

## Authority Paper

<b>Committee:</b>	Authority Meeting
<b>Meeting Date:</b>	5 <sup>th</sup> September 2007
<b>Agenda Item:</b>	8
<b>Paper Number:</b>	HFEA (05/09/07) 396
<b>Paper Title:</b>	Hybrids and Chimeras: Findings of the Consultation
<b>Author:</b>	Helen Coath, Policy Manager
<b>For Information or Decision?</b>	Decision
<b>Resource Implications:</b>	The Hybrids Review has significant resource (financial and staff) implications and is an addition to the Business Plan.
<b>Communication:</b>	A Statement detailing the Authority's decision will be issued following the meeting. In addition, a report detailing the findings of the consultation will be published in the autumn and sent to stakeholders and respondents.
<b>Organisational Risk:</b>	High – The consultation process is likely to be scrutinised by many stakeholders.
<b>Recommendation to the Committee:</b>	Members are invited to consider the recommendations made at section 8 of the paper.
<b>Evaluation:</b>	The consultation will be evaluated independently by Diane Warburton from Shared Practice.

### 1. Introduction

- 1.1. In November 2006, the Human Fertilisation and Embryology Authority (the Authority) received two research licence applications to derive stem cells from embryos created by Somatic Cell Nuclear Transfer (cloning) using animal eggs.
- 1.2. At its meeting on 10 January 2006, the Authority concluded that in the light of current scientific opinion it believes that the regulation of research using human-animal embryos is probably within its scope. In addition the Authority decided that a full public consultation should be held on the ethical and social implications of creating such entities.
- 1.3. The Government is currently considering its policy on human-animal embryos in the light of the comments of the Joint Committee on the Human Tissue and Embryos (Draft) Bill. A summary of Government and Parliamentary comment on this issue can be found at Appendix A, along with a chronology of decisions taken to date.
- 1.4. The aim of the consultation exercise has been to examine the issues arising from the creation of human-animal embryos. One aspect of this has been the exploration of the social and ethical issues, the other being the examination of the scientific background. The consultation ran for three months, from 26 April to 20 July 2007.
- 1.5. Further evidence (including legal advice and scientific opinion) has also been gathered to inform the Authority's decision on whether human-animal embryos fall under the regulatory remit of the HFEA. This information is presented in the confidential part of the Authority meeting.

- 1.6. The findings of the consultation are presented in this paper under the themes which emerged through the analysis of responses. This illustrates the concerns that people have and gives an insight into how and where people draw the limits they do.
- 1.7. In order to arrive at a decision, the Authority may find it useful to consider the information presented in this paper alongside the decision tree outlined below. The purpose of this decision tree is to assist the Authority in looking at whether research of this kind generally is desirable and necessary. This process has no bearing on the decisions regarding individual licence applications which will be decided on their own merits.

**Does the HFEA have the legal remit to license research involving the creation of human-animal embryos?**



**Is the research desirable?**

Is there evidence that:

- there are important benefits to be gained by this research?
- the scientific community and the public recognise the potential benefits of the research?



**Is the research necessary?**

Is there evidence that:

- there is scientific information to suggest the research is necessary?
- the balance of ethical concerns supports the need for this research?
- there are no alternatives to pursuing research of this kind, which have the potential to achieve the same benefits?

## **2. Scientific context**

### *History of animal-human constructs in research*

- 2.1. The mixing of human and animal genetic material has a long history in science and has been used in a number of different ways to greatly progress medical research. The fusion of human and animal cells (to create somatic cell hybrids) is extensively used in research and was a technique first used in 1970s/80s in the mapping of the human genome and to investigate the interactions between the nuclear and mitochondrial genomes.
- 2.2. The HFEA has previously licensed the creation of true hybrids, with hamster eggs and human sperm, as a diagnostic test for the quality of human sperm. However, the Act prohibits any such embryos from developing further than the two cell stage.
- 2.3. The creation of transgenic animals, in which a human gene is introduced into the germline of an animal and therefore transmitted to all cells in the offspring, is a long

established technique used for production of pharmaceutical products and as a model for human disease. The production of growth hormone in the serum of transgenic mice in 1982 was the first example of the production of a human therapeutic protein from an animal. The introduction of gene sequences into mice has allowed scientists to identify and understand the role of particular genes in a large number of diseases e.g. mouse strain with the gene for Alzheimer's disease. Further examples are outlined in section 1.1 of Appendix B.

- 2.4. Animal chimeras, which are created by the transfer of human cells to animal embryos (or at later stages of development), have proven to be a useful tool to test for the pluripotency of human stem cells.
- 2.5. Scientists have been creating cytoplasmic hybrid embryos, of various animal species, for over a century. This technique has been used to investigate interactions between nuclear mitochondrial genomes and to attempt to clone endangered species. Details of the various types of cytoplasmic hybrids which have been created, and the stages of development which they reached, are outlined in section 1.2 of Appendix B.

