of part B (articles 6–11) to medicinal products is confined to the release of transgenic medicinal substances and compounds for direct human use and does not cover the production process.

[131] Schmieder 2005:49,51; in this sense also EFSA 2006a:8; cf. Ostertag 2006:233; contra Voß 2006:158.

There are some counter-arguments. In pharming, the material derived from the release as such is not transgenic and the placing on the market of the pharmaceutical is already covered by the authorization granted under Regulation 726/2004. If one justifies the part C regime attached to the placing on the market by a resulting greater access of releases to the environment, one has also to underline that in pharming the impact of the release remains locally limited. The wording of some national laws relating to marketing is limited to the placing on the market of material that contains, or consists of, GMOs,[132] so that these laws would need to be interpreted extensively or amended. Finally, both article 12 [2] Directive 2001/18 and article 6 [2] Regulation 726/2004 declare the entire marketing regime to be inapplicable to the marketing of pharmaceuticals containing, or consisting of, GMOs where an authorization has been secured under Regulation 726/2004. It is doubtful whether it would make sense to apply it to the cultivation of the transgenic plants or the keeping of transgenic animals that, as such, are not made available to third persons.[133]

Nevertheless, the better arguments militate for the proposition that the whole production process, where it occurs in an open system, needs to be performed under a marketing authorization. The authorization granted under article 6 [2] Regulation 726/2004 must be based on the environmental risk assessment of the release and therefore also covers the GMO-specific aspects of the production process. This is not true of the authorization for pharmaceuticals that are simply derived by recombinant DNA technology without containing, or consisting of, GMOs. There is a need for a GM-specific scrutiny of the whole production process, which is best performed under the part C regime of Directive 2001/18.

Instead of an open release, a contained use under national law based on Directive 90/219 has to be considered. In selecting between the contained use and the marketing regimes, arguably the operator has a choice. Article 2 [4] 2nd indent of Directive 2001/18 exempts activities in the framework of a contained use under national law, that is equivalent to Directive 90/219, from the requirements applicable to placing on the market. Production under the contained use regime is more protective of human health and the environment than that in an open environment because a significant exposure does not take place. The finished product does not normally contain any GMOs. Other risks associated with the pharmaceutical, including the adventitious presence of GMOs, have already been fully assessed. Therefore, there are no strong arguments that militate for exclusive reliance on the part C regime under Directive 2001/18.[134]

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[132] Exception: Section 14 [1] No. 4 in conjunction with No. 2 German Act on Biotechnology.

[133] Ostertag 2006:217.

[134] In favour of the contained use regime also Voß 2006:155; EMEA 1995c.

However, it should be underlined that the existing framework conditions for the pharming production process are very complex and unclear. The interplay between the horizontal concept underlying Directive 2001/18 and the sectoral concept of the regulation of pharmaceuticals is not well defined.[135] This creates legal uncertainties that may hamper innovation and entail unnecessary transaction costs, and in the worst case may cause regulatory gaps. The operator has a legitimate interest in legal certainty and protection of his/her investment. For the future, a clarification in Regulation 126/2004 appears desirable.

In the rare case where the producer intends to market the transgenic plant developed by him/her as seed for (exclusive) use as a pharming platform, an authorization under the seed regime, especially Directives 2002/53 and 2002/55 and national law implementing the directives, is required as well. Presently, there is no Community rule in place that declares environmental risk assessment carried out under seed regulation to be equivalent to that required by Directive 2001/18. The national seed authorization depends on a preceding national authorization for a release of GMOs (article 4 [4] Directive 2002/53, article 4 [2] Directive 2002/55). An alternative is a Community authorization for the marketing of GMOs for cultivation.[136]

The obligations of operators to provide information and perform a risk assessment, and the prerequisites for granting the marketing authorization under part C of Directive 2001/18 (articles 4, 12-24, annexes II, III and in addition annex IV) and national law implementing the directive[137] are by and large identical to those under part B. In view of the experience gained with the preceding releases, taking safety measures is no longer a permit prerequisite but can be imposed as a condition. The fact that the geographic scale might be larger does not normally play a particular role regarding pharming activities. Therefore, the operator who had developed the transgenic pharmaceutical under the release regime can largely rely on the documentation provided in the preceding release authorization procedure, and add information about experience gained so far (see article 13 [2] subparagraph 2, [3] Directive 2001/18). A major substantive difference to the release regime is the requirement of post-marketing monitoring, which is designed to detect unexpected adverse effects presented by the ongoing cultivation of transgenic plants and keeping and breeding of transgenic animals (arti-

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[135] In this sense also European Commission 2004:6,7.

