

**HORIZON SCANNING INTELLIGENCE GROUP**

**Gene therapy – potential health and safety implications**

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**Issue**

1. Outcome and recommendations of the horizon scanning project on gene therapy. A review of the scale and extent of development of the technology and the current regulatory framework has been completed and is attached in Annex 1.

**Recommendation**

2. The Intelligence Group is invited:
  - to consider the review of gene therapy and the points made against the horizon scanning 'criteria for Escalation of Issues' guide.
  - to agree that no further horizon scanning work is required at present. However, HSE will continue to develop strategic partnerships with relevant stakeholders to ensure sensible and pragmatic regulation of this developing area, eg with the Gene Therapy Advisory Committee.
  - to agree that the Biological Agents CTG in partnership with HSL horizon scanning group keep a watching brief in this area.

**Background**

3. Gene therapy is a new branch of medicine with the potential to treat inherited disorders, cancer and some genetic diseases. The technology may, however, have occupational health and safety implications. Most of the health and safety concerns about gene therapy arise from the use of infectious viruses as gene delivery systems because of the potential for spread to workers, other patients, and the wider community. This, combined with the ongoing media coverage and public scrutiny any emerging genetic treatment receives, made gene therapy an important candidate for horizon scanning activity in HSE
4. Work on this project started before the cross-cutting HSE horizon scanning system was set up and was carried out as a joint project between the Biological Agents Unit (HID SI4) which also has the Corporate Topic Group responsibility and Corporate Science and Knowledge Unit (CoSAS).

## **Gene therapy – current status of development**

5. The initial focus of gene therapy research centred on the principle that, if a disease is caused by a faulty gene, then it could be replaced by a correct version, so controlling or preventing the disease. As a result, single gene conditions, eg. those that give rise to severe combined immunodeficiency – SCID and cystic fibrosis, have been the subjects of significant research effort. However, as the technology has developed, the scope of application of gene therapy has broadened. It is now being considered as a potential treatment for a variety of clinical conditions such as cancer, infectious disease and cardiovascular disease.
6. Nearly 800 clinical trials of gene therapy treatments have taken place worldwide since the first formally approved trial in 1989. Approximately 100 of these have been UK based. The majority of trials have been small studies whose main objectives have been to demonstrate patient safety and gene transfer. Only one gene therapy has been licensed for routine use; a cancer treatment approved by the Chinese medicines authority. Annex 1 contains further background. To date most trials have had an acceptable patient safety profile, but with only limited clinical benefits. There have been 2 notable exceptions, the death of a patient undergoing gene therapy for an enzyme deficiency and 2 cases of acute T-cell leukaemia reported in patients undergoing treatment for SCID. HSE recently issued a safety alert concerning a particular group of gene therapy vectors following reports of tumour formation in a small animal model.

## **Gene therapy – current regulatory controls**

7. Many of the gene delivery systems that have been used to date involve the use of genetically modified viruses, and as such are defined in UK (and EU) law as genetically modified organisms (GMOs).
8. There have been regulations controlling all contained use (ie laboratory) work with GMOs in the UK since 1978. The legislation has evolved over the years, partly due to changing technology and increased knowledge, but also because of a European Directive on the contained use of GMOs. This legislation was not developed to regulate gene therapy, but is relevant to some gene therapy activities. The Scientific Advisory Committee on Genetically Modified Organisms (Contained Use) advises on the health and safety aspects of activities notified under these regulations, including gene therapy applications. The Gene Therapy Advisory Committee (GTAC) is the UK Research Ethics Committee for Gene Therapy and oversees the conduct of clinical research in this area.
9. Another EC Directive which deals with the deliberate release and marketing of GMOs, implemented in Great Britain by The Genetically Modified Organisms (Deliberate Release) Regulations 2002 (as amended in 1995 and 1997), may also apply to some gene therapy activities.

## **Potential risks and control measures**

10. The populations potentially exposed to the GMOs used in gene therapy include:

- a. those involved in the preparation of the material for treatment, eg laboratory staff, pharmacy staff;
- b. those involved in the administration of the treatment eg doctors, nurses;
- c. those who may be incidentally exposed to the GMO eg others in the hospital (both employees and non-employees); and
- d. those, eg family and friends and the wider general public, who may be incidentally exposed to the GMO following discharge of the patient from the hospital.