#### *Why scientists propose to create interspecies cytoplasmic hybrids*

- 2.6. The creation of embryos using the technique of somatic cell nuclear transfer (SCNT), and development of these embryos to blastocyst stage will, in theory, allow the production of embryonic stem cells which are genetically related to the donor cell. This technique holds the key to potentially significant advances in medicine as it could be used to produce disease specific embryonic stem (ES) cell lines in order to model diseases and screening for drug therapies. Also, ES cells produced in this way could be differentiated into most cell types and in theory used as a source of patient specific cells to replace damaged tissue (the concept known as therapeutic cloning). There is already evidence that human ES cells, derived from IVF embryos, have the potential to develop into a vast array of cell types (see Appendix B).
- 2.7. It has also been suggested that embryos created in this way could be used to investigate the mechanism used to reprogram DNA to a pluripotent embryonic state and this knowledge could potentially be used to create methods to produce stem cells from somatic cells (therefore avoiding the use of human eggs and embryos). In addition as cytoplasmic hybrids will contain animal derived, and possibly some human derived mitochondria, they could be a useful tool to study mitochondrial disease and the relationship between the mitochondria and the nucleus.
- 2.8. However, the technique of SCNT to produce ES cells still needs investigating as, although there has been success in animals (see section 2 of Appendix B), it has not been proven to work with human eggs. To date there is only one example of this technique being used to create a human embryo, which developed to blastocyst stage but did not lead to the derivation of stem cells.
- 2.9. The availability of human eggs and embryos is a major limiting factor for investigating and utilising this technique in humans. Therefore scientists have suggested that one alternative is to use eggs from another species which are accessible in abundance. There has already been a report, from China, of pluripotent ES cell lines, with many properties of conventional human ES cells, being derived from human-rabbit cytoplasmic hybrid embryos (see section 1.2 of Appendix B).

### **3. International perspective**

- 3.1. Most countries have not formed specific legislation to cover the creation of human-animal hybrid embryos. Countries that already prohibit the creation of human embryos

for research, including many in Europe, may not feel the need to review their legislation. Some countries with more permissive policies, such as China, Japan and South Korea, already allow the creation of embryos for research through SCNT. The majority of these do not specifically prohibit human-animal embryos, which is why studies that have created cytoplasmic hybrid embryos have been able to go ahead in China.

- 3.2. To date only Australia, Canada and the USA have passed legislation on human-animal embryos. Australia allows embryos to be created for research but the Prohibition of Human Cloning for Reproduction and the Regulation of Human Embryo Research Amendment Act 2006 prohibits creating human-nonhuman chimeric and hybrid embryos. The only exception is that researchers can apply for a licence to create a hybrid embryo for the purpose of testing human sperm quality. The Canadian Assisted Human Reproduction Act (2004) prohibits the creation of human chimera embryos. In addition the Canadian Institutes of Health Research (CIHR) and the Tri-Council Policy Statement (TCPS), which covers Canadian stem cell research, prohibits the creation of human-animal hybrid embryos. Currently in the USA, federal funds can only be used for human ES cell research using specified pre-existing stem cell lines and no federal funds can be used to create new human ES cell lines. Specifically, the USA Draft Human Chimera Prohibition Act of 2005 (S.1373) prohibits creating or attempting to create a human chimera. In this draft legislation, some human-nonhuman hybrids would come under the definition of a chimera.
- 3.3. Appendix C gives further information on the legislation in Australia, Canada and the US, and details the general policies on human embryo research of other countries.

#### **4. Consultation: the approach taken**

- 4.1. The consultation was structured in two distinct parts. The first being a consultation document and public dialogue work, designed to gain an insight into the views of members of the public. The second being a scientific consultation and literature review, intended to build a picture of the scientific context to the consultation.
- 4.2. At its widest point, the consultation has sought the views of members of the public through an opinion poll. This provides an indication of the views of the UK population by the sampling of a representative group. The deliberative work helps to interpret the findings of the opinion poll, focusing on how people's views change and develop when introduced to different information. The written consultation and the public meeting provide an insight into those with a specific interest in the issues, however as the participants were self-selecting the findings from these strands of the consultation are not necessarily representative.
- 4.3. The consultation provided a flavour of public opinion, from which it has been possible to identify key themes. This helped to categorise some of the areas of concern and gauge the levels of acceptability for creating human-animal embryos for the purpose of research. In carrying out the consultation, efforts were made to ensure that a representative group of the public was engaged and their voices heard.
- 4.4. To ensure the consultation was effective in gauging public opinion and attitudes, it was undertaken with the support of Sciencewise, a programme run by the Office of Science and Innovation (part of the Department for Business, Enterprise and Regulatory Reform) which helps policy maker's commission and carry out public dialogue activities. Sciencewise provided the HFEA with a grant of £60,000 and helped to ensure that the consultation was run in line with the Government's Guiding Principles for Public Dialogue on Science and Technology.

## *Consultation document*

- 4.5. As a basis for the consultation, the HFEA wrote a consultation document which explained the science involved in creating different types of human-animal embryos for research. This document also explained some of the social and ethical arguments for and against the research and great care was taken to ensure the document was accessible to all audiences. The following questions were posed in the document, with responses gathered via an online questionnaire:
- a) The following types of embryo research are legally permitted and licensed in the UK. Which of them in your view are acceptable?
    - Research using human embryos donated by IVF patients
    - Research using human embryos created specifically for research from donated eggs and sperm
    - Research using cloned embryos created specifically for research through cell nuclear replacement (CNR)
    - No research using human embryos is acceptable
    - Not sure/undecided
  - b) Do you think that the HFEA should issue licences to allow research using cytoplasmic hybrid embryos?
  - c) Do you think that the law should in future permit the creation of true hybrid embryos for licensed research purposes?
  - d) Do you think that the HFEA should in future issue licences to allow research using human chimera embryos?
  - e) If you have answered yes to questions 2 to 4, what limits do you think should be placed upon human embryos research?
- 4.6. Respondents to the written consultation included both organisations and individuals. Of the 810 that responded via the online questionnaire, 74 (9%) responded on behalf of an organisation and 736 (91%) responded as an individual representing their own opinion. The findings from the written consultation can be found at Appendix D.