[136] As to the question whether Regulation 1829/2003 covers seeds, see articles 5 [5] [1], 17 [5] [2], 18 [3] [c]; Ostertag 2006:76–84 with further references.

[137] Germany: Sections 15 [1], 16 [2]-[5] Act on Biotechnology, section 6 Biotechnology Procedure Regulation; United Kingdom: Sections 109 [5], 111 [1] Environmental Protection Act, sections 14, 16 Genetically Modified Organisms (Deliberate Release) Regulations 2002; France: Articles L533-5, R533-26 and R533-27 Code de l'environnement.

cle 20 [1] of the directive and implementing national law).[138] Given the relatively small geographic scale of pharming production activities, compliance with this requirement is not overly burdensome.

As regards waste disposal and occupational safety and health, there are no particularities of the production phase (see sections 8.2.5 and 8.4).

What is different, though, are the procedures and institutional arrangements. Under article 15 [2] Directive 2001/18, the competent national authority has exclusive competence for denying an application for placing on the market, although all other member states and the Commission must be given an opportunity to discuss outstanding issues. Where the national authority intends to grant the authorization, it can only decide on it in the absence of a reasoned objection by another member state or the Commission; otherwise the decision on the pending application is elevated to Community level. The Commission or eventually the Council decides on the application in the regulatory procedure (articles 15 [3], 18 of the directive). Under article 28 [1] of the directive EFSA is involved in the preparation of the decision; the obligations of cooperation with expert bodies of member states, established by articles 28-30 Regulation 178/2002, apply. In view of the usual lack of consensus or at least a sufficient majority on GMO issues among the member states, the Commission and EFSA occupy a key position. Specific guidelines for the risk assessment of GMOs used as production platforms for pharmaceuticals do not exist. However, EFSA is preparing guidelines for the risk assessment of genetically modified plants used for non-food or non-feed purposes (PPP guidance).[139]

Directive 2001/18 provides for some form of public participation in the centralised procedure, more specifically in the preliminary procedure. Under article 24 [1[of the directive, the Commission must make available to the public summaries of the dossier submitted by the applicant, as well as positive national assessment reports. There is an opportunity to make comments to the Commission. Once the central regulatory procedure has commenced, there are no further opportunities to participate in the preparation of the decision. However, the high degree of politicization of GMO policy may result in extended possibilities of the public to indirectly influence the decision through pressure exerted on national governments represented in the regulatory committee. As regards access to information, under Regulation 1049/2001 (as amended by Regulation 1367/2006) all members of the public may request access to the full documentation submitted by applicants, unless it is confidential.

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[138] Germany: Section 16c Act on Biotechnology; United Kingdom: Section 112 Environmental Protection Act 1990, section 16 [2] [g], [5] Genetically Modified Organisms (Deliberate Release) Regulations 2002; France: Article R533-32 [6] Code de l'environnement.

[139] EFSA 2008. For a concrete case of EFSA involvement in the marketing authorisation of a non-food/feed transgenic product see *supra* note 45.

There is widespread criticism of the technocratic performance of EFSA's advisory functions. In particular, it has been claimed that EFSA does not adequately consider inputs from national governments and that expert bodies are generally biased in favour of GMOs. In response to this criticism, EFSA has tried to strengthen relationships with member states. It has referred to its rules on scientific independence which include the requirement for panel members to declare conflicts of interest. Finally, EFSA has developed a policy of openness and transparency, whereby the summaries of the GMO applications and all EFSA opinions are published and made available on the EFSA website.[140]

In EU practice, due to the high degree of politicization of GMO issues, central decision-making on the marketing of GMOs has become the rule. However, the geographic scale of pharming production operations is normally small, although their environmental effects will extend beyond the area of cultivation, and the resulting products do not contain, or consist of, GMOs. Therefore, it may be expected that objections by other member states or the Commission will be less frequent and limited to cases where the experimental release had already been controversial or production will occur on several sites. This may give more room for decisions being taken by the national authorities. The strategic interests of the Commission in favour of centralized decision-making may be a counterbalancing factor.

