The Chimbrids project

A. Preface

Under the direction of Professor Dr. Jochen Taupitz the Institute for German, European and International Medical Law, Public Health Law and Bioethics (IMGB) coordinated the international and inter-disciplinary research activities of over 25 high-ranking scientists from sixteen countries with regard to the topic "Research on Chimeras and Hybrids". Central to the project were unresolved questions about research with human-animal-mixed creatures with potential benefit to medical science for the treatment of diseases like Alzheimer's disease, Parkinson's disease or multiple sclerosis. The scope of this EC-funded[1] research project, acronymed "CHIMBRIDS", encompasses natural sciences, medicine, ethics and law.
The outcome of "Chimbrids" successfully sheds light on the chances and risks of chimera and hybrid research and provides legal solutions to existing problems in order to help decision-makers fulfil their tasks in an informed and efficient manner.

The following abstract, titled „Summary, Conclusions and Recommendations", represents the essential project results including practical recommendations for decision-makers.

The complete results with descriptive reports for the legal situation in specific countries and in-depth analysis of all scientific, medical, ethical and legal implications will be published in the second quarter of 2008 in one comprehensive volume, "**Chimbrids-** Chimeras and hybrids in comparative European and international research – scientific, ethical, philosophical and legal aspects**",** edited by Professor Dr. Jochen Taupitz and Marion Weschka in the Springer Publishing House, Berlin.

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[1] *This article reflects only the authors' views; the European Community is not liable for any use that may be made of the information contained therein.*

B. Summary, Conclusions and Recommendations

I. General remarks

1. Mixing of living human and animal biological material to create chimeras or hybrids ("chimbrids") challenges our understanding of what it is to be a member of the human species.

2. Cellular, embryonic, foetal and post-natal human-animal mixtures raise a wide range of conceptual, ethical and legal problems. General scientific, ethical and legal issues have to be considered as well as the potential benefits and risks involved, primarily for human beings, but also for animals. Moreover, the social consequences and the impact on the environment of mixing human and animal biological material are likely to be significant. However, when considering the overall balance of interests, the principle of freedom of scientific research must be taken into account.

3. Public concerns, a general lack of knowledge of the development of science in this area, and a lack of understanding of the potential consequences of mixing of human and animal biological material, generate the need for both reflection and discussion in relation to the complex ethical and legal questions arising from the creation of human-animal mixtures.

4. One particular problem in this area is the need to clarify the terminology used. This is not restricted to chimbrid terms, but includes common terms such as "human being" and "embryo", our understanding of which can be called into question by new scientific developments. Whichever definitions are employed, the terms used will be value-laden and this will have an impact on social acceptance and legal aspects etc. Furthermore, the terms that are used determine the applicability of regulatory frameworks.

5. A chimera is generally defined as a biological unit containing cells of distinct entities. A hybrid is generally understood as the result of interbreeding between two different species, i.e. an ovum from one species is fertilised by the sperm of another species. By contrast to a chimera, the cells of a hybrid all have the same genome. However, there are cases, such as somatic cell nuclear transfer cloning, in which the applicability of these definitions is problematic. In order to avoid these difficulties, our project created the word "chimbrid" as a comprehensive term to cover chimeras, hybrids and similar genetic mixtures that are not directly covered by one of the aforementioned definitions.

6. Whereas chimbrids can be either interspecies or intraspecies mixtures, our project only deals with human-animal chimbrids. Therefore, in this project the term "chimbrids" will refer only to human-animal mixtures if not otherwise specified.

7. The Chimbrids project focuses on the scientific, ethical and legal implications of the creation of and research involving human-animal mixtures. While research with chimbrids is in progress world-wide, its potential and boundaries have not yet been comprehensively analysed. National, European and international concepts and strategies concerning the ethical and legal framework of this research are still lacking to a large extent. As many scientific, ethical, philosophical and legal questions remain unsolved, the dynamic nature of the development of chimbrid research creates uncertainty on the part of decision-makers and society at large; with its interdisciplinary and international approach, the Chimbrids project wishes to contribute to a solution to the existing problems, shed light on the opportunities and risks of chimbrid research and suggest regulatory solutions in order to help decision-makers fulfill their tasks in an informed and responsible manner. In this context, a sound

understanding of the scientific procedures used for the creation of chimbrids and the specific issues involved in chimbrid research is a necessary prerequisite for the determination of the relevant ethical and legal framework.

II. Scientific overview of human-animal mixtures

The intentions of scientists and physicians in generating human-animal mixtures (chimbrids) are divergent. Some lines of enquiry, such as embryology and ontogeny of mammals, serve to answer questions in basic biology. Others have more applied goals, such as regenerative therapies or reproductive medicine.

For the purposes of studying human embryology and development, scientists transplant stem cells from humans into embryonic or adult animals. The cells can be derived from early embryos and may be pluripotent, as is the case with embryonic stem cells. Or they may come from later embryonic stages, or adults, and exhibit less developmental capacity, such as neuronal or bone marrow stem cells. Routinely, human tumour cells are transferred into immune-compromised mice to study their growth characteristics and evaluate therapeutic options.

In order to allow the use of embryonic stem cells for human regenerative therapy, some scientists have transferred the cell nuclei of patients into animal oocytes and attempted to develop pluripotent stem cell lines from the resulting reconstructed embryo: these cells should not be rejected by the patient's immune system. However, these techniques may become obsolete when therapeutic cloning becomes possible with purely human material or when the (currently promising) reports about the reprogramming of differentiated cells becomes a routine procedure.