## *Public Dialogue: Deliberative work*

- 4.7. The HFEA commissioned Opinion Leader (a research based consultancy) to undertake a public dialogue on the issues raised in the consultation document. There were three distinct strands to the public dialogue; deliberative work, an opinion poll, and a public meeting. The development of these strands was assisted by a Stakeholder Advisory Group, who advised and commented on the plans for this work and the development of materials to be used with members of the public. Advisory Group members represented a range of organisations that have a special interest in stem cell research.
- 4.8. The main focus of the public dialogue work was the deliberative work, undertaken to explore and understand various public perceptions, motivations and attitudes to creating human-animal embryos for research. The first stage of this work involved establishing deliberative groups. In these groups participants were taken through the different types of human-animal embryos and the science behind them, and initial reactions were also gathered. 104 people took part in this first stage, which consisted of 12 groups held in London, Manchester, Newcastle, Belfast, Glasgow and Swansea.
- 4.9. The second part of the deliberative work consisted of a full day workshop held in the first week of June. 44 of those that participated in the deliberative groups attended this

meeting; participants were selected at random to ensure a representative mix. The aim of this second stage was to explore how the views and opinions of participants changed when exposed to different information. Expert speakers were used to illustrate the different issues and arguments relating to the consultation, thereby stimulating questions and debate. The workshop was recorded and a short film of the day was shown to the audience at the public meeting. This film was also made available for viewing via the HFEA website. The detailed findings of the deliberative work, including both the group work and the workshop, can be found at Appendix E of this paper.

#### *Public Dialogue: Opinion Poll*

- 4.10. In early July 2007 an opinion poll was conducted to gauge the views of 2,000 residents of Great Britain and 60 residents of Northern Ireland. Participants were selected at random, with quotas set on age, sex, geographical regions, and housing tenure. To ensure a representative sample, data was weighted against the profile of the United Kingdom.
- 4.11. The questions for the poll were developed with the assistance of the Stakeholder Advisory Group and built on the early findings of the deliberative work. The full results of the opinion poll can be found at Appendix F.

#### *Public Dialogue: Public meeting*

- 4.12. A key aim of the consultation has been to engage with the public in a meaningful way, informing the debate by ensuring that the public are aware of the various arguments for and against the creation of human-animal embryos.
- 4.13. 153 people attended the meeting and all participants were self selected and therefore not representative of the general public. 37% of participants described themselves as members of the public, 36% attended as a representative from an organisation with an interest in the area and 27% were from a scientific or academic background. No other information was gathered about participants.
- 4.14. To encourage debate of the issues a panel of speakers, holding various views, were asked questions by the audience and a lively debate between the panel and the floor ensued. An audio recording was made of the debate which was then made available on the HFEA website. Electronic voting was used during the meeting to capture the views of those who attended. A full account of the meeting, including the results of the electronic voting, can be found at Appendix G.

#### *Scientific literature review*

- 4.15. The Executive has completed a comprehensive literature review of the scientific context and issues surrounding the creation of human-animal embryos for research. It outlines the history of interspecies constructs in research, the reasons why scientists propose to create cytoplasmic hybrids and explores whether this is a feasible technique. The review investigates the potential biological issues with creating cytoplasmic hybrids including nuclear reprogramming, interaction of the nuclear and mitochondrial genome and mixing human and animal mitochondria. Alternative avenues of research and sources of stem cells have also been outlined. This review can be found at Appendix B of this paper.

#### *Scientific consultation*

- 4.16. In addition to the literature review, the Executive consulted a small number of stakeholders on specific scientific questions. Responses were gathered from external

stakeholders, the HFEA's Scientific and Clinical Advances Group (SCAG) and the HFEA Horizon Scanning Expert Panel (HHSEP). The external stakeholders included the British Fertility Society (BFS), Human Genetics Alert, Scottish Stem Cell Network and the Motor Neurone Disease Association.

- 4.17. The purpose of this exercise was to gain an understanding of the scientific issues surrounding human-animal embryos. The findings of the scientific consultation can be found at Appendix H.

## **5. Ethical Overview**

- 5.1. Before turning to the findings of the consultation, members may find it useful to consider an overview of the ethical issues surrounding the creation of human-animal constructs. The ethical issues surrounding hybrids and chimeras can be roughly categorised into three areas: intuitive responses, moral considerations and arguments based on human dignity. It is important to note that much of the ethical literature tackles hypothetical scenarios of brought-to-term hybrids or chimeras, and does not specifically address the creation of hybrids, chimeras, or cytoplasmic hybrid embryos.

### *Intuitive responses*

- 5.2. When people express intuitive or gut reactions to ethically controversial issues, it may represent a deeper ethical objection. For some, the prospect of hybrids and chimeras invokes a feeling of repugnance, because they believe that it is simply unnatural to mix human and animal components. Uncovering the source of such responses is important in revealing precisely what it is that is being objected to. This is because simple disgust at something may be just that and not in any way a real moral objection.
- 5.3. 'Yuck' responses may originate from the notion of taboos. Taboos, argues Karpowicz, are "social conventions that emerge from diverse historical and cultural contexts".<sup>1</sup> Because taboos are rooted in traditional ways of thinking, care must be taken when applying them in the contemporary context. Prohibiting practices by social convention could mean that progress is stifled as change can often challenge long established beliefs.
- 5.4. Alternatively, these gut reactions may be attributable to underlying moral unease. Some people possess strong feelings but are unable to communicate precisely why they are repulsed by the creation of hybrids or chimeras. The notion of 'playing God' concerns a number of people who feel that human intervention, in the natural order of things, is intrinsically wrong. Those who do not believe in God may still believe that it is very wrong for humans to make such significant changes to nature.

### *Moral considerations*

- 5.5. It has been argued that the introduction of animal matter into human life forms, or the other way around, may in some people give rise to "inexorable moral confusion".<sup>2</sup> This confusion possibly arises from a reassessment of our existing social relationships as humans and our future relationships with animal-human beings.
- 5.6. Others have argued that these moral concerns are not, however, especially strong or coherent in their substance. Moral rejections tend to rely upon a species distinction between animals and humans, but it is unclear whether such a distinction can be

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<sup>1</sup> Karpowicz P, Cohen C & Van der Kooy D (2005) Developing human-nonhuman chimeras in human stem cell research: ethical issues and boundaries. *Kennedy Institute of Ethics Journal* 15(2):107-134.

