

**SACGM(CU) Annual Report  
2004**

# SCIENTIFIC ADVISORY COMMITTEE ON GENETIC MODIFICATION (CONTAINED USE)



## ANNUAL REPORT (JANUARY TO DECEMBER 2004)



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## Foreword

It gives me great pleasure to present the first Annual report of the Scientific Advisory Committee on Genetic modification (Contained Use). The committee was established in January 2004 to replace the much respected Advisory Committee on Genetic Modification and its technical sub-committee.

As you will see from the contents of this report, it has been a busy year with the Committee delivering advice on technical issues relating to a range of diverse notifications, providing advice on risk assessments and continually developing and updating guidance on all aspects of genetically modified organisms and contained use activity. In addition, the Clinical studies working group chaired by Professor Martin Gore has developed guidance for conduct of clinical studies including gene therapy and GM vaccine trials.

We are committed to openness, and now have a new website and publish the agenda and minutes for all of our meetings. It is vital that we make the public aware of the rigour and independence of our deliberations. To illustrate this we have held one of our normal business meetings in open forum to demonstrate to a diverse audience how we reach our decisions.

I would like to take this opportunity to thank all my fellow committee members for all of their hard work and expert contribution to our deliberations without which we would not be able to operate effectively.

Finally, I am also very grateful to the hard working and efficient secretariat. Their efforts to ensure efficient and effective conduct of Committee business is appreciated by all members.

A handwritten signature in black ink, appearing to read 'Janet Bainbridge', written in a cursive style.

Prof Janet Bainbridge, OBE

October 2005

## **1 Introduction**

The Scientific Advisory Committee on Genetic Modification (Contained Use) (SACGM (CU)) was established in January 2004 to provide technical and scientific advice to the UK Competent Authorities (UK CA) on all aspects of the human and environmental risks of the contained use of genetically modified organisms (GMOs).

SACGM (CU) replaces the Health and Safety Commission's long-running Advisory Committee on Genetic Modification (ACGM) together with its Technical Subcommittee (TSC). ACGM, and latterly the TSC, played a key role in the development of the comprehensive and highly successful legislation now in place for the contained use of GMOs, namely the Genetically Modified Organisms (Contained Use) Regulations 2000 (GMO(CU)).

The SACGM(CU) was set up as a Government scientific advisory committee in accordance with the Office of Science and Technology's Code of Practice for scientific advisory committees and operates in accordance with the Nolan principles. Compliance with Government good practice relating to scientific advisory committees is intended to ensure that independent expert scientific advice is provided when considering key scientific issues relating to the contained use of GMOs.

## **2 UK Competent Authorities For Genetic Modification (Contained Use) Activities**

The Health and Safety Executive (HSE) and the Secretary of State for the Department for Environment, Food and Rural Affairs (Defra) form the Competent Authority in England and Wales for GMO(CU). In practice, these functions are delegated to HSE and Defra officials. In Scotland, the Competent Authority comprises the Scottish Ministers and HSE and similarly these functions are delegated to officials of HSE and the Scottish Executive. Although not part of the Competent authority, the National Assembly for Wales and Northern Ireland are included in all UK CA considerations and are invited to all SACGM(CU) meetings.

The roles and responsibilities of the different members of the Competent Authorities are set out at Annex 1. HSE provides the Secretariat for SACGM(CU). The Secretariat liaises closely with the Chair and prepares papers, organises and hosts SACGM(CU) meetings.

## **3 Terms Of Reference**

The SACGM(CU) terms of reference are:

To provide technical and scientific advice to the UK Competent Authorities on all aspects of the human and environmental risk of the contained use of GMOs. In particular:

- At the request of the UK CAs, to advise on technical issues on individual activities notified under GMO(CU);
- To provide advice on risk assessments for contained use activities involving GMOs other than Genetically Modified Microorganisms (GMMs);
- To develop and update guidance on all aspects of contained use of GMOs including the Compendium of Guidance;
- To provide advice and guidance to others on the technical aspects of genetic modification contained use activities.

#### **4 Genetic Modification**

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. Typically, genetic modification of microorganisms involves the removal of DNA, its manipulation outside the cell and reinsertion into the same or another organism. The aim of genetic modification is often to introduce a new or altered characteristic to the target organism.

The organism, which has been modified, is referred to as a genetically modified organism (GMO). GMOs may be plants, animals or (most commonly perhaps) microorganisms (including bacteria, viruses, parasites and fungi). Where the GMO is a microorganism it is typically referred to as a genetically modified microorganism (GMM).

An important point to note about GMOs is that in the case of humans, even if they have undergone genetic modification as a result of, for example, gene therapy, they are not regarded as GMOs. This is because humans are specifically excluded from the definition of an organism. The result is that GMO(CU) does not apply to humans.