In the United States, regulation of releases of GMOs under the Plant Protection Act also applies to the cultivation of pharming and other non-food plants for commercial use. Normally, a permit is needed so that the permit procedure under the applicable regulations (7 C.F.R. § 340.2) must be performed. This may include an environmental assessement. However, there is the possibility to secure a determination of non-regulated status based on past experience with a similar release, e.g. a preceding experimental release (7 C.F.R. § 340.6).

8.7.2 Coexistence between pharming and conventional and organic agriculture

8.7.2.1 The problem

Directive 2001/18 does not cover adverse socio-economic effects associated with the acceptance of transgenic agriculture. As already stated, whenever GMOs are introduced into the environment, spread beyond the place or area where they are handled cannot be ruled out. The safety measures that already need to be taken in order to manage potential risks to human health and the environment, including the agricultural environment, also provide a shield of protection against socio-economic harm. Nevertheless, plant

[140] See, e.g., EFSA 2006c; see also EFSA News 2006 No. 13:1; 2007 No. 14:1; No. 16:2.

pharming may lead to some out-crossing through pollen drift and other spread of GMOs into fields with traditional or organic crops and adversely affect these crops or the seeds derived from them. Moreover, although the transgenic plants used in pharming are not designed as feed, and therefore the risk of commingling appears to be low, it cannot be entirely ruled out. For example, commingling can occur in the harvesting process when the same harvesting machines are used. As a consequence of "genetic contamination" caused on these pathways, conventional and especially organic farmers may suffer economic losses due to applicable mandatory or voluntary labelling requirements (for example the loss of GM-free or organic status). They may incur increased costs when they have to take technical measures to prevent and monitor adventitious admixtures. In the case of pharmaceutical properties, marketability of crops may be totally threatened because consumers and manufacturers alerted about "genetic contamination" may refuse to buy the products. The policy of securing compatibility between GM cultivation and conventional and organic cultivation is denoted as coexistence.

8.7.2.2 Sources of regulation

Directive 2001/18 empowers the member states to regulate in this field (article 26a). The Commission Recommendation of 2003 on coexistence[141] discusses the issues raised here and gives some guidance to the member states on how to shape their regulation. As yet, only few member states have coexistence regulation in place.[142] One of the reasons for this is that cultivation of transgenic crops is only envisaged for the future. However, in a number of member states new regulation is under preparation. The most important laws regulations that exist are:

- Germany: Sections 1, 16a, 16b and 36a Act on Biotechnology of 1990 in the consolidated version of 1993, as amended (relevant amendments in 2004 and 2008);
- Denmark: Sections 9–12 Act on the Growing etc. of Genetically Modified Crops (Act No. 436 of 2004), Executive Order on the Growing etc. of Genetically Modified Crops of 2005 and Executive Order on Compensation for Losses due to Certain Occurrences of Genetically Modified Material of 2005;
- Netherlands: Regulation of the Comodity Board for Arable Farming on the Coexistence of Crops of 2005;
- Portugal: Decree-Law 160/2005 on the Cultivation of Transgenic Varieties Ensuring Coexistence and Order of 2006 on the Establishment of GMO-free Areas;

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[141] *Supra* note 57.
[142] See COM 2006, 104 final; GMO Safety 2007.

– Austria: sections 62c and 78k of the Law on Biotechnology of 1994, as amended (relevant amendment in 2005), and provincial laws. [143]

As spelt out, for instance, in section 1 No. 2 of the German Act, the purpose of the laws and regulations on coexistence is to ensure that products, in particular food and feed, can be produced conventionally, organically or by use of genetically modified organisms and placed on the market. The structure of the laws is quite different. They may contain duties of care that are directly applicable but may also need to be specified by the government. Often they only have an enabling character, according the central government or, as in Austria, the provincial governments powers to adopt regulation.