### **Criteria for Escalation**

11. In line with the criteria for 'Escalation of Issues' guidance we have considered the following points:
12. **Scale of Impact** – Depending on the success of developments in, for instance cancer treatments, the technology could become mainstream and available routinely in regional hospitals. However, it may become as a niche treatment for specific diseases. The direction is not clear at present. The Department of Health are investing over £10 million in gene therapy work such as research into single gene disorders, access to high standard gene therapy vector production facilities and long-term patient safety work.
13. **Economic Impact** – The costs to the NHS if things went wrong are potentially significant however, there are also, again potentially, major gains to the UK economy if the technology takes off. Gene therapy may require hospital investment for better-equipped pharmacies and the impact of accidental contamination would be contained within the pharmacy.
14. **Social impact** – People with life threatening diseases, will by the nature of this treatment, be the most affected by this technology.
15. **Specific effect on workplaces and practices** – A different approach to worker training eg for pharmacists, nurses and doctors would required to clearly convey the risks from working with gene therapy treatments. Hospital pharmacies may need to be adapted so gene therapy vectors can be contained.
16. **Business impact** – None (for HSE)
17. **Reputational impact** –It is difficult to assess at present due to the early stage of the technology. The potential reputational damage could come two ways, one in allowing the technology to progress and then things go wrong or by holding up the technology and depriving people of treatment. HSE must be seen to facilitate progress whilst ensuring the health and safety of those potentially exposed is protected.

18. **Political Sensitivity** – There continues to be general unease about Genetic Modification, but not, at present, about medical uses. This could change with a mishap/accident. To date the two cases of adverse effects from gene therapy have prompted reviews and recommendations but not complete cessation of trials.

19. **Societal/collective preferences** – The technology has probably raced ahead of understanding, in many cases the pattern being straight from lab into volunteers. The risks to patients and others exposed are not yet fully understood. But society views the technology in a positive light.

20. **Time** – After 15 years of research no gene therapy has been commercialised. Some areas are reaching maturity and entering late stage clinical trials. If the technology continues to develop it is likely that there will be a break through within the next 5-10 years. Current stem cell research may also have an impact on understanding and delivery. However, the expected developments are well captured in an extract from the Foreword of 11<sup>th</sup> Gene Therapy Advisory Committee Annual Report: *“We need to be realistic about what gene therapy has achieved so far and is likely to achieve in the near future. While there is no place for over-hyped optimism, one should not ignore the emerging successes. My view is that we are beginning to learn more and more about the circumstances in which gene therapy may ultimately provide an alternative treatment strategy. Different diseases are likely to require different approaches. Importantly, the potential of gene therapy has been recognised by the government in its 2003 Genetics White Paper. I hope that long-term public funding will continue and will allow the UK to maintain its position of leading Europe in gene therapy research”*

#### 21. **Uncertainties.**

- **The risk:** To date, most of the gene therapy clinical trials in the UK have used Class 1 GMOs, of no or negligible risk. However, given the limitations posed by using such GMOs on the efficacy of the treatment, the technology is progressing into higher risk delivery systems which increases the risks to humans.
- **The technology:** nearly 75% of the trials that have been notified to GTAC to date have used viral vectors; however there is increasing use of non-viral systems. It is likely that there will be considerable technological changes as researchers and companies hone delivery systems and these could impact on health and safety considerations.
- **Control measures:** there is a fundamental requirement in the contained use regulations to limit contact of the GMO with humans and the environment. In addition to the principals of good occupational health and safety, there are a number of specified containment measures to be applied according to the Class of the activity. Containment measures appropriate for work with the GMO vector in the laboratory setting are well accepted. However work needs to be done to agree suitable control measures in the clinical setting.

## **Consultation**

22. The consultation process has involved Department of Health, GTAC, SAGCM and the Advisory Committee on Releases to the Environment (ACRE).

## **Conclusions**

23. In summary:

- It is likely that there will be a breakthrough in the technology in the next 5-10 years but there is still some degree of uncertainty over how it will take off and the extent to which it will become a mainstream product or a niche treatment.
- The impact on HSE strategy and resources is likely to be minimal.
- The current regulatory framework is on balance adequate for the technology as it stands at the moment.

## **Action**

24. The Intelligence Group are invited to consider the horizon scanning review findings and agree the recommendations made.

**July 2005**

## HSE Intelligence Group Gene therapy – potential health and safety implications

### Scale and extent of development of gene therapy technology

Note: this section is not intended to be a detailed review of the techniques that have been/are being developed but an overview of the current state of play, based on more detailed commentaries (see references).

#### **Introduction**

1. The concept that faulty human genes could be ‘fixed’ was considered a possibility as early as the 1960s, as the potential of the newly emerged science of molecular biology was debated by the scientific community (Anderson, 1997). Subsequent experiments carried out in animal models proved that it was possible to ‘cure’ a genetic abnormality by insertion of a gene (Anderson, 1984) and a number of candidate human diseases were soon identified.

**Definition of gene therapy:** GTAC 2004 – “The deliberate introduction of nucleic acids into human somatic cells for therapeutic, prophylactic or diagnostic purposes.”