In attempts to study the role of human genes in physiology and pathophysiology, single genes or whole chromosomes are transferred into early animal embryos and the effect of the additional gene(s) is studied in the resulting transgenic or transchromosomic animals. The same technology is employed for the production of human proteins in farm animals for pharmaceutical purposes. Such genetically altered animals may also be created to serve as donors for the transplantation of organs into human patients, a procedure called xenotransplantation.

Some techniques for creating chimbrids are applied in reproductive medicine. Human sperm quality has been tested by its ability to penetrate hamster eggs. In controversial experiments, methods for reproductive cloning are tested using animal host embryos for the transfer of human nuclei; other comparably contentious ways to mix human and animal embryos or gametes are technically feasible but are, as yet, of no scientific interest. Such techniques have, however, been performed in the past.

The possible procedures to mix human and animal material (creating chimbrids) are summarised in the table below, although not all of them are currently performed.

Methods for classifying hybrids and chimeras have been attempted by various organisations and authorities. Classification was performed based on donor and recipient considering the combinations of specific cell types, tissues and organs[2] on procedures[3] or on the resulting

[2] Scottish Council on Human Bioethics, Edinburgh, 2006
[3] Beyleveld D et al, Chimbrid Report, Mannheim, 2006

products.[4]

In order to provide an overview for ethical assessments and regulatory proposals the following table places major emphasis on procedures and resulting organisms. The table also contains information about the developmental stage and properties of donor- and recipient-organisms. This is of relevance because the listed procedures use, in many cases, biological entities recovered from persons, human foetuses or embryos in a reproductive context and are therefore subject to particular ethical evaluation and specific legal regulations.

The given compilation is within the scope of the Chimbrids project, and is restricted to interspecies animal-human and to reciprocal human-animal combinations. As an exception, recent experimental human-human combinations such as human somatic cell nuclear transfer into human oocytes are referred to only in the context of interspecies nuclear transfer experiments, which prepared the ground for experiments leading to therapeutic and (eventually) human reproductive cloning. Animal-animal combinations are not covered, although the experience gained and the results obtained with mouse models and others are essential prerequisites, and give early signals for future applications involving human entities.

The listed experimental procedures and results reflect the present "state of the art". Starting with "historical" basic and clinical research reports, the attempt was to demonstrate the development of concepts and techniques (for example, in the field of xenotransplantation). More recent experiments are included if they point to novel avenues and applications using new techniques and elements such as the derivation of embryonic stem cells from various sources, the transfer of somatic cell nuclei into enucleated oocytes and the cultivation and use of the resulting cytoplasmic hybrid embryos (microchimeras) for research and therapeutic applications.

A retrospective compilation cannot provide an overview of what will or may be done in the long run. An extrapolation of developments in the field of basic research remains questionable due to the intrinsic quality of these necessarily explorative activities. As a consequence, the table preferentially refers to published key scientific experiments in order to provide a working tool for selecting a number of relevant and exemplary case studies to be evaluated by ethical and legal experts. Examples of procedures with already established applications are given, as well as descriptions of intended potential applications, because the table should present a scientific overview for foresighted ethical assessments and proposals regulating research and applications in the area of chimeras and hybrids. More remote and rather theoretical options and applications render the task rather more difficult. We chose to qualify these topics as being of "no apparent scientific interest". It seems important to consider such theoretical experiments, as one cannot exclude the possibility that they are undertaken for other reasons and may represent the type of intentional misuse most relevant for regulatory action.

[4] Shimoda M, Chimbrid Report, Mannheim, 2006

Chimeras and Hybrids: Human-Animal mixtures (Chimbrids)

	Human-Animal				Animal-Human			
Procedure	**Donor (Source)**	**Recipient (Stage)**	**Result (Organism)**	**Application (Examples)**	**Donor (Source)**	**Recipient (Stage)**	**Result (Organism)**	**Application (Examples)**
Stem cell (SC) transplantation	Human: embryonic stem cell, adult stem cell	Animal: Blastocyst, Post-gastrulation embryo	Chimeric organism donor/recipient ratio depending on developmental stage and evolutionary relationship	Research on human development and differentiation[5]	Animal: Embryonic stem cell, Adult stem cell	Human: Blastocyst, Post-gastrulation embryo	Chimeric organism donor/recipient ratio depending on developmental stage and evolutionary relationship	No apparent scientific interest
Cell, tissue organ transplantation	Human: Cells, Tissues Organs	Animal: Embryo, Postnatal stages	Animal chimera	Studies of the human immune system[6]; oncology	Animal: Cells, Tissues, Organs	Human: Embryo, Postnatal stages	Human chimera	Xenografts for medical treatments[7] [8]
Somatic cell nuclear transfer (SCNT)	Human somatic nucleus	Enucleated animal oocyte	Human-animal cytoplasmic hybrid embryo[9]	Source of human embryonic stem cells for therapy,[10] Bioassay for reproductive cloning[11]	Animal somatic nucleus	Enucleated human oocyte	Animal-human cytoplasmic hybrid embryo	No apparent scientific interest
Chromosome transfer	Human somatic cell	Animal embryonic stem cell	Animal with human chromosome(s)	Studies of human chromosome expression[12]	Animal somatic cell	Human embryonic stem cell	Human embryonic stem cell with animal chromosome(s)	No apparent scientific interest
Gene transfer	Human cDNA library	Animal: Fertilised oocyte, Embryonic stem cell,	Animal with additional human gene(s)	Production of human proteins in animals[13] Animal models for gene and drug testing	Animal cDNA library	Human: fertilised oocyte, Embryonic stem cell,	Humans with additional animal gene(s)	No apparent scientific interest
Embryo transfer[14]	Human embryo	Animal foster mother	Parent and offspring exhibiting microchimerism	no apparent scientific interest	Animal embryo	Human foster mother	Parent and offspring exhibiting microchimerism	No apparent scientific interest
Embryo mixing[15]	Human embryo	Animal embryo	Chimera	no apparent scientific interest	id	id	id	id
Gamete fusion	Human sperm	Animal oocyte	Activated animal oocyte	Clinical fertility testing[16]; historic[17]: Human /ape hybrid generation	Animal sperm	Human oocyte	Hybrid embryo	No apparent scientific interest