As regards the regulatory instruments used, one can especially distinguish between administrative regulation (including recommendations issued by the government), labelling and retracing requirements, mandatory information about the site and time of releases (which exists in many member states), and liability.

8.7.2.3 Confinement and protection measures

A common practice to ensure coexistence is the determination of mandatory or recommended crop-specific separation (safety) distances, to be observed in fields where transgenic crops are grown (especially for maize and oilseed rape), and sometimes combined with buffer zones and/or differentiated according to whether conventional or organic farming is to be protected. However, not all member states that possess coexistence regulation have established safety distances. Although the setting of safety distances is normally justified with scientific findings, the figures show a great degree of national variation which cannot be simply explained by differences in climatic conditions and agricultural practices.[144] The Commission[145] voices some concern about the more stringent segregation distances introduced or proposed by some member states on the grounds of proportionality. However, as reliable empirical evidence is missing, the scientific basis of this criticism remains unclear. A crucial question is whether the precautionary principle can also be applied with respect to the protection

[143] For a detailed analysis of most of these laws see Grossman 2007a:370–388. In France, a new coexistence law (proposal No. 149, 19 December 2007, new articles 663.8 to 663.10 Code rural) which would introduce agency empowerments to require strict protection measures such as separation distances, especially for the protection of controlled cultivation zones ("appellation d'orgine contrôlée"), and establish strict liability of GM farmers is under parliamentary discussion.

[144] For instance, with respect to maize, these distances range from 15/50 meters in Sweden to 200 meters in Denmark and to 800 meters in Bulgaria and Luxembourg; regarding oilseed rape the distances are 200/400 meters in Finland, 3000 meters in Luxembourg and 4000/6000 meters in Latvia. Portugal and Germany have introduced safety distances for maize that distinguish between conventional and organic farmers.

[145] European Commission 2006:6.

of the economic interests of conventional and organic farmers. Section 16b [1] and [2] of the German Act on Biotechnology German law expressly provides for this in formulating duties of care.

A radical form of segregation of transgenic agriculture and conventional and organic agriculture is to declare large areas of a country as GMO-free zones. An attempt by the Austrian province Upper-Austria to declare the whole province as GM-free has been held by a recent judgement of the European Court of Justice[146] to violate article 95 [5] EC Treaty, that in the case of a directive based on the legislative competence for harmonization permits the taking of more stringent national measures only under very defined circumstances. More limited segregation models are practiced in other Austrian and some Italian provinces and in Portuguese municipalities. Their compatibility with article 95 EC Treaty or, which would seem to be more appropriate, with Directive 2001/18 itself, has yet to be tested.

A more general approach (which can be combined with safety distances) is the prescription of general duties of care. For example, section 16b of the German Act on Biotechnology provides that all persons who cultivate and process transgenic crops have to take precautionary measures to avoid a significant impairment of coexistence by a transfer of genetically modified properties, commingling and other dispersal of GMOs. Cultivation and processing is not permissible where, according to the circumstances of the individual case, achievement of coexistence is not ensured. In the cultivation and other handling of plants, these requirements are deemed to be complied with by observing the rules of good professional practice. The Act specifies these requirements with respect to cultivation by naming minimum distances, the selection of plant varieties, combating volunteers or use of natural pollen barriers for preventing gene spread at the time of seed and harvest, as well as out-crossing to other crops and wild relatives. Other rules of good professional practice relate to storage and transportation. Here commingling must be prevented, in particular by segregation of GM and non-GM products and cleaning of the premises, containers and means of transportation. However, as there are no sanctions provided for any violation of this duty of care, one should not overestimate its effectiveness. Its major impact lies in the field of liability.

Duties of care also exist in other countries, for example relating to growing intervals, handling of seed for sowing, harvesting crops, transport of harvested plant material and handling of waste plants and plant materials. Often they are not formulated in a general fashion but are crop-specific (for instance in Denmark).

These regulatory approaches are in principle also useful with respect to pharming.

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[146] 2007 ECR I 7141 – Land Oberösterreich and Republic of Austria/Commission, confirming European Court of First Instance, 2005 ECR II 4005 – Land Oberösterreich/Commission; for a discussion of the problems associated with GMO-free zones see Grossman 2007a:364–366.

