

Comprehensive table of contents

Preface	VII
Foreword.....	IX
List of abbreviations	XIX
1 Introduction	1
References	7
2 The technology of pharming	9
2.1 Recombinant pharmaceutical proteins – the advent of biotechnology	9
2.2 Plants as a production platform for recombinant biopharmaceuticals	11
2.2.1 Genetic engineering of the host plant	13
2.2.1.1 Gene constructs	13
2.2.1.2 Post-translational modifications	14
2.2.1.3 Plant transformation method	15
2.2.2 Transient expression using viral vectors	20
2.2.3 Choice of species and site of production	21
2.2.3.1 Leaves	21
2.2.3.2 Cereals, legume seeds and oilseeds	22
2.2.3.3 Fruits and vegetables	22
2.2.3.4 Plant cell cultures and hairy root systems	22
2.2.4 Cultivation.....	24
2.2.5 Purification of biopharmaceuticals from transgenic plants.....	24
2.2.5.1 Purification of biopharmaceuticals from whole plants	24
2.2.5.2 Purification of biopharmaceuticals from plant cell cultures and hairy root cultures	26
2.3 Animals as a production platform for recombinant biopharmaceuticals	27
2.3.1 Transgene constructs used for animal pharming	27

2.3.2	Methods of producing transgenic livestock	29
2.3.2.1	Pronuclear DNA microinjection	30
2.3.2.2	Viral gene transfer	34
2.3.2.3	Sperm-mediated gene transfer	38
2.3.2.4	Embryonic stem cells	39
2.3.2.5	Embryonic germ cells	42
2.3.2.6	Nuclear transfer	43
2.3.2.7	Spermatogonial stem cells	47
2.3.2.8	Adult stem cells	48
2.3.2.9	Overview	48
2.3.3	Choice of species and site of production	48
2.3.3.1	Milk	53
2.3.3.2	Urine	56
2.3.3.3	Seminal fluid	57
2.3.3.4	Blood	58
2.3.3.5	Bird eggs	58
2.3.4	Production of proteins from transgenic animals	59
2.3.4.1	Analysis of transgenic animals	59
2.4	Quality and safety of the product	63
2.5	Choice of expression systems	64
2.6	References	66
3	Risk assessment of plant pharming and animal pharming.....	73
3.1	Environmental risks and co-existence of plants genetically modified for production of pharmaceuticals	73
3.1.1	Legal framework and basic principles of risk assessment of GM plants	74
3.1.2	Risks of pharming plants	78
3.1.2.1	Risks of unintended exposure	78
3.1.2.2	Transgene dispersal	80
3.1.2.3	Horizontal gene flow.....	91
3.1.3	The environmental risks – will pharming plants differ from the current GM plants?	92
3.1.4	Concluding remarks	93
3.2	Environmental risks of animal pharming	93
3.3	References	95
4	The welfare of pharming animals.....	101
4.1	Introduction	101
4.2	Animal welfare risks	102

4.3	The concept and assessment of animal welfare	104
4.4	Animal welfare considerations in the animal pharming production phase	105
4.4.1	Housing and management	106
4.4.2	Protein collection and excess offspring	108
4.4.3	Reproduction	108
4.4.4	Effects of genotype	109
4.5	Animal welfare considerations in the development phase	109
4.5.1	Transgenesis, expression of medicinal protein, and transgene evaluation	110
4.5.2	Reproductive technologies	112
4.5.2.1	Developmental problems in somatic cell nuclear transfer (cloning)	112
4.5.2.2	Donor animals and foster mothers	114
4.5.3	Excess offspring	115
4.6	Conclusions	115
4.7	References	117
5	Public views and attitudes to pharming	121
5.1	Introduction	121
5.2	Methodological considerations	126
5.3	Attitudes to pharming in advanced societies: awareness and evaluative perspectives	131
5.3.1	Awareness about pharming	132
5.3.2	Evaluative perspectives	132
5.4	A differentiated landscape of perceptions of pharming	136
5.4.1	Ranking of biomedical and socio-economic goals and acceptance of plant pharming	137
5.4.2	The specifics of the means in the acceptance of plant pharming	138
5.4.3	Ranking of biomedical and social goals and acceptance of animal pharming	140
5.4.4	The specifics of the means in the acceptance of animal pharming	140
5.5	Preferences for methods of production of pharmaceuticals.....	142
5.6	Awareness and acceptance of plant and animal pharming	143
5.7	Elements of an explanatory model	144
5.8	Conclusions	152
5.9	Tables	153
5.10	References	176