2. The initial focus of research centred on the principle that, if a disease is caused by a faulty gene, then it could be replaced by a correct version so controlling or preventing the disease (Fry and Wood, 1999). As a result, single gene conditions such as adenosine deaminase deficiency (which gives to severe combined immunodeficiency – SCID) and cystic fibrosis have been the subject of significant research effort. However, as the technology has developed, the scope of application of gene therapy has broadened. It is now being considered as a potential treatment for a variety of clinical conditions such as cancer, infectious disease and cardiovascular disease.

3. Nearly 800 clinical trials of gene therapy treatments have taken place worldwide since the first formally approved trial in 1989. The majority of trials have been small studies whose main objectives have been to demonstrate safety and gene transfer. To date most trials have had an acceptable patient safety profile, but with only limited clinical benefits. There have been 2 notable exceptions, the death of a patient undergoing gene therapy for an enzyme deficiency and 2 cases of acute T-cell leukaemia reported in patients undergoing treatment for SCID.

#### **Approaches to gene therapy**

4. There are a number of strategies that can be employed, including:
- **Gene augmentation therapy** - the addition of a functional copy of a gene to replace one that is not functioning (Richardson *et al*, 2002). This approach could be used in the treatment of inherited disorders caused by the loss of a functional gene product. There are, however,

other means by which the inserted gene can have a therapeutic effect, for example:

- **Gene inhibition therapy** – the inserted gene's product inhibits the expression of a pathogenic gene or interferes with the activity of its product. This is suitable for the treatment of infectious diseases, cancer and inherited disorders caused by inappropriate gene activity.
- **Killing of specific cells** – the inserted gene could code for an enzyme that converts a harmless prodrug into a highly toxic molecule or else code for a protein that makes the cells vulnerable to attack by the immune system. This is suitable for diseases such as cancer that can be cured by eliminating certain populations of cells.

5. The therapy itself can be applied:

- *Ex-vivo* – cells are removed from the patient and transfected, and the engineered cells re-implanted. This is a patient specific approach (because of issues with immunogenicity) which has implications for cost of treatment as well as manufacturing and QC (Mountain, 2000)
- *In-vivo* – the vector system is applied directly to the patient, either direct to the tissue/organ in question or systemically.

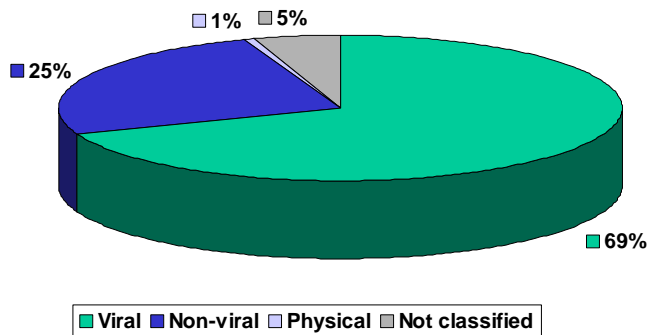
### **Gene delivery systems**

6. There are a variety of methods that can be used to deliver the gene to the target cell or tissues but there are three main types (Mountain, 2000):

- Viral;
- Non-viral biological systems; and
- Physical (e.g. ballistic delivery systems)

7. The systems that are the subject/have been the subject of clinical trials carried out across the world are shown in Figure 1. This shows that the most commonly used systems are currently viral (data adapted from Journal of Gene Medicine clinical trials website). A similar picture is seen in the UK, with approximately 67% of the trials approved to date using viral vector systems (GTAC, 2004).

**Figure 1. Vectors used in clinical trials**



8. It has become increasingly obvious that there is no such thing as a good universal vector (Fry and Wood, 1999), and that each system has its advantages and disadvantages (reviewed below). But, to be 'successful', a system needs to:

- Have target specificity ie the inserted gene only functions as required in the specific target cells/tissue;
- Ensure that the inserted gene expresses at the appropriate level for the required length of time eg gene integrates the inserted gene into host cell DNA to allow long term effect if required. However, with cancer gene therapies, once the malignancy has been eliminated the therapeutic gene may no longer be needed; and
- Ensure that delivery and expression of the gene is carried out safely ie there is no immune response or other harmful sequelae such as insertional mutagenesis (see paragraph 16).

### **Viral vectors**

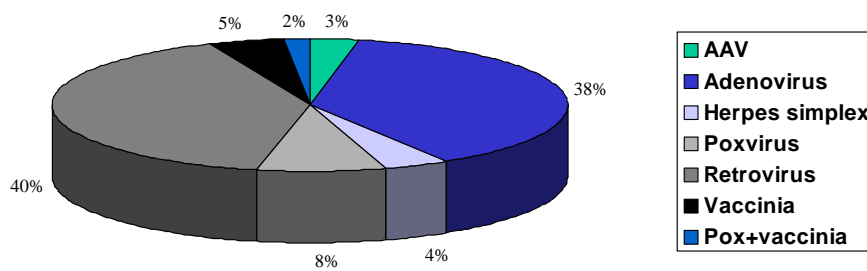
9. Viruses have a number of properties that have led to them being considered as suitable candidates for vectors in gene therapy (Rubanyi, 2001), they can:

- Recognize and enter cells;

- Move within the cytosol to the nucleus; and
- Translocate into the nucleus and express their genes in the host cell.