<sup>2</sup> Robert J S & Bayliss F (2003) Crossing Species Boundaries. *American Journal of Bioethics* 3(3):1-13.

maintained: “We all know a human when we see one, but, really, that is all that is known about our identity as a species”.<sup>3</sup>

- 5.7. There are a number of approaches to determining species boundaries but they all seem to come unstuck on the question of at what point a human stops being a human, or an animal stops being an animal. Julian Savulescu has seized upon this uncertainty asking, “Why does having a certain genetic structure, for example 46 chromosomes, morally matter?”<sup>4</sup> Alluding to the incidence of Turner’s syndrome, which is characterised by a missing X chromosome, he concludes that it cannot.
- 5.8. For some people, their moral concerns stem from religious doctrine. Some Christians interpret Genesis Chapter 1:26<sup>5</sup> as prohibiting the introduction of animal material into human life and some believe Leviticus Chapter 18:23<sup>6</sup>, the prohibition of bestiality applies by logic to hybrids and chimeras.

### *Human dignity*

- 5.9. Humans are often thought of as possessing a certain uniqueness and intrinsic worth that attracts the notion of ‘human dignity’. The value of human dignity is derived by the virtue of humans being distinct from animals. The existence of hybrids or chimeras may blur this boundary between animals and non-animals, threatening the distinctiveness of human beings as a species, thus undermining their dignity. This conceptual threat becomes somewhat weaker, however, when one considers how human dignity could be undermined in practice.
- 5.10. Objections based upon human dignity rely on the idea that hybrids and chimeras are brought to term. The resulting beings may undermine what it means to be human by possessing the qualities and traits that constitute ‘humanness’, thus blurring species boundaries. It should be made clear, however, that research proposals concern only hybrid and chimera embryos and are not suggesting we produce fully-fledged beings. It is not evident how a human embryo containing animal material undermines human dignity along these lines.
- 5.11. Alternatively, not to conduct research using hybrids and chimeras may present a clearer and more immediate threat to human dignity. The purpose of such research is ultimately to help meet healthcare needs, which supports, rather than denigrates human dignity. Thus dignity can either operate as a constraint to research or a justification to actively pursue research.

## **6. Themes emerging from the consultation**

### *The use of human embryos in research*

- 6.1. During the course of the consultation it quickly became clear that there are a large number of respondents who are against any type of embryo research. This view was overwhelmingly represented in the responses submitted to the written consultation and was also dominant at the public meeting. It was also evident in the deliberative work and the opinion poll, although to a significantly lesser extent.

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<sup>3</sup> Ibid.

<sup>4</sup> Savulescu J (2003) Human-animal transgenesis and chimeras might be an expression of our humanity. *American Journal of Bioethics* 3(3):22.

<sup>5</sup> “And God said, Let us make man in our image, after our likeness: and let them have dominion over the fish of the sea, and over the fowl of the air, and over the cattle, and over all the earth, and over every creeping thing that creepeth upon the earth”

<sup>6</sup> “Neither shalt thou lie with any beast to defile thyself therewith: neither shall any woman stand before a beast to lie down thereto: it is confusion.”

- 6.2. As research using human embryos is currently licensable by the HFEA, the purpose of the consultation has not been to gauge public opinion of embryo research in general. However, in the context of the consultation it is useful to be able to distinguish those objecting to the fundamental notion of using human embryos in research, from other respondents, to explore where others might impose limits.
- 6.3. Those not against the use of human embryos in research were generally supportive of research using spare embryos donated from patients undergoing fertility treatment and, to a slightly lesser extent, research using human embryos created from donated gametes.

*“I think its better to donate them than just leave them, put them in the freezer, and argue over it when you get divorced.”* Swansea man, participant in the deliberative work

*“Why would you object to donating your embryos if it goes to a good cause? Abortion goes to nothing.”* Glasgow man, participant in the deliberative work

- 6.4. At the public meeting the majority considered that it was not acceptable to use animal eggs as an alternative to human eggs. Whilst in the deliberative work a more permissive view was expressed. Indeed it was deemed a necessary option rather than a preferable one. There were also some respondents who appeared concerned about the risks associated with the donation of human eggs.

*“Given the difficulty and potential risks to women who donate eggs this would be a safer and potentially richer source of eggs.”* James King, in response to the written consultation

- 6.5. In 2006 the HFEA consulted on whether women should be allowed to donate their eggs to research projects and, if so, how to ensure their interests are best protected. As part of this consultation the HFEA hosted a meeting of scientists involved in stem cell and embryo research. The meeting raised issues regarding alternative sources of eggs and embryos for research and some experts expressed views on the creation of hybrids.
- 6.6. Some of the researchers felt it was too soon to be carrying out somatic cell nuclear transfer research with human materials as human eggs are in such sort supply and there is still a great deal that could be learnt using animal studies. Those that held this opinion fell into two groups. The first group felt that the field could benefit from further research using only animal materials (not using human eggs or nuclear material). One researcher commented that creating hybrid embryos would result in a confusion of information and that it would not tell us what we need to know.

The other group felt that it was too soon to use human eggs for this research but it was appropriate to use hybrids. One researcher commented that although there could be complications in using animal eggs and human nuclear material it would still be possible to obtain high quality data. There were also those who felt that stem cell research could benefit from work using human eggs.

#### *Creating human-animal embryos*

- 6.7. As mentioned in the scientific context, the mixing of human and animal material is not new. However, for many people this is the first time they have been aware of the intention to create embryos with a mix human and animal material. It is therefore perhaps unsurprising that some initially view this idea with disgust.

6.8. Certainly at the outset of the deliberative work, many of the participants expressed an initial repugnance in reaction to the suggestion of mixing human and animal material. Associations were drawn with incidents such as the Northwick Park drug trials, myths and legends, and the elephant man. However, when further factual information was provided and further discussion took place, the majority of participants became more at ease with the idea, although as one participant observed, *“The gut reaction is hard to overcome”*.