8.7.2.4 Labelling requirements

Regulation 1829/2003 sets forth rules for mandatory labelling of food and feed that contains, or consists of, GMOs or is produced from GMOs or contains ingredients that are produced from GMOs.[147] The notion of GMO must be interpreted to the extent that it includes natural propagation of a transgenic plant or animal. Regulation 1830/2003 supplements the labelling rules by more technical provisions relating to traceability. The labelling rules are primarily designed to ensure free consumer choice, but also have a particular relevance for coexistence between transgenic cultivation on the one hand and conventional and organic cultivation on the other. The duty of care and the rules of good agricultural practice in this respect aim to avoid a significant impairment of coexistence through gene spread and commingling. The labelling thresholds are an indication of what is tolerable although, as regards organic farming, some states have introduced a more stringent regime.

The general labelling threshold is 0.9 percent for the adventitious or technically unavoidable presence of GMOs in food and feed (articles 12 and 24 Regulation 1829/2003). Under article 23 [3] Regulation 324/2007, this threshold will also apply to organic food (as from 2009). National law may set stricter requirements for positive labelling as "GM-free".[148] However, in spite of the traceability rules under Regulation 1830/2003, the regulation still suffers from a lack of common analytical methods for determining non-compliance.

In any case, the 0.9 percent labelling threshold is of little legal relevance in the field of pharming. It is confined to GMO traces contained in food or feed that are (directly or indirectly) authorized for use in food or feed (articles 4 [2], [4], 16 [2], [4], 47 Regulation 1829/2003). This can be ruled out with respect to pharming plants because GMOs with pharmaceutical properties are not fit as food or feed. The consequence is that there is a zero tolerance level for pharming material. Any – analytically detectable – presence of such GMOs converts food or feed into an unauthorized transgenic product. As can be derived from article 47 in conjunction with articles 4 [2] and 16 [2] Directive 2001/18, placing on the market or use of such products is illegal.[149] Their sale and use can be prohibited by an administrative order, although the competent authorities have a certain margin of discretion in

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[147] See Grossman 2007b:32–62; Canfora 2006:170–189 (also regarding national law).

[148] For instance in Germany no GM feed may be used.

[149] Ostertag 2006:159–168,212–217,230–236; Schmidt-Eriksen 2001:97; Mecklenburg 2006:229; contra Linke 2003:154. See also the definition of GMO under section 3 No. 3 German Act on Biotechnology.
Transitional provisions which set a threshold of 0.5 percent for unauthorized GMOs pending authorisation proceedings (article 47 Regulation 1829/2003) are not relevant either. In any case they have expired in the meantime.

deciding whether, in case of adventitious presence of such GMOs, they go against the relevant farmers and/or sellers.[150] The zero tolerance level does not violate the principle of proportionality.[151]

As regards seeds, there are at present no specific rules regarding the adventitious presence of GMOs. This means that there is a zero tolerance level, with the result that all detectable traces of authorized transgenic material must be labelled and the sale of seeds with unauthorized material is prohibited. Although the Commission is willing to set special labelling rules and had made various proposals in this respect, wide-spread opposition by member states and environmental and organic farming associations has led to a stalemate in the rule-making process.[152]

Of course, due to the limits of possible analytical detection the zero tolerance level cannot be complied with completely. For practical reasons, one normally accepts a GMO content up to 0.1 percent.[153] It may also be assumed that, because of the fragmentation of the legal rules and the difficulties for the competent authorities to detect and prove violations, the degree of compliance is relatively poor.

In the case of highly bioactive GMOs with pharmaceutical properties, one should aim to achieve the highest scientific limits of possible analytical detection. Accordingly, the practical confinement and protection measures may have to be more stringent than those for the cultivation of transgenic food or feed crops. A more radical approach for preventing possible adventitious gene spread would be to limit plant pharming to non-food and non-feed crops or require total containment.