10. Despite advances made in the development of viral vectors, further work on certain issues is still required. For example, the ability to both establish and regulate expression of the inserted gene (Lundstrom, 2003), the ability to access the target cell where this is inaccessible eg in solid tumours or in the respiratory tract (cells masked by mucus blanket) and ability to effectively repeat doses of the vector.

11. Various different virus systems have been the subject/are subject of clinical trials. The seven most commonly used systems are shown in Figure 2 (Data adapted from Journal of Gene Medicine clinical trials website). In the UK, the use of vaccinia based systems appears to be used marginally more frequently than adenoviral or retroviral systems (21% compared with 19% and 16% respectively) (GTAC, 2004). The advantages and disadvantages of some of the key systems are compared in Table 1.



**Figure 2: Viral vectors used in clinical trials**

### Non-viral vectors

12. Non-viral vectors have been developed to overcome some of problems encountered with viral systems, such as immunogenicity, insert size limitations and ease of manufacture (Mountain, 2000). However, they are not as currently as efficient as regards gene transfer compared with some of the viral systems available (Smith, 1999). The advantages and disadvantages of some of the key systems are compared in Table 1.

**Table 1: Advantages and disadvantages of gene delivery systems (Adapted from refs )**

<b>Vector</b>	<b>Advantages</b>	<b>Disadvantages</b>
<b>Viral</b>		
<b>Adenoviruses</b>	High transfection efficiency in vivo and ex vivo	Limited insert size capacity (approx 7.5kb) although third generation 'guttled' vectors can accommodate inserts upto 30kb
	Can infect dividing and non-dividing cells	Short duration of expression
	Wide host cell range	Immunogenic (repeat dosing therefore ineffective)
<b>Retroviruses</b>	No immune response	Only infects dividing cells
	Reasonable duration of expression	Limited insert size capacity (approx 8kb)
	Integrates into host cell genome	Potential safety risk of insertional mutagenesis
	High transfection efficiency ex vivo	
<b>Lentiviruses</b>	Can infect dividing and non-dividing cells	Safety concerns because of origin of vector system (most vectors based on HIV)
	Reasonable duration of expression	Limited insert size capacity (approx 8kb)
<b>Adeno-associated viruses</b>	Can infect dividing and non-dividing cells	Inefficient large scale virus production
	Reasonable duration of expression	Very limited insert size capacity (approx 4.5kb)
	Low immunogenicity	
<b>Alphaviruses eg Semliki forest</b>	Wide host cell range	Short duration of expression although at high levels
	Low immunogenicity	Limited insert size capacity (approx 7.5kb)
<b>Herpes simplex virus</b>	Large insert size capacity (approx 30kb)	Safety concerns – reports of wild type virus replication lytically in the brain causing encephalitis
	Long term expression	
	Low toxicity	
	Wide host cell range – can infect neuronal cells	

**Table 1: Advantages and disadvantages of gene delivery systems (Adapted from refs )**

<b>Vector</b>	<b>Advantages</b>	<b>Disadvantages</b>
<b>Vaccinia</b>	Infects nearly all mammalian cell types	Induces strong T-cell response therefore not useful for chronic disease treatment but could be used in treatment of solid tumours
	Large insert size capacity (approx 25kb)	
<b>Non-viral</b>		
<b>Lipid based</b>	Simple to manufacture	Very short duration of expression
	Very low immunogenicity	Very inefficient infection in vivo (although efficient ex vivo)
<b>Naked DNA</b>	Simple to manufacture	Very short duration of expression
	Very low immunogenicity	Very inefficient infection ex vivo and in vivo

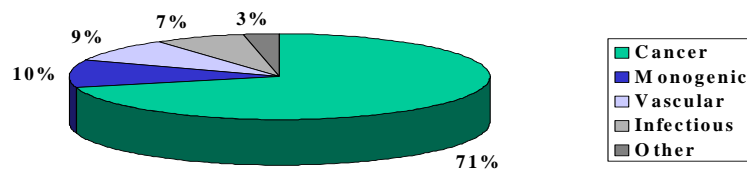
### **Gene repair**

The gene delivery systems described result in new genetic material being added to a cell's genome, they do not correct the underlying genetic defect (Morgan and Blaese, 1999). A number of different approaches are now being developed that aim to correct the mutation; the molecular targeting approach. The aim is to correct the mutation, without altering the surrounding genetic material, so that the gene that has been repaired can still be properly controlled (Ferber, 2001). Techniques include:

- Triplex forming oligonucleotides;
- Small fragment homologous replacement;
- Viral gene targeting; and
- Chimeroplasty.