6.9. There were some suggestions of a compromise approach in the deliberative work, at the public meeting and in the responses written consultation. Some supporting the research if it had the potential to lead to a better understanding of the biological processes, but expecting further work to then be undertaken with human eggs.

*“I think they should use these eggs to understand better how it works – they’ll use human eggs after that won’t they.”* Glasgow woman, participant in the deliberative work

*“It may be necessary to do it for a short time in order to see how cells re-programme, and you can’t possibly do that without looking at these kinds of stem cells from embryos.”* Speaker at the public meeting

6.10. In the deliberative work, opinion poll and written consultation there was more support for the creation of cytoplasmic hybrids than for other types of human-animal embryos. Of those who did feel differently, some felt unconvinced by the need for creating other types of embryo, whilst others questioned whether there would ever be any benefits in creating any of the other types of human-animal embryos where there was more than 0.1% animal present.

*“People need to know what it’s for rather than research for research’s sake, there has to be an end in sight.”* Manchester man, participant in the deliberative work

#### *Citing the benefits*

6.11. After expressing their initial reactions, participants in the deliberative work were intrigued to understand why scientists would want to create human-animal embryos.

*“If I thought it would have some benefit I would go for it.”* London man, participant in the deliberative work

Throughout the deliberative work it was made clear that there are no guarantees that the research will lead to any significant advances. However, in both the deliberative work and from the opinion poll it emerged that the *potential* benefits of the research had a significant impact on opinion. The key issue for most was whether there is a clear rationale for the research. Some felt it was acceptable if the research could yield results to further our understanding of disease, whilst others considered that the potential applicability of the research to human diseases was the key to whether the research should take place.

6.12. This shift in opinion was not replicated at the public meeting, where the majority of participants felt that the potential benefits failed to outweigh their ethical concerns. This may have been because the audience were self-selecting, having already formed a view. One participant suggested that citing potential benefits is misleading, particularly as there is no guarantee that the research will result in any.

*“I think it’s fraudulent to tell people with diseases that you will generate useful data.”* Audience member at the public meeting

This highlighted what was found in the deliberative work: the importance of communicating the complete factual picture, explaining the science alongside a realistic explanation of the potential benefits.

*Scientific worth: Views from the consultation*

- 6.13. Introducing information about the potential benefits of the research in the second part of the deliberative work, the full day workshop, also prompted some questioning of the scientific worth of using animal material.

*“I personally think that if it is humans they’re trying to cure then it is human they should be trying to do it with, not animals.”* Glasgow woman, participant in the deliberative work

*“We could go through it all and decide that it is never going to work anyway because it is not going to be the same as getting it from the humans.”* Swansea woman, participant in the deliberative work

This concern was reflected at the public meeting, with audience and panel members questioning whether the research is in fact safe and how applicable any findings would be to human beings.

*“We do not know whether such hybrids will lead to diseases and genetic illnesses being transmitted from the animal species to the human species, for example.”* In response to the written consultation

*“Can you really guarantee that there will be no abnormality in the stem cells that are produced combining humans and animals?”* Audience member at the public meeting

*“It seems unsafe to carry out procedures that are unnatural in the sense of being impossible by natural processes. It seems risky to do something that nature prevents.”* In response to the written consultation

- 6.14. In the written consultation, those against the creation of cytoplasmic embryos were largely against the proposal for ethical reasons. Some respondents raised the issue of safety, the majority citing cross species contamination as the basis of their concern.

*Scientific worth: Evidence from the scientific literature review*

- 6.15. As outlined in the scientific literature review, in order for this technique to result in the creation of embryos, the somatic genome of the donor cell must be reprogrammed to allow the correct expression of genes for embryonic development. This is a hurdle for the successful creation of all embryos by the process of somatic cell nuclear transfer (SCNT), not just interspecies hybrids. This process is likely to be more problematic in interspecies hybrids as different species may have different mechanisms for reprogramming.
- 6.16. There has been only one credible report of a human embryo being created, following SCNT. This embryo developed to the blastocyst stage but did not result in the derivation of stem cell lines. There are limited reports of the creation of human-animal cytoplasmic embryos but studies from the US and Korea have reported successful development of human-cow embryos to blastocyst stage. Analysis of these embryos by one US group demonstrated that the embryos contained human genomic DNA specific for the individual DNA profile of the donor cells.
- 6.17. A study from China reported the creation of human-rabbit embryos which developed to blastocyst stage and lead to the derivation of stem cell lines (see section 1.2 of

Appendix B for more details). The use of this technique in animals has shown mixed success. Examples of the animal-animal hybrids, and the stages of development they reached, are outlined in section 1.2 of Appendix B. Few studies have demonstrated the establishment of ES cell lines from animal-animal embryos although recently mouse ES cell lines have been derived from embryos created with mouse somatic cells and cow eggs.