[5] *Muotri et al.* (2005) Development of functional human embryonic stem cell-derived neurons in mouse brain. Proc Natl Acad Sci USA 102:18644-8; *Lee et al.* (2007) Stem cells act through multiple mechanisms to benefit mice with neurodegenerative metabolic disease. Nat Med, 13:439-447.

[6] *McCune et al.* (1988) The SCID-hu mouse: murine model for the analysis of human hematolymphoid differentiation and function." Science 241:1632-9.

[7] *Fink et al*. (2000). Porcine xenografts in Parkinson's disease and Huntington's disease patients: preliminary results. Cell Transplantation 9: 273-278.

[8] *Bailey et al.* (1985) Baboon-to-Human Cardiac Xenotransplantation in a Neonate. JAMA. 254: 3321-3329.

[9] *St. John and Lovell-Badge* (2007) Human-animal cytoplasmic hybrid embryos, mitochondria, and an energetic debate. Nature 9: 988-992.

[10] *Chen et al.* (2003) Embryonic stem cells generated by nuclear transfer of human somatic nuclei into rabbit oocytes. Cell Res 13: 251-263.

[11] *Illmensee K.* (2007) Mammalian Cloning and its Discussion on Applications in Medicine. J Reproduktionsmed Endokrinol. 1/2007: 6-16

[12] *O'Doherty et al.* (2005) An aneuploid mouse strain carrying human chromosome 21 with Down Syndrome phenotypes. Science 309: 2033-2037.

[13] *Ebert K. M. et al.* (1991) Transgenic Production of a Variant of Human Tissue-Type Plasminogen Activator in Goat Milk: Generation of Transgenic Goats and Analysis of Expression. Bio/Technology. 9: 835-838.

[14] *Nan et al.* (2007) Increased Th1/Th2 (IFN-gamma/IL-4) Cytokine mRNA Ratio of Rat Embryos in the Pregnant Mouse Uterus. J Reprod. Dev. 53:219-228.

[15] *Fehilly et al.* (1984) Interspecific chimerism between sheep and goat. Nature 307: 634-636.

[16] *Yanagimachi et al.* (1976) The use of zona-free animal ova as a test system for the assessment of the fertilizing capacity of human spermatozoa. Biol Reprod 15: 471-476.

[17] *Rossiianov* (2002) Beyond species: Il'ya Ivanov and his experiments on cross-breeding humans and anthropoid apes. *Sci Context.* 15:277-316.

III. Ethical Aspects

Chimbrids pose a special challenge for ethics (as well as legal regulation) since the majority of our traditional moral convictions, ethical principles, ethical theories and regulatory frameworks presuppose that there is a moral difference between the ways we may treat animals in comparison to human beings. In addition, research involving chimbrids is very diverse, which frequently makes it difficult to judge how realistic the research aims are, how necessary the research is, how realistic it is to expect therapeutic outcomes and what the risks involved might be.

We therefore propose to discuss the attendant ethical issues on four levels:

1. The impact of different conceptualisations of *moral status* for the chimbrids-debate.
2. Moral evaluation of the *research aims*, (possible) *risks*, *benefits, insecurities* and *scientific alternatives* of actual research involving chimbrids.
3. Animal ethics.
4. Appearance and symbolic meaning.

1. Moral status

a) Ethical theories differ widely on the features they consider to be morally relevant. We propose to distinguish four positions:

i.) Some (e.g. utilitarian) theories base the moral status of a being on the capacity of that being to feel pleasure and pain. For those theories it is not relevant *per se* to which species the being belongs. Rationality and self-consciousness are, for utilitarians, only relevant insofar as they influence the capacity to feel pain and pleasure.

ii.) Other theories (such as Kantian, contractarian, rights-theories) consider the ability of beings to *develop self-consciousness and rationality* as the basis for granting moral status. These theories primarily ask whether or not it is likely that the research object can develop those capacities. However, for

(1) some ethical positions within this camp, the mere fact that an entity has the potential to develop into a self-conscious person grants it moral status; whereas

(2) others see that potential not as a reason for granting a moral status at all. For the former group, where the chimbrids involved have the potential to develop self-consciousness and rationality, research on chimbrids before this potential is realised is intrinsically problematic, whereas for the latter group it is not.

In either case, however, species-membership as such is not a sufficient reason for granting moral status.