#### **5 Genetically Modified Organisms (Contained Use)**

The general remit of the S<sup>EU</sup>GM(CU) is to provide advice on the safety of activities involving the genetic modification of organisms in “contained use”. Contained use is where control measures (e.g. physical, chemical or biological barriers) are used to limit contact between GMOs and humans and the environment so as to provide a high level of safety. Currently, approximately 99% of genetic modification activities being undertaken in the UK are conducted under contained use. In practice, this involves work in research facilities (e.g. laboratories, glasshouses); industrial sites (e.g. large-scale fermenters); and clinical settings (e.g. vaccine, gene therapy trials). All of these activities are regulated under GMO(CU).

This is a well-established regulatory area, driven by risk assessment, which includes clear direction on control measures required, and permissioning for the highest risk work. The GMO(CU) are unique in requiring the establishment of a local genetic modification safety committee (GMSC) to advise upon risk assessments for GM activities taking place at a GM facility. HSE and ACGM guidance recommends that the GMSC include management and worker representatives, a biological safety officer and appropriate experts.

The GMO(CU) requires classification of GM work according to the containment and control measures required to minimise the risks. Additionally for Class 2 GM activities (low risk) the UK CA must be notified of the work before it takes place (work being halted if the UK CA expresses concerns). For Class 3 and 4 GM work (moderate and high risk) formal consent is required prior to beginning work. Also required, where appropriate, is an emergency plan to be prepared and made available to the local authorities and the public. The public also have access to records of notifications and risk assessment for GM activities through the GM Public Register, though some notifications have been withdrawn from the register on grounds of national security<sup>1</sup>.

All GM premises must register with UK CA and at the end of 2004 there were 971 registered premises and 513 active GM centres in England, Wales and Scotland. The number of employees involved in GM contained use work is more difficult to estimate as GM centres vary from Universities and pharmaceutical laboratories, hospitals to plant breeding facilities and waste inactivation sites (e.g. incinerators, rendering plants). HSE has an active inspection programme supporting the GMO(CU) regulatory framework.

SACGM(CU) provides independent scientific and technical advice on some of these notifications. GM technology is expanding constantly and there are numerous new organisms being created and methods developed and used. The current regulatory framework has the flexibility to accommodate these advances, however, there is a need to seek expert advice on the risks from the novel organisms and methodologies. The membership of the committee is competency driven, ensuring expert scientific advice can be provided to Government in this cutting edge area of scientific endeavour.

The GMO(CU) regulations were made under powers contained in the Health and Safety at Work etc. Act 1974 (HSWA) and the European Commission Act, and give effect to Council Directive 90/219/EEC on the contained use of GMMs, as amended by Directive 98/81/EC, which lays down common environmental and human health and safety measures for such operations. The GMO(CU) regulations also cover the human health and safety aspects of

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<sup>1</sup> The Anti-Terrorism, Crime and Security Act 2001 identified a list of pathogens (including genetically modified versions), which could potentially be used by bioterrorists and should be subject to biosecurity requirements. It was considered inappropriate for the UK Government to provide a list, in the public domain, of GM activities involving these pathogenic organisms and where the work was taking place. These activities are therefore withdrawn from the Public Register in the interest of national security.

contained uses of GMOs that are not microorganisms (e.g. animals and plants). However, they do not cover the environmental aspects of such uses. These are controlled under provisions in Part VI of the Environmental Protection Act 1990 (EPA) and the Genetically Modified Organisms (Risk Assessment) (Records and Exemption) Regulations 1996 (as amended) (GMO RARER).

The aim of GMO(CU) is to:

- Protect persons against risks to their health, whether immediate or delayed, arising from activities involving GMOs (including GMMs); and
- Protect the environment against harm from activities involving GMMs.

The aim of EPA and GMO RARER is to protect the environment against harm from activities involving GM animals or plants.

Sources of further information on the legislation and its requirements can be found in Annex 5 or by contacting HSE's Biological Agents Unit (HID SI4).

It is perhaps important to clarify the GM activities that do **not** fall within the GMO(CU) regulatory framework and so are out with SACGM(CU)'s remit. These include:

- Deliberate release of GMOs into the environment (e.g. crops in field trials covered by Genetically Modified Organisms (Deliberate Release) Regulations) – further information on this can be obtained through Defra who are also the secretariat for the Advisory Committee on Releases into the Environment (ACRE);
- Food safety aspects – further information on this can be obtained through the Food Standards Agency (FSA);
- Product approval/marketing approval – further information on this can be obtained through Medicines & Healthcare Regulatory Authority (MHRA).