- 6.18. As hybrid embryos develop towards the blastocyst stage the gene products (proteins and RNA (ribonucleic acid: single stranded molecule transcribed from DNA in the cell nucleus and mitochondria, the structure and base sequence of which determines protein synthesis)) will gradually become more human derived. By 14 days the embryo will be entirely human with respect to protein and RNA apart from 13 proteins encoded by the animal mitochondria.
- 6.19. Animal mitochondria will be present in the cytoplasm of the enucleated recipient egg, so cytoplasmic hybrids will contain at least some animal mitochondria, and therefore animal mitochondrial DNA (see section 3.1 of Appendix B for background information on mitochondria). It is also likely that some human cytoplasm, containing human mitochondria, will be transferred with the nucleus during the creation of hybrids. As outlined in section 3.2.2 of Appendix B the amount of human mitochondria transferred is likely to depend on the technique used for transfer of the nucleus.
- 6.20. A number of mechanisms need to be effective for hybrid embryos to develop successfully and for cells derived from these embryos to be viable:
  1. A particular number of mitochondria must be present
  2. Mitochondria must be capable of replicating and expressing their proteins
  3. Proteins encoded by the nuclear and mitochondrial genomes must interact together in order to allow the cell to produce energy
- 6.21. There is a risk that in hybrid embryos humans may be too distant in evolutionary terms from other mammalian species, such as rabbits and cows, for the genomes to be compatible. Animal-animal cytoplasmic hybrid studies indicate that the energy production mechanisms (oxidative phosphorylation function and ATP production, for more information see section 3.3 of Appendix B) of these embryos are compromised and that these mechanisms will become less functional when the evolutionary distance between the two species is increased.
- 6.22. However, survival of human-rabbit and human-cow embryos to the blastocyst stage suggests that this is not always problematic. This may be due to the human nucleus preferentially replicating the human mitochondria present. Human mitochondria have been found to be present in human-cow embryos up to blastocyst stage, however, they are unlikely to account for the majority of mitochondria present.
- 6.23. These issues are investigated in more detail in Appendix B. However, there is little literature investigating the interaction of the nuclear and mitochondrial genomes in inter-species embryos and therefore it is hard to reach any certain conclusions about development of human-animal hybrids and functionality of any cells derived from them.
- 6.24. Some scientists have suggested that human-animal hybrid embryos, or any cells derived from them, may only be functional if they are inserted with supplementary human mitochondria.

#### *The alternatives to using human-animal embryos*

- 6.25. In all strands of the consultation, a key theme was the alternatives and whether creating human-animal embryos for research purposes was justifiable when other

sources of stem cells are available. In the course of the deliberative work participants debated the issue of alternative methods of research, with many of the participants concluding they were content with the creation of human-animal embryos alongside alternative research methodologies, with the proviso that such research was conducted under strict regulation.

*“If there was another way of doing it (e.g. a skin cell) I would much prefer this route. However I still feel that we should try it both ways.”* Participant in the deliberative work

6.26. The majority of participants in the deliberative work felt that using other sources of stem cells avoided the ethical dilemmas. However, it was generally felt that all avenues of research should be pursued if there is potential for greater understanding of disease.

6.27. Some respondents to the written consultation held the view that it would be better to invest more energy in other types of research, believing that promising advances were being made through alternative research methodologies.

*“More funding should be given to researchers who are getting good results from using adult stem cells, and women who have given birth should be asked to donate the umbilical cord for stem cell work.”* In response to the written consultation

*“Is it not true that New York Scientists have produced the equivalent of embryonic stem cells in mice without destruction of embryos.”* In response to the written consultation

6.28. There are two main alternative research options to creating human-animal embryos. The first option is to use an alternative source of stem cells, such as adult or cord blood stem cells. Adult stem cells are found in many tissues and can develop into a range of cell types related to the tissue they are derived from. They are involved in tissue renewal and repair, and established treatments include bone marrow, skin and corneal transplants. Animal models and clinical trials using adult stem cells are being developed for the treatment of heart disease, type 1 diabetes, spinal cord injury, stroke, Parkinson’s disease and Huntington’s disease. Cord blood cells, isolated from the blood of the umbilical cord, have been successful in the treatment of leukaemia and other blood disorders, especially in children.

6.29. The second option is to directly reprogram somatic cells to produce embryonic-like stem cells. Recent studies in mice have reprogrammed fibroblast cells without transferring the cells into an egg or creating an embryo. The resulting cells are termed induced pluripotent stem (iPS) cells and have similar properties to embryonic stem cells. Another alternative technique uses fertilised eggs as hosts for SCNT, instead of unfertilised eggs. Fertilised human eggs that have extra sets of chromosomes are automatically discarded from IVF treatment. In mice, these have been successfully used as hosts for SCNT, and the resulting embryos could potentially be used to derive embryonic stem (ES) cell lines. These, and further alternative research options, are explored in more detail in Section 5 of Appendix B.

6.30. Although a very important avenue of research, adult stem cells are limited in the types of cell or tissue they can give rise to. Not all tissues contain stem cells whilst others are inaccessible, such as stem cells from the central nervous system. Populations of adult stem cells are also highly heterogeneous, making them hard to isolate and purify. Some studies have tried to induce adult stem cells to broaden the range of potential tissues they can form. However, though some stem cells appear more flexible than previously thought, the mechanisms controlling this process are poorly understood. At present there is only a very limited range of diseases that can be treated using adult stem cells. Cord blood stem cells are also limited in the disorders they can treat and

although there are some claims that these cells have wider potential, these have not been substantiated.

- 6.31. Adult and cord blood stem cell research is significant; however ES cells may offer a potentially more flexible range of research options if the different differentiation pathways can be directed. Research on other sources of stem cells, and alternative ways of deriving embryonic stem cells without destroying viable embryos (see Section 5, Appendix B), is at a very preliminary stage and does not currently offer a viable alternative to human-animal embryos.
- 6.32. The process of reprogramming somatic cells into iPS cells has been achieved by three separate groups, which shows positive support for the results. However research is still at a very early stage and the reprogramming process is inefficient. Different factors may be involved for humans than those identified for mice. The process of using fertilised eggs for SCNT has only had one successful study published to date and similarly the technique has not been attempted in humans.
- 6.33. Members of the scientific community are of the opinion that all avenues of research, including adult stem cells, human-animal embryos and direct reprogramming of somatic cells, should be explored.

*Concern for the future: The boundaries to research*

- 6.34. The findings of the deliberative work and the opinion poll highlighted that there is concern that a slippery slope would be embarked upon if the creation of human-animal embryos were to be permitted.