## Potential applications – clinical trials

13. Nearly 800 clinical trials have taken place worldwide since the first formally approved trial in 1989. The data in Figure 3 shows the types of diseases that are being targeted worldwide, nearly 2/3 being for the treatment of cancer (data adapted from Journal of Gene Medicine clinical trials website). In the UK, nearly  $\frac{3}{4}$  of the approved trials are for cancer therapies.



**Figure 3: Diseases being treated by gene therapy**

14. The majority of trials have been small Phase I/II studies whose main objectives have been to demonstrate safety and gene transfer, and to obtain information to guide dose selection for Phase II and III efficacy studies (Mountain, 2000). To date most trials have had an acceptable patient safety profile but with only limited clinical benefits (Smith, 1999). There have been 2 notable exceptions,

- the death of a patient undergoing gene therapy for ornithine transcarboxylase deficiency (OTCD). The patient died from multiple organ failures 4 days after starting the treatment. Death is believed to have been triggered by a severe immune response to the adenovirus carrier.
- 2 cases of acute T-cell leukaemia reported in patients undergoing treatment for X-SCID (see paragraph 16).

15. A small number of studies have progressed to Phase III trials but only one has reported final results. The study used a retroviral vector to deliver a herpes virus derived therapeutic gene to patients with glioblastoma. The gene therapy was used as an adjuvant to the standard therapy (surgery plus radiotherapy). However, there was no significant difference in survival time when comparing standard therapy with the standard plus gene therapy, although the feasibility and good biosafety profile of this gene therapy strategy were further supported (Rainov, 2000).

16. The success of the clinical trial for treatment of X-SCID has been tempered by the recent reports of 2 cases T-cell acute leukaemia in two of the ten subjects, three years after their otherwise successful treatment (Juengst,

2003). The cancer was thought to have been caused by the insertion of the retroviral vector near the promoter of a proto-oncogene (Williams and Baum, 2003). The event came as a surprise because none of the preclinical studies had shown any evidence of cancer in animal models. In addition, while the possibility of gene insertion activation oncogenes has always been considered a possibility, there is no evidence to indicate that this has taken place in the ten years of clinical trials to date (Cavazzana 2004).

17. This event led to trials involving retroviruses being halted in a number of countries (Phillips, 2002), with the exception of the UK. Here, the Gene Therapy Advisory Committee (GTAC) reviewed the current state of knowledge about the risks of insertional mutagenesis in retroviral gene therapy and made a number of recommendations in relation to retroviral gene therapy and UK retroviral gene therapy trials (GTAC, 2003). Subsequently, the US, France and Germany reopened trials (Cavazzana-Calvo, 2004).

18. To date, only one gene therapy has been licensed for routine use; a cancer treatment using an adenoviral vector that inserts the p53 gene (a gene that triggers cell death). The product has been approved by the Chinese medicines authority (Westphal, 2003).

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## Current Regulatory Framework for Gene Therapy

### **Introduction to the regulatory controls on gene therapy**

1. Currently, in the UK, all gene therapy activity is still at the research and clinical trial stage; there are no UK licensed gene therapy medicines. The regulation of this relatively new technology covers safety to human health and the environment, patient safety and product safety. HSE's primary concern is the control of the occupational health and safety risks of the technology. It is not involved in aspects of patient or product safety
2. As described in previous sections, gene therapy involves novel technological procedures which generally involve the use of microbiological vectors (mainly viruses) as gene delivery systems. These procedures may have potential human health implications both for employees working with the trials/therapies and possibly for the public at large.
3. As with any emerging technology that induces public concern and scrutiny there is a need for appropriate regulatory control. HSE/C need to consider their role in the regulation of this new technology, striking the right balance between protecting employees and others from harm whilst supporting innovation/enabling development of the technology.
4. The following section provides information on the regulatory framework which applies to gene therapy activities, and the role played by HSE and others in the application of this framework to occupational health and safety. To provide further context on the whole range of duties relating to gene therapy activities information is also provided on other regulatory aspects, for example patient safety.

### **Current UK Regulatory framework**

#### **Introduction**

5. Gene therapy requires the delivery of genes to target cells and tissues using an appropriate vector or carrier system. The GM vectors used in gene therapy come under the definition of a Genetically Modified Organism (GMO), defined by the Genetically Modified Organisms (Contained Use) Regulations, as:

*“micro-organisms, plants and animals that have had their genetic material altered by artificial means. This is also known as genetic modification, modern biotechnology, genetic engineering, gene technology, recombinant DNA technology.*

*Genetic modification (GM) occurs where the genetic material of an organism (either DNA or RNA) is altered by use of a method that does not occur in nature and the modification can be replicated and/or transferred to other cells or organisms.*

*The organism which has been modified is referred to as a genetically modified organism (GMO). GMOs may be plants, animals or (most commonly) microorganisms (including bacteria, viruses, parasites and fungi).”*