SACGM(CU) also does not get involved in some areas closely related to contained use, but for which there are other specific advisory bodies. These include matters of animal welfare (Home Office) and patient safety (e.g. in relation to gene therapy (Gene Therapy Advisory Committee (GTAC))). While SACGM(CU) (and ACGM before that) does not advise on patient safety with regard to gene therapy, where the therapy administers GMMs, this has usually, constituted a contained use activity and has involved asking the Committee's advice on safety in relation to the medical safety of staff, patients' relatives and other close contacts of the patients.

## **6 Membership From January To December 2004**

The SACGM(CU) comprises a Chairperson and 17 members, although this may change with time according to the needs of the Committee. Members have expertise/ representation in the following areas:

- Molecular virology;
- Molecular bacteriology;
- Clinical applications (e.g. gene therapy, vaccine development, clinical virology, molecular oncology);
- Plant biology;
- Environmental microbiology;
- Biological safety officers; and
- Non-Governmental Organisations.

The members' biographies and interests declaration are attached (Annexes 2 & 3). While ACGM was a Health and Safety Commission committee with a typically tripartite membership (*i.e.* an employer/employee/independent membership profile), SACGM(CU) also has two members specifically selected to represent employers and employees.

## 7 Key Issues Discussed By Sacgm(Cu)

In 2004, SACGM(CU) held three meetings (21<sup>st</sup> January; 19<sup>th</sup> May and 22<sup>nd</sup> September) and also an *ad hoc* meeting on the 9<sup>th</sup> November. In addition, a subgroup of SACGM(CU) - the Clinical Trials Working Group - met during the year. This section provides an outline of the key issues discussed at these meetings, however, more comprehensive information including agendas and minutes is available on the SACGM(CU) website at <http://www.hse.gov.uk/aboutus/meetings/sacgmcu/>

### 7.1 First Meeting

At the 1<sup>st</sup> meeting on the 21<sup>st</sup> January members:

- Received a short induction on the role, operation and work plan of the committee; Members were asked to provide a short biography and register of interests for the SACGM(CU) website;
- Agreed that the name of the committee should be the Scientific Advisory Committee on Genetic Modification (Contained Use), SACGM(CU);

#### **Risk assessment enquiry: Invasive *E. coli* K12 cloning host containment and classification**

- Discussed the classification of a modified *Escherichia coli* K12 strain that had been engineered to express the *inv* gene from *Yersinia pseudotuberculosis* and the *hly* gene from *Listeria monocytogenes* from a low copy non-mobilisable plasmid. The modification, which allowed the bacterium to enter mammalian cells and to break out of the endosome, is being developed as a novel method of delivering genetic material to mammalian cells (e.g. to deliver clones of mutant vaccine strains of Marek's disease virus into cultured avian cells);

- Considered the scientific properties of this novel gene delivery system and any potential means of causing harm *i.e.* could the modified bacteria colonise the intestine of animals, survive for prolonged periods in the environment (including gut), and/or facilitate gene transfer (via the plasmid carrying the *inv* and *hly* genes) to wild-type *E. coli*;
- Concluded that whilst few data were available for this particular *E. coli* strain, it is likely the disabled strain could survive for some time, but would not be able to colonise the gut (*i.e.* K-12 derived DAP mutant would be rapidly degraded inside animal cells); the possibility of gene transfer of *inv* and *hly* genes to a wild-type background to produce an invasive *E. coli* though feasible, is low due to the use of a low copy number non-mobilisable plasmid (*i.e.* not a 100% barrier to gene transfer); Although the disabled host was considered suitable for containment level (CL) 1, the risk assessment for activities involving this transfer system need to consider the effects of the gene sequences being transferred and expressed, when determining the classification of the activity (e.g. using the system to deliver herpes viruses to cells to which they would not normally have access);
- Agreed that this is a useful transfer system that may become widely used in the future hence further guidance should be included in the updated Compendium; and the likelihood of gene transfer, to and from the modified *E. coli* in the gut of infected animals should be the subject of further investigation, for which funding should be sought.

### **Safety of viral replicons: use of a foot-and-mouth disease virus (FMDV) replicon system**

- Discussed the safety of viral replicon systems, particularly FMDV replicons. In this example, replicons are described as self-replicating RNAs derived from positive sense RNA viruses. They can be used to generate infectious virus or in this case, have deletions in the structural capsid genes that preclude virus particle production *i.e.* FMDV replicon system can only replicate RNA and not package RNA into viruses. The FMDV replicon system is used to study different parts of the viral replication cycle and kills the cells within a few hours of transfection, presumably through toxicity of expressed proteins, or the hijacking of the cellular transcription and translation machinery;
- Listened to presentations, on picornavirus replication and the molecular development of the FMDV replicon system; and, on the notifier's work with FMDV proteins (e.g. mechanism of the 'primary' 2A/2B polyprotein cleavage) and the proposed studies using the FMDV replicon.
- Considered the scientific issues relating to the use of the FMDV replicon system and any safety concerns raised by such work *i.e.* could the replicon system be an inadvertent source of FMDV; could residual capsid sequences act as a "hotspot" or focus for recombination; could

recombination between the bacterial plasmid carrying the cDNA coding for the replicon and other plasmids carrying the capsid genes occur; what is the likelihood of trans-encapsidation of FMDV replicon RNA by the capsid from other picornaviruses; could introduction of the replicon sequences into animals compromise antibody screening procedures (e.g. “false positive” antibody test); could primary or bovine cell lines be a means of complementation for the replicon;