*“It is human nature; you always want to push the boundaries to see what is going to happen if you just go a little bit further.”* Swansea man, participant in the deliberative work

Another view expressed was that the risks associated with the slippery slope argument are outweighed by the potential benefits to be gained. In the deliberative work, some felt that their concerns about starting on a slippery slope were lessened by the fact the research would be tightly regulated. However, caution was still called for by some, as regulation can only control what is done within the UK and consequently the slide down the slippery slope maybe embarked upon elsewhere.

*“I think this is a dangerous direction for research to go, especially since scientists in other countries may take the information gained here and use it to create hybrids that will not be destroyed at 14 days.”* In response to the written consultation

- 6.35. A proportion of those concerned by what the research may lead to, cite situations which occurred in the past, revealing a level of distrust for scientists and their work.

*“This surely follows on from Nazi experiments during World War II.”* In response to the written consultation

*“For instance we have allowed abortion - now murders of children are almost daily events. ... If this research on human-animal embryos is permitted, what is to say that in a few years laws will be passed to legalise bestiality.”* In response to the written consultation

Many of the participants felt quite far removed from medical research and considered there to be a lack of communication about scientific and medical advancements.

*"It seems to be secretive. I don't think that we the general public feel as though we are in touch with it, or we're being informed."* Manchester man, participant in the deliberative work

Some participants were concerned that there are a small number of scientists who are irresponsible in their pursuit of knowledge, regardless of the controls in place.

*"I'm sure they've done it already (mix of human and animal material)."* London woman, participant in the deliberative work

*"How do you control illegal research by people that are not applying for licenses?"* Participant in the deliberative work

However, others expressed great trust in the work undertaken in by scientists and medics.

#### *Regulation: Limits and controls*

6.36. Those who supported research involving the creation of human-animal embryos appeared to agree that such research should only be undertaken in a regulated environment.

6.37. A small number of respondents to the written consultation considered that such research should be completely unregulated.

*"We should remove the time limit for all research and allow unfettered scientific exploration. It is only the fear of an imaginary being that makes some people claim that we should not investigate ourselves. If 'moral' objections apply, it should be up to the producer of the egg to decide whether experimentation is allowed, not the 'authority' vested in some religious leader by a fairy tale."* In response to the written consultation

*"You have to rely on the people with expert knowledge in the field. We cannot limit the researchers as the future of medical health for me and my children may well depend on these people being able to work without fear of restriction."* In response to the written consultation

6.38. During the course of the deliberative work the issue of regulation arose frequently and was often cited as a proviso when support was given to the creation of cytoplasmic hybrids. Throughout the consultation the current regulatory framework was considered to be appropriate, although some felt that those who breached the standards imposed should be subject to penalties.

*"But what would be the punishment if they did keep it longer [than 14 days]? They'd have to take away the licence then they couldn't work."* Newcastle man, participant in the deliberative work

#### *Levels of understanding*

6.39. The majority of those that attended the public meeting appeared to know about the debate around human-animal embryos, however this is hardly surprising given that the audience was self-selecting. The results of the opinion poll however indicated that the general public know only a little about using human embryos for research, stem cell research or the possibility of creating cytoplasmic hybrid embryos.

6.40. Throughout the consultation it was clear that a number of misunderstandings are held by the public. During the course of the deliberative work, comments were made about the lack of information, and even misinformation about medical research including the

benefits that had been achieved. Again this raises the need for full and accurate information to be made available to the public.

- 6.41. Nearly all of those that attended the public meeting thought that it was important to consult the public on issues such as this and the majority of participants went on to say that they would be responding to the consultation, or had already done so.

## **7. Conclusions**

- 7.1. The general view of the organisations we consulted, and the view expressed in the Academy of Medical Sciences' recent report on inter-species embryos<sup>7</sup>, was that currently there is no reason why scientists would want to create human transgenic embryos, true hybrids or human chimera embryos. However, although there is not currently a demand for the creation of these entities it is always difficult to predict how scientific research may develop in the future. There is evidence for success of these techniques in animal studies, so in theory it could be technically possible to create such entities using animal material.
- 7.2. The Academy of Medical Sciences suggested that researchers will at some stage have good reasons to conduct research involving the creation of human-human transgenic embryos. These techniques could facilitate the investigation of gene function in early embryo development or, for example a gene could be introduced in a human embryo to increase the efficiency of the derivation of stem cells. However, as during the consultation it was not possible to provide the public with a comprehensive account of the scientific need for creating all types of human-animal embryos, the debate very much focused on the topic of cytoplasmic hybrids.
- 7.3. Throughout the consultation there was some questioning, mostly by members of the public, of the scientific worth of creating human-animal embryos. However, the scientific community appears to feel confident that the creation of cytoplasmic hybrids is an avenue of research worth exploring and, in particular, it could be a viable alternative to using human eggs, to investigate the mechanisms of creating patient matched embryonic stem cells. As this research has not been undertaken in this country yet and it is still in the very early stages of development elsewhere, it is not possible to make any firm conclusions on the potential of this research. Despite this, in all strands of the consultation, there were calls for all avenues of research to be pursued, which is the approach that has generally been taken in the UK to date.
- 7.4. The potential benefits of creating cytoplasmic hybrids has had a significant affect on public opinion. Many appeared to view a clear rationale for the research as the key to determining whether it is acceptable or not. The potential benefits of creating cytoplasmic hybrids are outlined in section 2 of this paper.
- 7.5. In all strands of the consultation there was discussion of alternatives. The use of adult or cord blood stem cells has been suggested as a viable alternative to the derivation of ES cells from human-animal embryos, and was cited throughout the course of the consultation. Although the use of adult and cord blood stem cells is already established in a number of treatments, including bone marrow, skin and corneal transplants, unlike ES cells they are limited in the types of cell or tissue they can give rise to. Research into expanding the types of cells that adult and cord blood stem cells can give rise to is at a preliminary stage and the mechanisms involved are poorly understood. The technique of directly reprogramming somatic cells to produce embryonic-like stem cells was also identified as an alternative option to creating human-animal embryos. Recent

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<sup>7</sup> 'Interspecies embryos: A report by the Academy of Medical Sciences'. June 2007

success has been achieved with this technique in mice, however, research is still at a very early stage and there has been no success in humans.