In the camp of those who see potentiality as a reason to grant a moral status we can distinguish further between those

(1.1) who see the potential as sufficient for granting *full* moral status,
(1.2) who see the potential as sufficient to grant *some* moral status that is significantly different in comparison to the status of persons,
(1.3) who see the end of pre-embryonic stage (14 days) as necessary to grant some or full moral status and
(1.4) gradualistic positions hold that the actual capacity of an embryo (e.g. brain

activity, sensitivity, capacity to live outside the mother, birth) is crucial for its moral status, and consider that from that capacity follows the status as a person. It has to be mentioned that there are some gradualistic positions that only refer to actual capacities for granting a moral status; however, most of the gradualistic positions that are under discussion (e.g. those that make a distinction in moral status after day 14, or after the development of some brain functions) require assumptions from some kind of potentiality argument.

According to position 1.2-1.4, protection during the phases before reaching full moral status is morally required, but it can (to different degrees) be outweighed by other important interests (e.g. the health of persons). After having reached the status of a person, there is no more possibility of outweighing their existence by other interests.

iii.) Some positions hold that *membership of the biological species homo sapiens* (usually every living human being as well as every entity with the (potential) capacity to become a living human being) is a sufficient reason for granting moral status. This position, however, is difficult to defend. It is not clear why the membership of one biological species should be a reason for granting a moral status. One would have to hold some kind of decisionistic theory (e.g. a divine command theory) to defend this claim, but such positions are highly arbitrary.

iv.) Some theories grant full moral status to persons but grant an *intrinsic value* to sensitive beings (animals) as well. This would mean that animals have, *prima facie*, some kind of value that makes it necessary to defend all kinds of behaviour that may harm this value. The relationship between having an 'intrinsic value' and having 'dignity' is, however, unclear and the defence of this status is in need of justification.

b) Implications for Chimbrids

The above considerations (concerning the relevant features that determine moral status) form the background for the debates about the production of chimeric embryos.

i.) For those ethical positions (a.i./a.ii.2) that give moral status only to entities that *actually* have interests, needs, rationality etc, it does not matter whether or not the embryo is animal or human: if it does not feel pain, or have interests, or lacks the capacity of reasoning, it need not be protected. Only if the embryo were implanted and brought to term would the consequences of the life conditions of the future person be morally relevant. It is debatable how to deal with cases where it is not possible to predict whether or not the entity will have the aforementioned capacities: this may be a reason enough for precaution.

ii.) For positions that evaluate the moral status of embryos as dependant on their potential to develop into a being that has morally relevant features, their status would depend, respectively, on the question of whether or not the chimbrid embryo is able to develop into a human being or a being with morally relevant characteristics. In many cases, however, it is not possible to prove this. For position a.ii.1.1, having the potential would be sufficient to make the whole experiment immoral. For position a.ii.1.2, it would be necessary to weigh the worth of the embryo against other goods. For those ethical positions that make a fundamental distinction between pre-embryos and embryos, or hold a gradualistic position (a.ii.1.3/4), experiments would be acceptable until this stage is reached.

iii.) For those positions that give moral status to human embryos from conception onwards (a.iii), it would make a significant difference whether or not the embryo is a human or an animal embryo. If the embryo is considered "human", experiments are not allowed at all. The

crucial question concerning chimbrids would then be: To which species do they belong?

iv.) Theories that accord *intrinsic value to animals* (a.iv.) generally assume that research with chimbrids is *prima facie* in need of justification. However, many of them would assume that the intrinsic value of animals may be weighed against high moral goods such as the expectation of valuable therapeutic outcomes for humans.

2. Human research ethics

There are six concrete moral considerations in the area of research ethics that are relevant to the Chimbrids project, although very different approaches will be involved in weighing them.

These considerations are:

1. Freedom of research;
2. Risks or costs to persons;
3. Social or environmental risks or costs: does it cover injuries to social values, the human species or future generations?;
4. Type and importance of the benefits of the research;
5. Probability of success; and
6. Issues of informed consent.

Different approaches will, to varying degrees, require a moral justification for all these considerations. Besides questions related to the use of embryos, in this context it makes a difference whether or not the research is limited to the laboratory or whether embryo transfer is planned. The lack of knowledge and the unknown consequences relating to the implantation of a chimeric embryo into a woman is a fundamental moral concern.

For the moral evaluation of *in vitro* research, it is relevant whether to evaluate the realistic possibilities of therapeutic outcomes and whether or not there are alternative means to achieve the research goals. If some chimbrids experiments are only scientifically relevant in the light of certain therapeutic options, the moral evaluation of those options would be of importance. That is relevant for all experiments that are justified in the light of further development of xenotransplantation. Justification of such experiments would depend on an evaluation of the development of therapeutic options in a broader sense.

3. Animal ethics

As with research ethics, there are six moral considerations for animal ethics:

1. Pain and suffering;
2. Substitutability/replacement;
3. Animal quality of life;
4. Treatment of animals appropriate to their species;
5. Species integrity; and
6. Debasement or adulteration of life.

Although the first four concerns are raised by conventional animal research, they may be intensified by projects involving chimbrids. For utilitarian positions or intrinsic-value-positions, the justification for using animals in such a way may be a concern. The 'replacement' of animal experiments is one of the standard criteria in animal ethics, and they may raise questions here, but they are not specific to chimbrids experiments.

Those positions that hold the view that non-human species should be granted some moral status may consider that chimbrids experiments are morally problematic. According to most of them, however, the suffering and quality of life of animals can be weighed against the benefits the experiments can produce. Some positions, however, see moral relevance only in the impact they may have on "wild" species. For them, the experiments would not be intrinsically morally problematic, but a release of chimbrids into the wild would have to be justified.