- Concluded that recombination between replicon RNA and capsid sequences to generate live virus could possibly occur if both were expressed within the same cell, however, both the replicon RNA and the capsid RNA have to be in replication complexes (*cf* pestiviruses); due to the packaging constraints and complexity of the capsid, it is very unlikely that any sequences other than FMDV capsid sequences could encapsidate the viral RNA - if this occurred, the resulting virus would behave more like the capsid-donor virus than FMDV (*i.e.* species specificity, transmissibility and detection); the most likely scenario for reconstitution of FMDV virus particles would be if the laboratory contained plasmids carrying capsid genes and plasmids containing the FMDV replicon, in which case, though highly unlikely, recombination may be possible - recombination with other sequences was not considered to be an issue; Members concluded that the FMDV screening procedure would not be compromised from replicon work since screening detected antibodies to the capsid proteins, which are not found in the replicon;
- Agreed that classification of replicon systems should be on a case-by-case approach *i.e.* where the replicon system is combined with a packaging system to produce infectious virus, containment would be based on that required for the virus, however, for disabled systems such as the FMDV replicon where no virus can be produced a lower level of containment would apply, in this case, CL2 (*i.e.* requirement to restrict access, use gloves); Containment for the FMDV replicon should include use of only established, characterised cell lines, no storage of the clones carrying the capsid sequences and the replicon in the same laboratory or freezers, separation of work (*i.e.* dedicated safety cabinets, incubators), appropriate training of staff, implementation of local rules and Standard Operating Procedures, and freezers containing locked storage boxes; Members recognised the importance of biosecurity in this matter, however, emphasised that it should be made clear what measures were required to work safely with the replicon system, and what additional measures were required for “security” reasons.

## 7.2 Second Meeting

At the 2<sup>nd</sup> meeting on the 19<sup>th</sup> May, members:

- Agreed to establish links to other relevant advisory committees (e.g. ACRE, GTAC) including a slot on the agenda, to keep abreast of any recent and relevant developments;

- Informed that the SACGM(CU) website had been set up and was in the process of being populated with agendas, minutes, guidance;

### **The safety of novel influenza A viruses and their use in the manufacture of vaccine**

- Discussed the legal status of reverse genetics systems and agreed that the GMO(CU) regulations apply to the process used to generate the virus rather than the end product hence the technique of reverse genetics is covered by the current GM legislation;
- Discussed the safety aspects of the proposed use of reverse genetics to develop a human vaccine against the H5N1 Hong Kong strain of avian 'flu, which the WHO assess as having pandemic potential. Reverse genetics will be used to circumvent the difficulties associated with conventional reassortment methods in producing a candidate vaccine strain *i.e.* the vaccine strain will consist of a backbone (6 internal genes) of human vaccine strain PR8 combined with the modified haemagglutinin (deleted polybasic cleavage site) and neuraminidase genes (HA and NA) from the H5N1 HK strain;
- Listened to presentations on development of the H5N1 HK vaccine strain and initial safety testing; on influenza vaccine production at pilot and large scale; and on the procedures and difficulties in inactivating large quantities of egg waste;
- Considered the main risks of the work to be the potential for reassortment between the vaccine strain (PR8/H5N1) and a circulating human influenza virus, resulting in the generation of a novel human virus expressing the H5 antigen. Such a scenario could theoretically result in a 'flu outbreak in a population with no background immunity with severe consequences;
- Concluded that the large-scale containment tables of GMO(CU) did not reflect the unique production conditions required to produce vaccines from eggs; CL3 was considered necessary to ensure that human health and environmental protection was achieved; acknowledged the difficulties involved in waste disposal from large scale CL3 activities, however any derogation from full CL3 needed to be fully justified; Members considered that in current circumstances where H5N1 is not prevalent in Europe, the use of RPE was required, unless the process could be fully enclosed; Members considered vaccination of staff to be a sensible prophylaxis to minimise the potential for reassortment, and should be a condition of being able to undertake this aspect of their work;
- Agreed that the current and proposed methodology for large scale 'flu vaccine waste inactivation and pilot scale H5N1 vaccine manufacture (*i.e.* use of 45 gallon sealed drums and incineration), are unsuitable for the large-scale H5N1 vaccine production - secretariat informed Members that HSE and the manufacturer would be working closely towards resolving this issue.