6	The ethical evaluation of pharming	179
6.1	Introduction	179
6.2	Foundations of moral reasoning	180
6.3	Common moral concerns regarding pharming	184
6.3.1	The moral status of plants and animals	185
6.3.2	Naturalness	189
6.3.3	Integrity	191
6.3.4	Aims and means of using and manipulating animals and plants for pharming	192
6.4	Risk assessment and risk-benefit analysis	193
6.5	References	198
7	The role of patents in the development of pharming	201
7.1	The general justification of patents	201
7.2	The existing regulatory framework	202
7.3	Basic rules on patentability of biological products, biological material and biological and microbiological processes	203
7.4	Extent of protection	205
7.5	Mandatory licenses	206
7.6	Patents as obstacles to innovation in pharming?	207
7.7	References	211
8	Legal problems of pharming	213
8.1	Introduction	213
8.2	Development phase I: Protection from risks to the environment caused by the use and release of GMOs	213
8.2.1	Sources of legal regulation and their scope of application	213
8.2.2	Development of recombinant medicinal products with containment	218
8.2.3	Development of recombinant medicinal products without containment	222
8.2.3.1	Scope of application and regulatory principles of Directive 2001/18	222
8.2.3.2	Information requirements and risk assessment	223
8.2.3.3	Authorization prerequisites	226
8.2.3.4	Special issues relating to animal pharming	235
8.2.3.5	Institutional arrangements	235
8.2.4	Coexistence between experimental cultivation of GMOs and organic and conventional agriculture	237

8.2.5	Waste disposal	238
8.2.5.1	GMO-specific regulation	238
8.2.5.2	Regulation under general waste law	240
8.2.5.3	Disposal of excess animals and animal parts	240
8.3	Development phase II: Animal protection	241
8.3.1	Sources of regulation	242
8.3.2	Animal trials: Scope of application of the relevant laws ..	242
8.3.3	The European Convention and Directive 86/609	244
8.3.4	National law	245
8.4	Development phase III: Protection of occupational safety and health in the development of recombinant medicinal products .	255
8.4.1	Contained use	255
8.4.2	Release without containment	256
8.4.3	General regulation of occupational safety and health	257
8.5	Development phase IV: Regulation of development medicinal products	257
8.6	Market authorization phase	258
8.6.1	Regulation 726/2004: Objectives and scope of application	258
8.6.2	Special regime for recombinant pharmaceuticals?	259
8.6.3	Authorization prerequisites and procedure	261
8.6.4	Labelling	266
8.6.5	Institutional design	267
8.7	Production phase	267
8.7.1	Protection against risks to the environment by use and release of GMOs	268
8.7.2	Coexistence between pharming and conventional and organic agriculture	272
8.7.2.1	The problem	272
8.7.2.2	Sources of regulation	273
8.7.2.3	Confinement and protection measures	274
8.7.2.4	Labelling requirements	276
8.7.2.5	Liability	278
8.7.2.6	Special issues in animal pharming	281
8.7.3	Animal protection	281
8.7.4	Production-related requirements under pharmaceuticals regulation	282
8.8	References	283

9	Conclusions and recommendations	291
9.1	Pharming technology and its market	291
9.2	Public attitudes and moral evaluation	292
9.2.1	Attitudes	292
9.2.2	Moral evaluation	293
9.3	The assessment and management of risks associated with pharming	294
9.3.1	Principles	294
9.3.1.1	Case by case	294
9.3.1.2	Risk-benefit evaluation	295
9.3.1.3	Independent risk assessment research	295
9.3.1.4	Transparent procedures and independence of risk assessment bodies	295
9.3.2	Product safety and information	296
9.3.2.1	Measures to prevent contamination and ensure product quality	296
9.3.2.2	New guidelines on pharming medicinal products and European Medicines Agency (EMA) committee on pharming products	297
9.3.2.3	Labelling and consumer information	297
9.3.3	Risks to the environment and food and feed chains	298
9.3.3.1	Experiments and cultivation with containment, and deliberate releases	298
9.3.3.2	Coexistence	300
9.3.4	Risks to animals in pharming	300
	Glossary	303
	Appendix: Examples of GM pharmaceutical crops and animals	315
I.	Production of molecular farmed human intrinsic factor (rhIF) in potato (<i>Solanum tuberosum</i>)	315
II.	Production of Molecular Farmed human lactoferrin (rhLf) in rice (<i>Oryza sativa</i>)	316
III.	Production of antithrombin in goats' (<i>Capra hircus</i>) milk	317
	References	321
	List of authors	323
	Index	329

Pharming

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

Reh binder, E.; Engelhard, M.; Hagen, K.; Jørgensen,
R.B.; Pardo-Avellaneda, R.; Schnieke, A.; Thiele, F.

2009, XX, 334 p., Hardcover

ISBN: 978-3-540-85792-1