There are more specific problems where chimbrid experiments are performed with "higher" animals; primates, especially, are a concern as they often develop and exhibit features similar to humans. Most ethical positions would consider a general prohibition of experiments involving primates to be appropriate.

4. Appearance and Symbolic Meaning

Beyond the scope of risks/benefit analysis, there are some morally relevant issues that are more difficult to weigh, such as the symbolic aspects involved in chimeric experiments.

The incorporation of animal material into humans may lead to alterations that affect appearance, behaviour, emotions etc. Also, the incorporation of human material into animals may also lead to animals developing similar capacities to persons.

This would raise serious moral objections: a person possessing features that he would experience as non-human, and would be deemed by others to be non-human, could cause serious identity problems. Due to the respect we owe to persons, it is morally problematic to perform experiments that could lead to such identity problems.

Furthermore, it is important for humans to live a life (and live in a world of) symbolic order that makes it possible to recognise humans as humans and animals as animals. In general, agents are able to spontaneously perceive another person as a person, and are able to act accordingly. This is important for our ability to develop a culture guided by moral recognition; such an ability would be severely hindered if chimbrid experiments produced humans with animal appearances, behaviour etc.

Even if there are no "technical" problems, where persons are born with the appearance of an animal, it is morally problematic to perform experiments that *could* lead to such situations. These issues present important moral matters for different kinds of ethical theories.

5. Plurality of ethical theories and legal regulations

For further recommendations, it is necessary to take more of a position on the plurality of ethical approaches. It would, however, in a report written by a variety of researchers, be arbitrary to just 'choose' one ethical approach. Nevertheless, it is necessary to discuss the presuppositions necessary for the recommendations.

It seems quite clear that no chimbrids experiments that use human embryos are morally permissible if one holds the position that either the potential for developing into a human person (a, ii. 1.1.) or the membership in the human species (a.iii.) is sufficient for granting full moral status.

It is also obvious that for positions that grant moral status only to beings that *actually* have morally relevant features (a. i., a, ii, 2 and a, ii, 1.3 and 4) there would be no need for regulations at all as long as these features are not realised.

For the last positions, only giving birth would be morally problematic (where there are reasons to assume that the being that is born would suffer from their situation), or if there were reasons to assume that their development as rational persons would be affected. Experiments involving beings before this position is reached would, as such, be morally permissible and no regulation would be needed whatsoever. Only if the experiments have fundamental risks for other people would they be a concern.

For the recommendations, the following presuppositions are made. All experiments with human embryos are in need of justification (meaning that embryos have some moral status). For the evaluation of those experiments it is, however, difficult to judge whether such an entity is a human or not. This demonstrates a significant problem in dealing with terms and notions such as 'humans', 'animals', 'persons' etc.

The term 'human' is on the one side used as a *biological term*: i.e. when we speak of 'human material' we mean biological material coming from a human being. However, if we speak of 'human dignity' or 'human rights' we are using an *evaluative term* that grants a specific status to a being, with specific features that are typically seen as being possessed by members of the human species. In this respect, we mean: a human is someone to whom we owe respect.

For the recommendations, it is important to distinguish between this 'biological term' and the 'evaluative term'. From the moral evaluation, we have seen that for only one specific moral position is species membership directly relevant, meaning the biological and the evaluative terms have (for this position) identical meanings. For all other positions there is tension between the two terms.

For chimbrids, there is a problem with identifying a being as "human" or "animal" in a biological sense. We can either focus on the *biological sources* used for the creation, in which case we see that material from humans and animals are involved. Or we start with the *features* of the *product*, the chimbrid entity must be evaluated in the light of an ethical theory.

First of all, it depends on whether our ascription refers to the *sources* that are used for the experiments or to the *product* as the result of the experiments. But even more important is the question concerning the kind of criteria that we could use to determine the legal and moral status of this entity as "human" or "animal"? All regulatory frameworks are, however, essentially presupposing a dichotomy between "animal" and "human"; there are different legal regulations for humans and animals. This means, in general, the *evaluative term* "human" (with all the moral and legal implications attached to it) is ascribed to entities that are identified by *biological* characteristics. Since the biological identification of these entities is, at least to some extent, difficult (if not impossible), the question is: "what does the evaluative term "human", in terms of owing respect, refer to"? Chimbrids experiments therefore pose an obvious and fundamental problem in respect to the relationship between biological and evaluative notions of "human" and "animal".

It is necessary to reflect on what the more general implications of all kinds of regulation are when considering the legal regulation and moral debate surrounding chimbrids. One can, to some extent, make smaller adaptations to the existing legal frameworks, but there is a danger

of the coherency of the law being undermined if the biological and evaluative notions of "human" are treated as interchangeable. This problem goes far beyond the scope of the regulation of chimbrid experiments.

It has only briefly been mentioned that, for our conclusions, the highly disputed relationship between law and ethics is also important. It seems quite clear that not all kinds of moral considerations can be directly implanted into legal regulations: not everything that is morally problematic must directly be prohibited by law, and not everything that is legally permitted is morally unproblematic etc. Nevertheless, the legal order in modern democratic states presupposes that there fundamental starting points that are morally acceptable. For example, the moral codification of human dignity, individual rights and the intrinsic value of the animal all represent the legal order directly referring to fundamentally important moral principles or values. It is therefore a necessary part of the discourse concerning the legitimacy of the legal order to explain and justify their fundamental starting points. Therefore, while the ethical debate is of central importance to the legal regulation, a simple model of the law as a straightforward codification of morality should be avoided.