## **Risk assessment enquiry – classification of selectively replicating herpes vectors for use in clinical trials**

- Discussed the use and classification of a selectively replication competent herpes simplex virus type 1 (HSV1), expressing the human GM-CSF protein for use in cancer gene therapy. In the light of phase I clinical trials, the notifiers wish to reclassify the work *i.e.* the revised risk assessment does not require patients to be kept in a side room under negative pressure;
- Listened to presentations describing the molecular development of the HSV1 vector, the clinical trial (*i.e.* 20-40 patients spread across 5 specialist carer facilities) and the rationale for altering the classification *i.e.* although oncolytic, the biological properties of the vector made spread through aerosol route highly unlikely hence revised assessment does not identify the need for negatively pressurised rooms;
- Considered the concerns raised regarding HSV1 selective replication in dividing cells and questioned the potential risk to foetal tissue and pregnant women – although pregnant women would not be a target group for treatment, risks to pregnant members of staff who may administer the treatment had not been considered; Members recognised the difficulties in applying the containment measures prescribed in GMO(CU) to a clinical setting;
- Agreed that there is no indication that HSV1 can be spread via an aerosol route, although there was a potential for splashing hence goggles should be worn as part of nursing standard operation procedure; Members agreed that there would be no requirement for patients to be nursed in negatively pressurised rooms.

## **Increased virulence associated with *M. tuberculosis* gene deletion mutants – Implication for Risk Assessment**

- Discussed a published scientific findings (Parish *et al*, 2003<sup>2</sup>) involving targeted gene deletions in *Mycobacterium tuberculosis*, where contrary to anticipated results that most gene deletions would lead to pathogens that are less virulent, strains of *M. tuberculosis* with engineered deletions in two-component regulatory signal transduction systems were shown to be hypervirulent using *in vivo* challenge experiments;
- Considered that it was not an unexpected phenomenon to produce something more dangerous by deletion of a regulatory gene and that not every gene deletion resulted in attenuation of a pathogen; It was also noted that gene insertion into regulatory sequences could also prove

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<sup>2</sup> Parish et al. 2003, “*Deletion of Two Component Regulatory System Increase the Virulence of Mycobacterium tuberculosis*”, *Infection & Immunity*, 71(3), 1134-40.

problematic; It was however, emphasised that the majority of gene deletions will result in some degree of attenuation;

- Concluded that the increase in virulence of the *M. tuberculosis* did not warrant any change in containment, since the bacteria would be handled in the same way as wild type; Members recommended that the *M. tuberculosis* and other examples of other deletion mutants of increased virulence, should be included in the revised Compendium of Guidance.

### 7.3 Third Meeting

At the 3<sup>rd</sup> meeting on the 22<sup>nd</sup> September members:

- Considered a tabled item on the use of reverse genetics to manufacture annual trivalent human influenza vaccines, where the genetic modifications introduced were equivalent to those produced by conventional reassortment methods; Members agreed that the technique is covered by the regulations (as concluded at the 2<sup>nd</sup> SACGM(CU) Meeting) however, since the increasing use of reverse genetics may lead to more perceived anomalies, broader discussion of reverse genetics should be the subject of a substantive agenda item at a future meeting;
- Informed of an issue raised at GTAC where recent scientific studies had been brought to their attention, which appeared to demonstrate that a widely used lentiviral vector was found to be oncogenic in an *in utero* animal model; Members agreed that an *ad hoc* meeting should be convened to specifically assess the implications of these findings for contained use activities.

#### **Risk assessment enquiry – containment and classification of a modified avian influenza virus with altered tropism**

- Discussed the proposed activity involving the genetic modification of highly pathogenic avian influenza virus (HPAI) using reverse genetics to investigate the viral determinants of replication efficiency and host range restriction. The proposed activity will provide an insight into the likelihood of HPAI strains being able to spread from birds to humans. The proposed modifications include introducing mutations in HPAI that may increase its replication efficiency in avian cells (including modification of the HA and NA genes) or alter the ability of the HPAI such that it would be able to replicate in human cells (*i.e.* modification of 5 internal genes PB1, PB2, NS1, NS2 and NP); The work was notified to the UK CA as a Class 3 activity;
- Listened to a presentation on the proposed activity (*i.e.* types of modifications, scale of the work (*i.e.* ~ 250ml of infectious 'flu virus, 2 to 3 laboratory workers), the advantages of using reverse genetics (*i.e.* introduction of intricate changes within genes, not possible using conventional reassortment) and the hazards associated with the work;