Similarly, in the United States there is a zero tolerance level for adventitious traces of GMOs that are not authorized or notified. Transgenic material from pharming plants may not be introduced into the environment without the permit required under the Plant Protection Act (7 U.S.C. § 7712). Food containing such traces is considered to be adulterated and misbranded in the meaning of sections 342 [a] [1] and 343 [a] Federal Food, Drug and Cosmetic Act because there is no reasonable certainty of no harm. The competent agencies have the discretion to decide whether and under what circumstances they proceed against the relevant plant growers and/or sellers and may decide that the transgenic material does do not pose a significant risk.[154] However, in the case of transgenic material with pharmaceutical properties, it would seem normal that, in addition to strengthening

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[150] For Germany see Section 26 Act on Biotechnology; Administrative Court of Appeal Münster, Neue Zeitschrift für Verwaltungsrecht 2001; Ostertag 2006:296–302,306–313; Schmidt-Eriksen, Mecklenburg and Linke, *supra* note 147 with further references.

[151] European Court of Justice 2004 ECR I 3465 Nos. 48–53 – Bellio Fratelli; contra Herdegen & Dederer 2001:11,13/14,20 *et seq.*

[152] See Grossman 2007a:355–360.

[153] Federal Ministry of the Environment, Umwelt 2003:479.

[154] See USDA/APHIS 2007:14650/51.

confinement and protection measures on the fields, action should be taken to prevent further sales of the contaminated food products.

8.7.2.5 Liability

Finally, liability has emerged as an important element in inducing behaviour that is protective of coexistence or to compensate non-GM farmers for financial losses due to gene spread.[155] Two models deserve attention because of their implications for plant pharming: the German model of strict liability of transgenic farmers and the Danish model of a compensation fund.

Section 36a of the German Act modifies the elements of substantiality and customariness of an interference and economic reasonableness of preventive measures that constitute the core of the strict liability rules of neighbourhood relations contained in sections 1004, 906 Civil Code.[156] Under the new law, a transfer or other dispersal of GMOs from neighbouring land is deemed to be a substantial interference where, contrary to the intentions of the owner or holder of the affected land, the agricultural products may no longer be placed on the market because of the transfer and other dispersal. The products need to be labelled as containing GMOs (because the labelling thresholds are exceeded) or the products can no longer be labelled in the way that they could according to the legal provisions applicable to the production method (for example as organic or GMO-free). The wording of section 36a of the German Act militates for the proposition that this does not only cover mandatory labelling under Regulation 834/2007 on ecological/biological products but also voluntary labelling according to the more stringent rules of associations of organic food growers.[157]

The market-based definition of substantiality, although hardly compatible with the use-related original system of the Civil Code, provides conventional and organic farmers a higher degree of protection because they do not need to tolerate interventions caused by transgenic cultivation *per se* on the grounds that the mere presence of GMOs is not substantial. However, conventional, organic and transgenic farming are all declared to be customary methods of cultivation under local relevant circumstances. Thereby, a defence against the introduction of transgenic crops predicated on priority is made impossible.[158]

In essence, the problem is shifted to reasonableness analysis and linked to compliance with the rules of good professional practice. Under section 906 [2] Civil Code, a substantial interference, although it is customary, can be enjoined where it could be prevented or mitigated by protective

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[155] See Rehbinder and Loperena 2006:266; Grossman 2007a:97–107.
[156] See in particular Kohler 2005:566; Wagner 2007:1017.
[157] Contra Arnold 2006:16/17; Wagner 2007:1024/1025.
[158] By contrast, section 79k of the Austrian Act on Biotechnology seems to accord the neighbour under like circumstances injunctive relief.

measures that are economically reasonable. Section 36a Act on Biotechnology declares measures for compliance with good professional practice to always be reasonable. Non-compliance with such rules can therefore lead to an injunction of transgenic agriculture. Nevertheless, compliance does not automatically dispense the transgenic farmer from the obligation to pay compensation. Section 906 [2] Civil Code accords a neighbour, who must tolerate an intervention because protective measures would be unreasonable, financial compensation where the customary use of his/her land or the revenue derived from it is impaired beyond a tolerable degree. Moreover, this liability for compensation also lies in the case of contributory causation. Under the circumstances where several neighbours could have caused the harm and it cannot be determined which neighbour has actually caused it, all relevant neighbours are severally and jointly liable, unless a particular neighbour can prove that he/she only caused part of the damage and estimation of the share is possible.