6. There have been strict safety regulations controlling all contained use work with GMOs in the UK since 1978. The legislation has evolved over the years, partly due to changing technology and increased knowledge, but also through implementation of European Directive 90/219/EEC on the contained use of genetically modified micro-organisms. This Directive was not specifically developed to regulate gene therapy, however, as it covers *“any activity..... in which genetically modified micro organisms are ....used in any way”* it has been taken to include gene therapy involving the use of viral (and other microbial) vectors.
7. The Directive underwent a major revision in 2000 and new national regulations were required to implement the amendments – The Genetically Modified Organisms (Contained Use) Regulations 2000. The amendments covered technical progress, introduced more risk based procedures and improved the applicability of the containment and control measures.
8. Another EC Directive (2001/18/EC) which deals with the deliberate release and marketing of GMOs, implemented by The Genetically Modified Organisms (Deliberate Release) Regulations 2002 (as amended in 1995 and 1997), may also apply to some gene therapy activity. These regulations replace earlier legislation in this field, the Genetic Manipulation Regulations 1989. To date all gene therapy trials in the UK have been considered to be “contained” activities, however, in many European countries, they are regulated under the “deliberate release” legislation.

### **Relevant Legislation**

#### **The Genetically Modified Organisms (Contained Use) Regulations 2000 (Contained Use Regulations)**

9. These regulations replace the earlier Genetically Modified Organisms (Contained Use) Regulations 1992 (and amendments thereof). They are concerned with protecting human health and, for genetically modified micro-organisms, the environmental risks. The regulations require that anyone carrying out any activity involving genetic modification (GM) must do so in conditions of contained use. The genetically modified vectors used in the development of gene therapy are classed as genetically modified micro-organisms.
10. The regime itself is self-regulating with the Competent Authority providing a challenge function. The main requirements:
  - require risk assessment of activities involving genetically modified micro-organisms and activities involving organisms other than micro-organisms. All activities must be assessed for risk to humans and those involving GMMs assessed for risk to the environment;
  - introduce a classification system based on the risk of the activity independent of the purpose of the activity. The classification is based on the four levels of containment for microbial laboratories;
  - require notification of all premises to HSE before they are used for genetic modification activities for the first time;
  - require notification of individual activities of Class 2 (low risk) to Class 4 (high risk) to be notified to the Competent Authority (which HSE administers). Consents are issued for all Class 3 (medium risk) and

Class 4 (high risk) activities. Class 1 (no or negligible risk) activities are non notifiable, although they are open to scrutiny by HSE's Specialist Inspectors who enforce the Regulations. Activities involving GM animals and plants which are more hazardous to humans than the parental non modified organism also require notification;

- require fees payable for the notification of premises for first time use, class 2, 3 and 4 activities notifications, and notified activities involving GM animals and plants.

11. Contained use is where control measures are used to limit contact between GMOs and humans and the environment so as to provide an appropriate level of safety. These can be any combination of physical, biological or chemical barriers. The risk assessment stage determines the level of containment required.

### **The Genetically Modified Organisms (Deliberate Release) Regulations 2002**

12. The deliberate release directive (2001/18/EC) defines "deliberate release" as:

*'any intentional introduction into the environment of a GMO for which no specific containment measures are used to limit their contact with and to provide a high level of safety for the general population and the environment'*.

13. These regulations control all deliberate releases of GMOs to the environment either for research purposes or for marketing. Consent must be obtained from the secretary of state before any release can take place. The legislation also covers marketing of products consisting of GMOs. Activities or products that have consent for a deliberate release (or marketing) fall out of the control of the Contained Use Regulations 2000.

14. The main requirements of the regulations are for a detailed human health and environment risk assessment, application for consent and disclosure of information and public registers.

15. An application for consent to release a GMO under the Deliberate Release Regulations is made to Secretary of State for the Environment (applications are processed by Department of the Environment, Food and Rural Affairs (DEFRA)). Copies of the application are forwarded to the Advisory Committee on Releases to the Environment (ACRE), which provides expert statutory advice and a decision as to whether consent to release should be granted. At present HSE is also part of the Joint Regulatory Authority (JRA), which scrutinises notifications made under Part VI of the EPA 1990 and the current Deliberate Release Regulations 2002. HSE provides advice on the human health and safety aspects of notifications to release GMOs, and signs consents for the deliberate release of GMOs. In assessing applications every possible precaution is taken to ensure that human health and the environment are protected. Only if the risks are considered to be very low will the release be allowed to proceed.