- Considered the risks associated with the proposed modification of HPAI *i.e.* potential to generate a HPAI with ability to replicate in human cells, the possibility that such viruses may be transmissible between individuals (pandemic potential) and the possibility of increased pathogenicity through modification of internal genes (e.g. NS1 glutamic acid substitution);
- Concluded that the work should be classified as a class 4 activity based on the HPAI being a SAPO category 4 pathogen, the requirements for control measures from CL4 (e.g. complete change clothing, double HEPA filters), the intention of the work to alter the tropism of the virus (*i.e.* extend avian virus replication to human cells) and the degree of uncertainty associated with the outcome warrants highest containment; the acceptability of derogation from full CL4 should be determined by science based risk assessment e.g. if it was clear that the virus was not associated with human infection, a Class II MSC might be adequate, however studies involving altering the virus tropism where it could infect humans, would require a Class III MSC; since safe and effective vaccines against seasonal 'flu strains were available and given the potentially severe consequences of a reassortment between H5N1 and circulating influenza virus then workers should be vaccinated prior to commencing this activity;
- Agreed that in general terms, changing tropism should increase the level of containment, however, the most appropriate containment measures should be determined by the risk assessment, where all aspects of the final viral construct (e.g. replication competence, mode of transmission) are considered.

### **Regulatory status of DNA vaccination and siRNA technologies**

- Discussed whether GMO(CU) covered a range of activities involving manipulations of naked DNA or oligonucleotides including for biophysical analysis, eliciting an immune response to the protein encoded by the directly injected DNA or interruption/ alteration protein expression using the technique of RNA interference (RNAi) or small interfering RNAs (siRNA)). Members considered draft guidance on how such activities could be interpreted under GMO(CU);
- Concluded that the draft guidance (after minor amendments) gave a clear and useful interpretation of these methodologies, and was considered very timely given the increasing use of such techniques; It was indicated that the views of ACRE on this guidance would be helpful; Following revision, the guidance should be placed on the website and included in the updated Compendium of Guidance.

### **Draft guidance on “self-cloning”**

- Discussed the widely used GM technique of “self-cloning”, which involves the cloning/modification of genetic material from an organism, or a very

closely related organism, and its re-insertion back into that organism. Where the resultant organism presents no or negligible risk to human health or the environment, then the self cloning activity is exempted from all of the GMO(CU) requirements except Regulation 17 (*i.e.* general principles of occupational safety and hygiene) of GMO(CU); However, it is not exempted from any part of the GMO(DR). Members considered draft guidance aimed at providing clarification on this topic, and through the use of examples, proposes a line to take in relation to this area of research;

- Considered the example of self-cloning in yeast, the possible use of self cloning experiments in Biology courses in high schools, the extension of the definition to plants and animals (not included as part of the EU Directive) and self cloning in microorganisms;
- Concluded that the use of antibiotic resistance markers needs careful consideration for work to meet the self cloning definition; HSE should discuss good, safe experiments and boundaries with the Department of Education if such experiments are to be added to the curriculum; It was indicated that the views of ACRE on this guidance would be helpful; Following revision, the guidance should be placed on the website and included in the updated Compendium of Guidance.

#### **7.4 Ad Hoc Meeting**

The meeting was called to discuss initial reports of the development of tumours in mice that had been exposed to lentiviral vectors either *in utero* or as neo-nates, as part of the development of novel approaches to gene therapy. HSE had been informed by researchers that animal were developing high rates of tumours, and concerns were raised about the safety of lentiviral vectors. Futhermore, a report in the literature suggested that in some circumstances, the woodchuck post-transcriptional regulatory element, WPRE, which is capable of expressing part of the X protein from Woodchuck Hepatitis Virus, may exhibit oncogenic properties.

The Gene Therapy Advisory Committee (GTAC) had put out some interim guidance to researchers wishing to use lentiviral vectors, and HSE needed to consider any additional risks to workers in the research environment.

At the *Ad Hoc* meeting on the 9<sup>th</sup> November members:

- Discussed the issue raised by GTAC in relation to the safety of lentiviral vectors;
- Concluded that as an interim measure, an information note should be sent to all GM centres informing them of recommendations of the meeting *i.e.* as a precautionary measure, undertake all work involving lentiviral vectors at containment level 2 until full research data is available; Information note reproduced at Annex 4.

## **8 SACGM(CU) Working Groups**

### **8.1 Clinical Studies Working Group**

A clinical studies working group was established to consider producing guidance for those wishing to conduct clinical studies, including gene therapy and testing of novel GM vaccines.

The group comprised members from SACGM(CU) and ACRE, as well as an MHRA and GTAC representative.