The new law imposes on transgenic farmers a high burden of liability. Apart from criticism based on systematic grounds, some authors[159] sustain that it accords organic farmers a preference, instead of ensuring coexistence, and therefore is not compatible with article 26a Directive 2001/18. However, in its report on the national implementation of this provision,[160] the Commission has abstained from challenging any liability rules. It is also argued that the new law violates the principle of proportionality, at least insofar as it protects self-chosen quality claims for organic products that are more stringent than Community regulation on organic farming.[161] However, in defence of the new liability rules one can state that they are justified in order to prevent a creeping "genetic contamination" and will foster cooperative arrangements between farmers and the establishment of GMO and GMO-free agricultural zones.[162]

As regards plant pharming, it should be noted that the duty of care and the rules of good professional practice under section 16b of the German Act on Biotechnology also apply where it is not, or not only, coexistence that is concerned but rather human health or the environment, for example in cases of unforeseen effects. Moreover, due to its general preventive effects, liability under section 36a of the Act can at least indirectly contribute to avoiding potential adverse effects on human health and the environment under such circumstances.

The Danish Act on the Growing etc. of Genetically Modified Crops of 2004 has introduced a collective compensation scheme for losses suffered

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[159] Dolde 2004:219; Wolfers and Kaufmann 2004:421; Schmieder 2005:49.
[160] *Supra* note 141:7.
[161] See authors cited *supra* note 159.
[162] Palme *et al.* 2004:176/77; Palme 2006:76. Cooperative agreements are now expressly admitted in Germany; § 16b Act on Biotechnology (as amended in 2008).

by conventional or organic farmers due to the occurrence of genetically modified material in their crop originating from transgenic agriculture in the neighbourhood (sections 9–12). The scheme is funded by a levy charged on all GM farmers (section 12)[163] and administered by the Plant Directorate. Insofar as compensation is paid, claims for damages that the victim may have against the person responsible for his/her loss under private law are subrogated to the state.

Compensation requires that, in the same growing season and within a specified area, a genetically modified crop of the same or a related variety has been grown and has crossbred with the crop of the victim. Administrative rules have fixed the relevant distances between the fields in a very restrictive manner, namely for maize at 300 meters, for beet at 75 meters and for potatoes at 30 meters. Moreover the GM crop must be identified in the crop of the farmer suffering the loss (section 9 [1] [i] and [i]). This latter prerequisite does not mean that, in case of several potential sources, the victim has to identify the precise field from which gene spread has occurred. Rather, it suffices that the presence of transgenic material from a GM crop, grown in the perimeter fixed by the administrative rules, can be determined by analytical methods. Otherwise, securing compensation would be very difficult once transgenic agriculture becomes more common. Under a collective system of compensation funded by all transgenic farmers, the identification of the precise source of gene spread does not make sense. It would introduce into the collective compensation system an element that is geared to traditional individual liability. In the case of organic farming, compensation may be paid at the discretion of the authority independent of these limitations (the distance requirement and the obligation to identify the transgenic crop of origin) where adventitious admixtures of genetically modified seed occur in the farmer's seed for sowing (section 9 [4]). In all other respects, conventional and organic farmers are treated equally.

Compensation comprises losses caused by lower sale prices for the products on the market, the costs of sampling and analysis and losses due to requisite conversion from organic to conventional farming resulting from the genetic contamination. However, compensation will not be granted for losses caused by the presence of GMs in the crop that do not exceed a threshold to be set by the competent Minister. This threshold has been set at 0.9 percent, and in the case of seed at the level that Community legislation will provide for special GMO labelling of seed (section 2 Executive Order).[164] This means that in contrast to Germany, self-chosen quality standards of organic farmers do not confer a right to compensation. In the case of pharming it is hardly satisfactory that liability should only apply

[163] This financing method has been approved by the Commission under article 87 EC Treaty; see State aid case N 568/2004.

[164] Executive Order on Compensation of Losses due to Certain Occurrences of Genetically Modified Material 2005.

when the threshold of 0.9 percent is exceeded, as this is not applicable to GMOs not authorized as food or feed.[165]

8.7.2.6 Special issues in animal pharming

The rules on coexistence are, in principle, also applicable to transgenic animals. States that have introduced general duties of care include the keeping of transgenic animals. Section 16b of the German Act on Biotechnology expressly provides that the obligation to ensure coexistence also applies to the keeping of transgenic animals. As an expression of good professional practice in keeping transgenic animals, their escape from, as well as the intrusion of other animals into, their premises must be prevented (section 16b [3] No. 2). In contrast, special liability for genetic contamination does not normally extend to transgenic animals. There is no urgent need to extend strict liability to transgenic animals beyond the existing law.