- 7.6. During the course of the public dialogue work the participants showed an interest in the issues and were keen to understand the complete picture for research involving the creation of human-animal embryos. Not only did the public want to understand the science, but also why the research needs to take place and the proposed benefits. Furthermore, this information appeared to be significant to those forming their opinion on the issue for the first time. So whilst some members of the public initially reacted with disgust, after hearing more information and discussing the issues with others, their opinion often shifted significantly.
- 7.7. From the public dialogue work it also appeared that explaining the regulatory controls (i.e. the 14 day rule) is crucial in helping the public to understand that the research being discussed would take place at a cellular level. Whilst some people still view the creation of any human-animal embryos as the start of a slippery slope, the regulatory context reassured many people who initially held this concern. Those that registered support for the use of human embryos in research were generally in favour of the creation of human-animal embryos, with the proviso that there are good reasons for undertaking the research and that it is carried out in a tightly regulated environment.
- 7.8. The consultation highlighted the need for increased communication with the public. There was great appreciation from participants in the deliberative work and the public meeting for being consulted and a strong desire from people to continue to learn about issues such as this. The distrust and suspicion around scientists, also indicates a need for the HFEA and scientists undertaking high profile research to establish ongoing communication with the public. In the course of the consultation there was a great deal of support for the current regulatory structure, with emphasis placed on the need to regulate such research tightly and with high levels of scrutiny. Furthermore, the suspicion surrounding medical research and scientists supports the need for the HFEA to communicate its role in regulating research and to be clear about the limits and the controls that it exerts. This links in with the recommendation made by the parliamentary scrutiny committee that the HFEA should 'improve and inform public understanding'<sup>8</sup>.

## **8. Recommendations**

- 8.1. Although the consultation document posed questions on a range of possible human-animal embryos, including true hybrids and human chimeras, there is insufficient information on the desirability of creating these entities. This is because there is limited information on why researchers might wish to create these embryos in future (most say they see no reason for doing so). Without this information, our attempts at public engagement or dialogue on the subject were unsuccessful as the public are reluctant to form a committed view without understanding the full context of research proposals.
- 8.2. We believe that sufficient evidence is available to the Authority to enable it to form a view on cytoplasmic hybrid embryos. The Authority may find it particularly useful to work through the decision tree (refer to 1.6) as part of the decision making process. This may also help clarify whether there is sufficient information to make a decision regarding true hybrids and human chimeras.
- 8.3. If the Authority concludes that there is insufficient evidence to form a view on whether this type of research is necessary or desirable, the Authority may wish to consider

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<sup>8</sup> Joint Committee on the Human Tissue and Embryos (Draft) Bill 1 August 2007. 'Human Tissue and Embryos (Draft) Bill Volume 1: Report'

monitoring developments through its horizon scanning function process. The Executive is regularly informed of new developments in a range of areas relevant to human embryo research, from experts in various fields, who are members of the Horizon Scanning Expert Panel and the Scientific and Clinical Advisory Group. These groups could be asked regularly whether they are aware of any suggested uses of human-animal embryos in research. Relevant developments are also regularly identified by the Executive, as was the creation of cytoplasmic hybrids, through reviews of published research and by attending conferences. The Authority may wish to consider formally revisiting any evidence gathered on other types of human-animal embryos next autumn and refrain from agreeing a policy on these entities until a time when further consultation is possible.

- 8.4. Throughout the consultation the Executive has built good relationships with members of the scientific community with an interest in this area of research. We are therefore confident that any intention to undertake research involving other types of human-animal embryos will be picked up well before an application is received. This would allow time for further evidence gathering to inform an updated policy decision. However, if an unexpected application was received, it would be open to the Authority to delay consideration of the application by licence committee pending further evidence gathering.
- 8.5. It is recommended that the issue of further public dialogue on this subject is considered in November, at which time the external evaluation of the consultation will be complete. At this time Members may wish to consider the issue of communication with the public in a wider context.

## **9. Next steps**

- 9.1. The consultation is being independently evaluated by Diane Warburton from Shared Practice and will be useful in identifying lessons to be learnt. The evaluation will look at:
  - How well the whole process worked in order to identify clear lessons to feed into future HFEA work.
  - The level of understanding among the public and the effectiveness of the information provided through this process in extending that understanding.
  - How the different elements of the consultation have interacted (e.g. issues from the initial public discussions feeding into the design of the open public meeting and the public opinion poll).
  - Whether there was demographic representation among those attending events and responding in other ways.
  - The impact of the findings of the consultation on HFEA policy and decision-making.
  - The extent to which the consultation process has adhered to the OSI guiding principles for public dialogue<sup>9</sup>.

The final report is expected in October and the findings will be shared with the Authority in November.

- 9.2. Following the Authority meeting a press statement will be made about the Authority's decision. Information will also be made available on the HFEA website. A full report on the findings of the consultation will be published in October. The report will be sent to

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<sup>9</sup> Office of Science and Innovation. *The Government's approach to public dialogue on science and technology*. OSI, September 2006.

those who responded and participate in the consultation and will be made available on the HFEA website.

- 9.3. Over the next 8 months the Biotechnology and Biological Sciences Research Council (BBSRC) and the Medical Research Council (MRC) will be undertaking a public dialogue on stem cell research. The project will bring together members of the public, scientists, policymakers and key stakeholder groups in a programme of activities over a period of approximately 12 months. A representative of the HFEA Policy Team has been asked to sit on the Steering group for this project, the first meeting of which will take place on 12th October 2007.