IV. Legal Aspects

1. The regulatory needs and challenges

a) Interests and values concerned

Chimbrids related activities may take place in many different forms and for many different purposes. It is clear that they may in individual cases concern a wide spectrum of interests and values that are generally considered to deserve judicial protection. These include freedom of research and the improvement of scientific knowledge, protection of public health and safety, protection of the person (autonomy, privacy/personal integrity etc), human dignity and the genetic identity and heritage of future human generations. Other relevant interests to consider are related to animal welfare, species integrity, environmental sustainability and biodiversity. The appropriate balancing of such important and sometimes conflicting interests, in a manner that can satisfy basic prerequisites for the rule of law, would by necessity require the involvement of some kind of legal regulation. To the extent that pre-existing legislation does not satisfactorily cover the chimbrids area, new regulation is needed.

The issues that need to be addressed include both the permissibility of creating different types of chimbrids on different levels (cellular to living creature) and the appropriate standards for treatment and protection of the interspecies organisms and individuals that are actually created (i.e. when to use animal standards, human standards or even a *sui generis* standard).

b) Some of the challenges

The determination of appropriate criteria for the distinction between the legal concepts "animal" and "human" constitutes the principal challenge in the regulation of chimbrids. Such criteria could be based on the source of the biological materials used to create the chimbrid, the resulting biological or genetic proportions, as well as specific qualifying properties or characteristics that can be observed in the chimbrid created. To what extent should different types of chimbrid creations be placed within the regulatory framework applicable to humans or that which is applicable to animals? Or should new legal standards be created for some chimbrid categories? To achieve well-balanced regulation of this complex issue, which may also have implications for fundamental perceptions of our identity as human beings, must be recognised as a demanding task. It could be argued that we should not put ourselves in a position where uncertainty may arise as to whether the chimbrids that are produced should be defined as human beings or animals.

Another difficulty, although a more general one, arising in many regulatory projects dealing with rapidly developing areas, concerns the lack of knowledge regarding both potential future value of, and the risks involved in, chimbrids activities. The necessary balancing of interests will therefore (to some extent) amount to a balancing of two unknowns, making it virtually impossible to reach any well-founded conclusions on proportionality. Rapid development also calls for flexibility, which could mean that the legislation should be subject to regular or even continuous revision, based on step-by-step consensus on scientific knowledge and sufficiently informed public debate.

Since the field of biomedicine is highly internationalised, the consequences of scientific tourism (i.e. researchers avoiding restrictions by moving their activities to more liberal countries) need also to be observed. Even so, it would prove very difficult, if not impossible, to reach agreement on a uniform chimbrids regulation acceptable to all countries concerned. In matters so influenced by the cultural and religious pluralism of values and norms, any more widespread consensus on all chimbrids related issues would seem highly improbable within the foreseeable future, should it be considered desirable. The diversity of national legal approaches also points to, and is influenced by, the pluralism of legal traditions; while this issue is of less fundamental importance, it may still prove problematic in certain areas.

Terminological ambiguity has already rendered the task of determining the extent of both agreement and disagreement in this area problematic, since basic concepts such as "embryo", "pre-embryo", "chimera" and "genetically modified organism" are by no means interpreted or used in a uniform way. This problem, however, is one that can be addressed and handled. Even without any normative consensus between different jurisdictions, it should be possible to clarify the relevant definitions in order to avoid misunderstandings and facilitate the identification of relevant legal differences.

2. Regulatory tools and strategies applied

a) Public international law

At present, no binding documents in public international law explicitly regulate chimbrids. The areas of assisted human reproduction and scientific research involving humans, including embryo protection, are subject to some international regulation (primarily European/regional), as are the environmental aspects on genetically modified organisms and issues related to animal welfare. In principle, these regulatory documents focus either on humans or on animals and do not specifically address human-animal mixtures.

There are also a numerous non-binding international declarations, guidelines and other soft-law documents that deal with scientific research, genetics, human reproduction etc, but for the most part, these do not address chimbrids issues either. Xenotransplantation is, however, an exception: several international and European policy documents have been produced on this area.

b) EU regulation

Explicit chimbrids legislation is also lacking at the EU level. This is not very surprising, however, since the regulatory competency of the EU is restricted in many ways and in principle does not cover areas such as national health care policies (including assisted reproduction) or ethical aspects of scientific research, for example the use of human embryos for research purposes. Nevertheless, chimbrids related activities may still be covered by more general EU legislation concerning, for example, clinical trials, medicinal products, public health, protection of the environment, animal welfare etc.

c) Domestic law

From the country reports and comparative reports produced within the project, it is clear that the development and contents of national law in the area of chimbrids vary considerably.

Looking at the countries that do have chimbrids specific legislation, quite a few of them would seem to have applied a step-by-step or ad hoc approach, resulting in sometimes detailed but not necessarily comprehensive regulation. In others, e.g. Japan, a more systematic approach can be seen. Lack of chimbrids specific regulation, on the other hand, may also in some cases be attributed to deliberate strategies, based on a wait-and-see approach or no-need/non-exceptionalistic policies. Nevertheless, it is clear that to some extent, the omission to address chimbrids issues is also due to ignorance or lack of foresight on the part of policy-makers.