Control of Substances Hazardous to Health Regulations (COSHH) 2002

16. The GM vectors (viral) used in gene therapy are also classed as biological agents so must comply with the requirements for classification, risk assessment and control measures as set out in COSHH and the associated Approved Codes of Practices. However, if the gene therapy project risk assessment is carried out for the purposes of the Contained Use Regulations there is no need for the process to be repeated for COSHH. Similarly, if notification of the activity is made under the Contained Use Regulations there is no requirement to notify the activity under COSHH as well. If the vector is not classed as a biological agent or GMO e.g., a chemical system or naked DNA, the COSHH regulations still apply.

How the regulations apply to gene therapy in the UK.

17. Currently there is no set “rule” under which regulations to notify a gene therapy project. In the UK all gene therapy projects using viral vectors have been notified under the Contained Use Regulations, requiring the use of appropriate physical, chemical or biological barriers to limit contact between people and the environment. Where contact with people and the environment cannot be appropriately limited the project is considered to constitute a deliberate release. At present no gene therapy projects (clinical trials) have notified under the Deliberate Release Regulations, although a small number of trial with GM vaccines have been through that system. Activities that are notified under the Deliberate Release do not need to be notified under the Contained Use regulations.

18. Any group planning to undertake research (whether preclinical or clinical) on gene therapy, involving the use of GMOs, would usually need to follow the requirements of Contained Use Regulations 2000. The project would have to be risk assessed and containment and control measures assigned.

19. The main stages in the process involve:

- Identification of potential hazard (harmful effects) to human health of GM virus
- Consideration of the likelihood, in the event of exposure, of actually causing harm to human health
- Assignment to a provisional containment level
- Consideration of the nature of the work to be undertaken and a detailed review of control measures necessary to safeguard human health
- Identification of any hazards to the environment
- Assignment of additional containment measures to protect the environment, then assignment of the final activity Class (1, 2, 3 or 4)

20. When the regulations are applied to the clinical setting particular attention has to be paid to the possibility that patients may shed the virus following treatment (either at the point of inoculation or in bodily excretions). If it is possible that there will be significant shedding, the gene therapy may constitute a deliberate release and be regulated under the Environmental Protection Act and the Genetically Modified Organisms (Deliberate Release) Regulations 2002. In general projects using replication defective

viral vectors (currently most gene therapy projects) are considered to be contained activities and likely to fall into activity class 1. Therefore they do not require notification to HSE other than an initial premises notification.

Organisations involved in the regulatory process:

### **HSE**

21. HSE has the lead responsibility for regulation of the safety (to humans and the environment) aspects of activities involving GMOs in containment. The Department for the Environment, Food and Rural affairs (Defra), and the Scottish Executive are joint competent authorities, scrutinizing the relevant notifications. Enforcement of the Contained Use Regulations is only dealt with by HSE.
22. The Deliberate Release Regulations are administered by Defra. Defra and the Scottish Executive are lead competent authorities, with HSE joint competent authority covering risks to human health. Application for consent to release a GMO under the Deliberate Release Regulations can only be made to Defra. Once made the application is forwarded to HSE (to scrutinise and agree on matters relating to human health and safety) and the Advisory Committee on Releases to the Environment (ACRE).

Scientific Advisory Committee on Genetic Modification (SACGM (CU))

23. The Scientific Advisory Committee on Genetically Modified Organisms (Contained Use) (SACGM (CU)) is a non-statutory body, which provides technical and scientific advice to the UK Competent Authorities (UK CAs) on all aspects of the human and environmental risks of the contained use of genetically modified organisms (GMOs). The committee was founded originally, in 1984, as the Advisory Committee on Genetic Modification, which played a key role in the development of the comprehensive and highly successful legislation now in place for the contained use of GMOs. The technological developments of gene therapy have been discussed by the ACGM, and advice and guidance has been produced on risk assessment and the safety of the range of vectors in use.

### **European control regimes**

24. The two European Directives on the Contained Use and Deliberate Release of GMOs were adopted to standardise the precautionary measures that need to be taken when working with GMOs. They were not specifically intended to apply to clinical situations dealing with human beings. As a result gene therapy clinical trials do not “fit” easily into this regulatory framework or either of the Directives.
25. The regulatory authorities around Europe are not consistent in their application of the GM directives. There is a divide between whether gene therapy clinical activity should be controlled under the Contained Use or the Deliberate Release Regulations. For instance France, Belgium, Holland, Ireland and Austria notify via the Deliberate Release route. Germany has made gene therapy clinical trials exempt from both regulations.
26. HSE is developing a paper describing the regulatory difficulties in relation to gene therapy clinical trials (and other clinical trials using GMOs) and is

promoting consideration by all parts of the competent authorities in the near future.