The group is chaired by Prof Martin Gore, who is Vice-Chairman of both SACGM and GTAC. Members of the group are:

Dr David Lewis – SACGM(CU)  
Dr Peter Coyle - SACGM(CU)  
Dr Peter Searle – SACGM(CU)  
Dr Jonathan Stoye – ACRE  
Dr Penny Hirsch – SACGM(CU) and ACRE

The group considered guidance to the community to help to facilitate the conducting of human studies in a clinical environment. Draft guidance was produced and this has been further amended. The group is due to meet to consider the latest draft of the guidance. Amongst the topics being covered are scoping guidance; the borderline between contained use and deliberate release; biological containment; and health surveillance.

## **9 Forward Look**

### **9.1 Clinical Studies Working Group**

Part of the remit of the group is to provide guidance on risk assessment and containment for GM activities undertaken in a clinical setting. Whilst GMO(CU) has the flexibility to encompass such activities, there is a need for clarification on the interpretation and application of GMO(CU) to this area. This guidance will form part of the revised Compendium of Guidance.

### **9.2 SACGM(CU) Public Meeting**

SACGM(CU) is committed to being open about what it does and wants to provide the opportunity for people to see how SACGM(CU) works and reaches its decisions. To this end, the first open meeting of SACGM(CU) will take place on Wednesday, 1<sup>st</sup> June 2005 at Rose Court, Southwark Bridge, London, SE1 9HS. The agenda will be posted on the SACGM(CU) website four weeks in advance of the meeting.

### **9.3 Compendium Of Guidance Update**

The ACGM Compendium of Guidance was substantially revised at the time of the introduction of GMO(CU). The UK CA plans to update the Compendium in 2005/6 to include, for example, more information on viral vectors, reverse genetics, siRNA, immune modulator genes, parasites, clinical activities (e.g. gene therapy), animal/plant containment, monitoring and waste inactivation. Whilst the Secretariat will undertake the drafting of the guidance, the majority of the scientific and technical advice on this will fall to the SACGM(CU).

### **9.4 Other Work Areas**

SACGM(CU) will contribute to a number of other work streams in 2005:

- Continuing to give scientific advice on issues arising from notifications made under GMO(CU) - in practice the SACGM(CU) scrutinises individual notifications where additional technical expertise is required;
- UK CA promotes continuous improvement in the industry through newsletters and guidance, which it distributes directly to the GM centres and/or posts on the Internet. SACGM(CU) may be asked to review the scientific aspects of newsletters or guidance prior to distribution.

### **SACGM Secretariat**

## **Annex 1 United Kingdom Competent Authority (UK CA)**

### **Competent Authority: Role**

**Health and Safety Executive (HSE):** HSE has lead responsibility for human health and safety throughout Great Britain. HSE administers the permissioning process for the whole of the competent authority, and maintains the Public Register and provides technical comment on the notifications. HSE undertakes inspections to check support the GMO(CU) regulatory framework. Permissioning provides intelligence for inspection and inspection provides intelligence for permissioning.

**The Department for the Environment, Food and Rural Affairs (Defra):** Acts on behalf of the Secretary of State. It has lead responsibility in England and Wales for all effects from the contained use of GMMs on the environment or living organisms supported by the environment, including indirect effects on human health that may result from environmental pathways. It is also responsible for the environmental effects of GM animals and plants in England and Wales in relation to contained uses that affect the former MAFF's interests, e.g. farmed animals (including fish and shellfish), plant varieties and seeds, veterinary medicines, fertilizers, animal feedstuffs, food and forestry, as well as the marine environment.

**The Scottish Executive (SE):** Has the same responsibility in Scotland for the effects of contained use of GMMs on the environment as Defra has in England and Wales, and for the environmental effects of GM animals and plants as Defra has in England. It is also responsible for those aspects of public health that do not come within the scope of the HSWA.

**The Welsh Assembly Government (WA):** Has no legal responsibilities for contained use activities involving GMMs, but are consulted upon the environmental aspects of such activities when they occur in Wales. The assembly has the same responsibility for the environmental effects of GM animals and plants in Wales, as Defra in England or the Scottish Executive in Scotland. This means that they have a legal responsibility to comment on environmental aspects of contained use activities involving GM animals and plants.

## **Annex 2 SACGM(CU) Members' Biographical Information**

### **Professor Janet Bainbridge OBE Senior Specialist Advisor - Government and Europe OneNorthEast**

Currently Janet is seconded to OneNorthEast to lead a series of activities to enhance the Regional success in accessing European framework funding. A Professor of Biotechnology and Food Science, she has worked in the NHS, and in the food manufacturing sector. As a qualified teacher she has worked in all branches of education except primary. She is an experienced reviewer of research and funding proposals and reviews for the Research Councils, DTI and the European Commission.

Janet was formerly the Dean of Science and Technology at the University of Teeside, and led the University to gain Investors in People (IIP) accreditation across the entire Institution. She was then seconded to a University spin-off Company, EPICC (European Process Industry Competitiveness Centre) and over 30 months turned the business around from a deficit in funding and outputs to a healthy profit.