The existing chimbrids specific domestic regulation can be divided into those addressing xenotransplantation and those related to other ways of creating chimbrids, e.g. by the involvement of gametes. The crucial definition of human vs. animal has not been legally regulated in any of the participating countries, nor the standards according to which a chimbrid creation should be treated.

Legislation on xenotransplantation seems to exist only in France and Switzerland. A number of countries have investigated the matter and in several there are formally non-binding guidelines, for example in the UK, the US and Israel, whereas others have reached no conclusive decision (e.g. Sweden). Accordingly, in most countries xenotransplantation is only covered by general legislation concerning, for example, patient safety and public health, transplantation, scientific research involving humans, animal welfare or genetically modified organisms. In general, the attitude towards xenotransplantation must be considered to be cautious rather than liberal, primarily due to unknown risks related to public health.

Several countries have legislation that to some extent explicitly addresses the creation of chimbrids by direct or indirect use of gametes, for example Canada, Germany, Japan, Spain, Switzerland, and the UK. In China, governmental guidelines exist, whereas no explicit regulation at all has been found in Austria, the Czech Republic, France, Sweden, Israel or the US. In these countries, such activities may still be covered by general, more or less detailed, rules on research involving human gametes or embryos, as well as animal welfare legislation etc.

Many countries thus have protective legislation on the use of human embryos and there are also domestic laws prohibiting or restricting the creation of hereditary genetic modification in future human generations. The approach in these regulations is in some cases very restrictive (for example in Germany) whereas in others more liberal (such as the UK and Sweden).

However, the definitions of fundamental concepts such as “human”, “fertilised ovum”, “embryo” or “functional embryo” are not always clear, and may still be decisive as to whether or not a certain procedure is lawful. The lawfulness of mixing human and animal gametes for reproductive purposes may also depend on whether the gametes of human origin are oocytes or sperm.

Although certain chimbrids related activities may be explicitly prohibited in some countries, the most common regulatory approach would seem to involve framework legislation with complementing procedural rules, where different agencies are authorised to make decisions

based on case-by-case assessment. The countries represented in the project show a large diversity of such decisions-making bodies entrusted with – in some cases considerable – discretionary powers to decide on chimbrids related matters. They thus range from the national, ministerial and local level, and may be appointed to address very specific issues, such as the use of human embryos, or far more general areas of research or environmental issues. Although in most countries, chimbrids research is subject to prior review by several different agencies, protecting interests related to humans, the environment or animals respectively, the decision-making bodies do not seem to be equipped to address and balance all the relevant interests.

3. Concluding remarks

a) Chimbrids activities constitute an area of biomedicine where fundamental interests are at stake and where our traditional perception of human identity is challenged. In such a field of research, it is of the utmost importance that any development takes place in openness, in order to increase general knowledge and awareness of the potential benefits and risks involved, and to stimulate public debate. Appropriate public discussion and consultation is also a requirement laid down in Article 28 of the Council of Europe Convention on Human Rights and Biomedicine, with regard to fundamental questions raised by the development of biology and medicine.

b) Although there are obvious obstacles to any comprehensive international consensus in the field of chimbrids related activities, the discussion of chimbrids issues should be brought to the international arena and the possibility of international action assessed. Since the international regulatory tools available range from binding international law to documents serving only as sources of inspiration, international organisations may also play an important role in education and public debate. The Council of Europe Recommendation Rec (2003) 10 on xenotransplantation is an example of such a non-binding document that could serve as a model for regulation. Due to the partly voluntary character of public international law, the varying traditions of implementation in domestic law and the limited access to effective international sanctions, however, the responsibility to offer appropriate judicial protection in the area of chimbrids will obviously be found at the national level.

c) The European Union has limited competency and legitimacy to regulate in the chimbrids area, with the exception of issues related to e.g. the fundamental principle of free movement, consumer safety and the protection of public health. For example, the upcoming Directive on advanced therapies deals with chimbrids products for human application, and it is possible that cross-border public health issues could be raised by xenotransplantation. Nevertheless, the legal regulation of chimbrids research cannot primarily be seen as a task for the EU. However, this does not exclude the possibility that the EU could use other forms of governance to influence research development in this area, for example by way of funding requirements.

d) At the national level, it may be appropriate to prohibit certain chimbrids related activities, with or without the possibility of exemptions (by way of special authorisation, in exceptional cases, for certain purposes etc). Detailed regulation may be needed with regard to issues involving particular risks (for example human reproduction, xenotransplantation and medicinal products). In other areas, it may be considered sufficient to make the activities subject to certain restrictions or conditions (notification, procedural assessment, approval or licensing, or substantive conditions such as a specified purpose). In order to provide sufficient flexibility, the regulation should not focus on certain techniques or methods, but primarily on results and risks to be achieved or avoided. It would seem an appropriate minimum

requirement, however, that all chimbrids related research is subjected to some kind of prior review by an independent body qualified to address both general and chimbrids specific considerations.

Regulation primarily focussed on procedures rather than fixed material rules will clearly provide more flexibility. Although this may be considered an advantage, a very generous delegation of powers could endanger democratic values in a way that is particularly problematic in areas where important interests may be at risk. Too wide a margin of appreciation may result in poor predictability and thus conflict with the rule of law. It is also more difficult to achieve uniform application if case-by-case assessment takes place at regional or even local level. This means that the discretionary powers left to lower level decision-making bodies should be very carefully considered and not only restricted by appropriate legislative frameworks, but also complemented by official guidelines etc.