### **Worldwide control regimes**

27. In the USA the National Institutes for Health (NIH) Guidelines for Research Involving Recombinant DNA Molecules cover gene therapy activity. Compliance with the Guidelines is mandatory for investigators at institutions receiving NIH funds (either directly or indirectly) for research involving recombinant DNA.
28. These guidelines include a comprehensive description of facilities and practices intended to prevent unintended release or inadvertent exposure to GMOs. The guidelines describe risk groups for agents used in recombinant DNA technology. They require that an initial risk assessment be carried out to decide on the appropriate level of containment followed by thorough consideration of the agent itself and how it is to be manipulated. A final assessment of risk based on these considerations is then used to set the appropriate containment. An Institutional Biosafety Committee must approve the risk assessment and the biosafety containment level for recombinant DNA experiments.
29. Gene therapy research in humans requires additional scrutiny by the Recombinant DNA Advisory Committee (RAC) review process (publicly reviewing human gene transfer clinical trial data).
30. The Food and Drug Administration's Center for Biologics Evaluation and Research (CBER) regulates human gene therapy products. It uses both the Public Health Service Act and the Federal Food and Drug Cosmetic Act as enabling statutes. The FDA has not yet approved any gene therapy product for sale.

### **Other aspects of regulation affecting gene therapy**

31. To provide further context on the whole range of duties relating to gene therapy activities information is provided here on patient safety.

### **Patient safety - European Clinical Trials Directive.**

32. The regulatory framework in relation to gene therapy is most well established in relation to patient safety. The Directive covering patient safety is the European Clinical Trials Directive (2001/20/EC) and is implemented into UK law by the Medicines for Human Use (Clinical Trials) Regulations 2004. The regulations came into force on 1<sup>st</sup> May 2004.

Background on the Directive.

33. The main aim is to simplify and harmonise the regulatory environment for clinical trials on medicines in Europe. Its effect is to adopt into law internationally recognised principles of good clinical practice. This will facilitate the internal market in medicinal products while at the same time protect individuals and help ensure trials produce reliable evidence.
34. These Regulations help to ensure that the rights, safety and well-being of clinical trial subjects are protected by requiring sponsors of trials to be responsible for designing, conducting, recording and reporting clinical trials according to internationally recognised principles of Good Clinical Practice

(GCP). The regulations cover all aspects of the conduct within the EU of human clinical trials with medicinal products, including gene therapy agents, whether sponsored by industry, Government, research organisation, charity or university.

35. The regulations introduce the following new provisions:

- standards for protecting clinical trials subjects, including incapacitated adults and minors
- establish ethics committees on a statutory basis
- covers certain licensing authority procedures for commencing a clinical trial
- require all clinical trials to be conducted in accordance with the principles of good clinical practice (GCP)
- requires inspection systems to be set up for good manufacturing practice (GMP) and good clinical practice (GCP)
- provides for safety monitoring of patients in trials
- sets out procedures for reporting and recording adverse drug reactions and events

36. Gene therapy clinical research on human subjects can only take place after authorisation by The Medicines and Health Care products Regulatory Agency (MHRA) and approval from the Gene Therapy Advisory Committee (GTAC). The ethical review (carried out by GTAC) and Licensing Authority authorisation (MHRA) takes place in parallel

### **Role of MHRA**

37. The MHRA are the competent authority for the UK, (acting on behalf of the Licensing Authority under the Medicines Act 1968) for the new European Clinical Trials Directive (2001/20/EC) and its' implementing regulations – The Medicines for Human use (Clinical Trials) Regulations 2004.

### **Implications for gene therapy trials**

38. Prior written authorisation is required from the MHRA to conduct a clinical trial using a medicinal product for gene therapy. The MHRA has 30 days to either issue a written authorisation or a notice refusing authorisation. There is special provision for extended ethics committee (GTAC) consultation before a gene therapy clinical trial commences. An application for a gene therapy trial is not required to consider occupational health and safety

### **Role of DH Gene Therapy Advisory Committee (GTAC),**

39. The Department of Health's Gene Therapy Advisory Committee (GTAC) is the National Research Ethics Committee for Gene Therapy. It was established in 1993 following the Clothier Committee recommendation that gene therapy should be limited to life threatening diseases or disorders. The new Clinical Trials Regulations gives legal basis to the decisions made by GTAC and formalises their powers of approval and monitoring of gene therapy trials.

40. GTAC advises on the ethical acceptability of proposals for gene therapy research on humans taking account of the scientific merits and the potential benefits and risks, and provides advice to UK health Ministers on developments in gene therapy research. GTAC approval must be obtained before somatic cell gene therapy (i.e. on any cell other than the sperm or egg cells) or gene transfer research is conducted on human subjects. All gene therapy research and recruitment of patients into research trials takes place under strict rules set out by GTAC, under principles elaborated by professional bodies and only after review of clinical protocols by GTAC.
41. The primary concern of GTAC is whether each research proposal meets accepted ethical criteria for research on human subjects. This includes both therapeutic and non-therapeutic research. GTAC will not, at present, consider proposals for germ line cell (egg or sperm) gene therapy. GTAC considers that gene therapy has not yet developed to the stage where it can be considered as treatment.

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