8.7.3 Animal protection

In the production phase, there may also be animal protection requirements that have to be observed. However, there are obvious gaps of protection at European and national levels because the more specific and more protective relevant texts only apply to normal farming activities. Pharming animals held for production are normally only subject to general requirements of animal protection.

Thus, the scope of application of the European Convention for the protection of animals kept for farming purposes is confined to "animals bred or kept for the production of food, wool, skin or fur or for other farming purposes". EC Directive 98/58, which has been adopted to give effect to the principles laid down in the European Convention, uses the same language for describing its scope of application (articles 1 [2] and 2 No. 1). It would arguably go beyond the perception and intention of the contracting parties to the convention and the EC institutions, who drafted the texts, to advocate a dynamic interpretation of the notion of "farming purposes" that includes the manufacture of pharmaceuticals only because the animals used are the same as those normally used in agriculture. Certainly, the notion of farming does not have a meaning that is fixed for all times. For example, we would perhaps not hesitate to conceive the production of agricultural raw materials for the generation of renewable energy, such as biogas or biodiesel, as agriculture. However, the historic perspective is highly relevant when interpreting international agreements. This prohibits an interpretation to the extent that an activity which is carried out at the borderline between agriculture and manufacture should be deemed to be for "other agricultural purposes".

[165] A more limited compensation fund that only covers accidental gene spread and commingling exists in Portugal under the Decree-Law 160/2005; see Grossman 2007a.

It should be noted that this gap of protection may be carried over to national law. While there is general regulation on animal welfare which also encompasses pharming animals, the more specific and more protective special provisions on the keeping of useful animals are not normally applicable to the keeping of pharming animals, because they do not serve agricultural purposes.[166] This is a regulatory anomaly that should be remedied.

However, in Germany, section 10a Animal Protection Act provides that interventions in, and treatment of, vertebrate animals for the purpose of production that may be associated with pain, suffering or harm, are only permissible when certain prerequisites applicable to the authorization of animal trials are fulfilled. These prerequisites are indispensability of the intervention, its ethical justification and the 3-R concept. The operator must notify the programme of work to the competent authority, which can prohibit it if the prerequisites of permissibility are not fulfilled. However, it would seem that normal manufacturing activities in the course of pharming are not affected by this provision, since the kinds of interventions covered by section 10a of the act are not performed at this stage. Besides, the general duty of care for the keeping of all kinds of animals under section 2 Animal Protection Act must be complied with. This duty can be summarized as the requirement of compatibility with the nature of the animal.[167] Similar requirements of a general nature apply in the United Kingdom and France, who do not possess specific rules relating to interventions into animals in the production phase (section 9 Animal Welfare Act 2006, article R214-17 Code rural).

8.7.4 Production-related requirements under pharmaceuticals regulation

In the production phase, the producer must comply with the management and control program provided in the marketing permit and documented in the application for the permit, with respect to the keeping of the production herd or cultivation of the transgenic plants, the gaining and processing of the crude bulk material and manufacturing the end product. In particular, the quality and safety requirements with respect to consistency and the absence of non-viral and viral agents and TSE, must be observed. In the light of experience with the ongoing production, adjustments may be necessary. New information about quality problems must be communicated to EMEA and the Commission (article 16 [2] subparagraph 1 Regulation 726/2004). Where the production herd is kept in the open environment with double fencing, protection against virus epidemics is practically impossible. In order to maintain production during possible epidemics, having several production sites that are separated by significant distances may be advisable in order to avoid market disruptions.

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[166] For Germany see Federal Administrative Court, Buchholz, Entscheidungssammlung des Bundesverwaltungsgerichts 418.9 Tierschutzgesetz No. 13 (2004); for Britain: AEBC 2002:34.

[167] Lorz and Metzger 1999: § 2 No. 16.

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