With flexible rules, the qualifications and legitimacy of the bodies making decisions in individual cases thus become increasingly important, and the need for public oversight and openness in the decision-making procedure, as well as the possibility of appeal. Overlapping competency between different decision-making bodies may result in rivalry or quite the opposite, leaving so-called orphan issues.

A regulatory system must also provide tools for monitoring and controlling the development in chimbrids research and applications. Such tools traditionally include, for example, the appointment of supervisory agencies, requirements for notification, follow-up, reporting of adverse events etc, as well as appropriate legal sanctions to be applied in case of unlawful activities.

V. Recommendations

1. Chimbrids research should only be conducted following careful consideration of its scientific merit, human research ethics, animal ethics, legal aspects and societal and environmental implications.

2. States should initiate public discussion and conduct public consultations regarding the complex ethical and societal issues raised by chimbrids research and application. States should also examine their existing regulations to evaluate the adequacy of current law or guidelines. States should then assess whether there is a need for further legal regulation.

3. Because of the international dimension of chimbrids research and application in biomedicine and biotechnology, there should be an assessment of the need and possibilities for action at the international level, including regulation. In particular, the Council of Europe and the European Union should consider appropriate methods of governance within their respective competencies.

4. Members of the scientific community should actively engage in public discourse concerning their work. They should also organise a discussion amongst themselves, on an international level, with regard to chimbrids research concerning the aims, motivations and implications of their work, including ethical and societal ramifications.

5. Research projects that aim to create chimbrids should be subject to an independent examination by an interdisciplinary body. Careful attention ought to be given to the composition of these review bodies to ensure that they are competent to assess the project

based on consideration of its scientific merit, human research ethics, animal ethics, legal aspects and societal and environmental implications. States should determine to what extent this review should be legally required or binding, and whether exemptions might be justified for specific subcategories of chimbrids research on the grounds that they present no significant issues in terms of the considerations mentioned above.

6. When considering chimbrids research, there must be a systematic examination of the way in which the terms 'animal' and 'human' are used in regulatory frameworks. There is an ambiguity in these terms. For example, on the one hand, "being human" is used to describe morally relevant characteristics or other evaluative aspects (a normative term), while on the other, this term is used to describe the biological origin of specific material (a biological term). The distinction between these uses must be transparent and unequivocal.

7. Assessment of chimbrids experiments should take into account the origin of the biological material, the procedure as well as the attributes of the resulting entity. The characteristic ethical issues raised by chimbrids research concerns the nature of the entity resulting from the experiment.

8. The ethical issues surrounding the incorporation of animal biological material into an existing human organism depend on the degree to which alteration might have effects on features of the existing or future person concerned, insofar that they are typically considered to be human (appearance, behaviour, cognition, intellect, emotion, senses, abilities etc). Likewise, the ethical issues surrounding the incorporation of human biological material into an existing animal organism depends on the degree of possible "humanisation" of the existing or future animal; the greater the probability of "humanisation" of animals and "animalisation" of humans, the stronger the need for restrictions. If the relevant knowledge is not available that would be a reason for exercising precaution. As the humanisation of animals or the animalisation of humans is problematic, so the creation of entities that will express such effects must also be governed by these principles. Although there are certain cases in which a prohibition is required, circumstances can be imagined where such a prohibition has to be reconsidered and regulatory frameworks have to provide mechanisms for reconsideration and/or exceptions.

9. With regard to animal-into-human-xenotransplantation, the Council of Europe Recommendations on xenotransplantation should be followed.

10. Whenever chimbrids create risks similar to those involved in xenotransplantation, equivalent safeguards should be applied.

11. Chimbrids created for and/or used in a reproductive context raise additional issues compared to other uses; this should be given appropriate consideration.

12. Because of the gravity of the ethical and legal issues involved in chimbrids research when embryonic stages of humans are involved, such projects, whenever permitted, should be subjected to legally required oversight.

13. Projects in which the incorporation of animal material into human embryos, foetuses or post-natal beings is likely to affect the genome of descendants should be prohibited. If scientific evidence becomes available that demonstrates that the risks are predictable and if the risks are ethically justifiable, the prohibition should be reconsidered.

14. Careful monitoring is required for projects in which the incorporation of human material into animal embryos, foetuses or post-natal beings is likely to affect the animal's germline because of the potential risks to, for example, human health and the environment, and the specific risk of a possible development of human gametes in an animal.

15. Accordingly, given the principles laid down in recommendation 8 the following cases need special consideration:

a) incorporation of human pluripotent cells into an animal blastocyst or into its preliminary embryonic stages,

b) incorporation of animal pluripotent cells into a human blastocyst or into its preliminary embryonic stages,

c) mixing human and animal gametes,

d) mixing of animal and human totipotent cells/embryos.

The application of the principles laid down in recommendation 8 suggests that the subsequent transfer to a foster mother (human or animal) or equivalent means of gestation should be prohibited.

16. The insertion of a human cell nucleus into an enucleated animal egg, followed by the transfer to a foster mother (human or animal) or equivalent means of gestation is a type of reproductive cloning and therefore should be prohibited.

17. The insertion of an animal cell nucleus into an enucleated human egg should be prohibited if followed by the transfer to a foster mother.

18. The transfer of a human embryo into an animal should be prohibited.

19. The transfer of an animal embryo into a woman should be prohibited.