Janet has had many senior Government Advisory roles including former Chair of Advisory Committee on Novel Foods and Processes (ACNFP), Member of EPSRC Council, member of Advisory Committee on releases to the Environment (ACRE) and Chair /member of several Foresight Committees.

Currently she Chairs the Scientific Advisory Committee On Genetic Manipulation (Contained Use), she is a member of the Borderline substances review group (MHRA), the New and Emerging Infections Panel and a trustee of the charity Sense About Science. Regionally she is a member of the Science and Industry Council and a Board member of IPPR (North).

### **Professor David Baulcombe FRS Senior Research Scientist Sainsbury Laboratory John Innes Centre, Norwich**

Professor David Baulcombe is a Senior Research Scientist at the Sainsbury Laboratory, located at the John Innes Centre, in Norwich, and holds a Chair at the University of East Anglia. He has worked for over twenty years on the genetic modification of plants and plant viruses. Much of his work has focused on the development of plants expressing viral sequences as an approach to developing disease resistance. More recently he has developed a range of plant viral vectors based on potato virus X and tobacco rattle virus, which have been used to express foreign proteins and for gene silencing. His group elucidated many aspects of the mechanisms of gene silencing, including the discovery of short silencing RNA molecules. David was the President of the

International Society of Plant Biology between 2003 and 2004, and is on the editorial board of a number of journals. He was elected as a Fellow of the Royal Society in 2001.

**Dr Gary Burns MBE**  
**Biosafety Adviser**  
**AstraZeneca UK Ltd**

Gary Burns is currently a biosafety adviser for AstraZeneca UK Ltd and has been employed in this role since 1999. He previously followed an academic career in biochemistry and molecular biology for nearly twenty years before joining the Health and Safety Executive as one of HM Inspectors of Health and Safety in 1993. In 1996 he transferred to a specialist role with HSE in the Biotechnology Section of what is now HSE's Biological Agents Unit (HID SI4) where his duties involved ensuring compliance with legislation governing both contained use and deliberate release activities. In addition to inspecting locations where these activities were carried out, Gary was also involved in providing advice and in drafting formal guidance on this topic. He was awarded a PhD by the University of Manchester in 1972 and a Post-Graduate Diploma in Health and Safety from Aston University in 1994. Gary was a member of the ACGM from December 2000, and of the associated TSC from May 2001, until they were replaced at the end of 2003.

**Dr John Carr**  
**Head of Molecular Virology**  
**Department of Plant Sciences**  
**University of Cambridge**

Dr John Carr is head of the molecular virology group at the University of Cambridge. The long-term objective of the group is to understand why some plants are able to actively resist microbial pathogens, while others remain susceptible. John's research interests are focused in three areas: signal transduction pathways in the induction of resistance to plant pathogens; the structure and protein composition of the replication complexes of tobacco mosaic virus and cucumber mosaic virus, and the role of viral counter-defence in determining the outcome of plant-microbe interactions.

**Dr Martin Carrier**  
**William Harvey Research Institute**  
**Barts & the London School of Medicine and Dentistry,**  
**Queen Mary College, University of London**

Dr Martin Carrier obtained a BSc in Biochemistry at Bristol University and his PhD at King's College London. After a post-doctoral fellowship in Paris he went on to spend 10 years in the Pharmaceutical Industry where his main interest was in the molecular mechanisms underlying cardiovascular disease. He then returned to Academia at the William Harvey Research Institute, Barts and the London, Queen Mary's School of Medicine where he has been for the

last 10 years. He divides his time between teaching and research. He has an overall responsibility for GM activities within Queen Mary College.

**Dr Peter Coyle**  
**Consultant Virologist**  
**Regional Virology Laboratory**  
**Belfast**

Dr Peter Coyle is a Consultant Virologist at the Regional Virus Laboratory at the Royal Group of Hospitals, Belfast. He is also an Honorary Lecturer at The Queen's University of Belfast Department of Microbiology, and Chairman of the Royal Group of Hospitals Genetic Modification Safety Committee. Peter obtained his medical degree from Queen's University of Belfast in July 1979. He has been a member of the Royal College of Pathologists since 1985, and was awarded an MD (by thesis) from Queen's University in July 1993. Peter is a member of Royal College of Pathology's Virology CATT-B Training Committee, and the Health Protection Agency's HIV Diagnostic Forum as well as its Expert SARS Advisory Group. His principal interest is in Respiratory Tract Infections. He was a member of the ACGM TSC for a short period prior to being invited to serve on the SACGM(CU).

**Professor Martin Gore**  
**Consultant Cancer Physician**  
**Royal Marsden Hospital, London**

Professor Martin Gore is Consultant Cancer Physician at the Royal Marsden Hospital and Institute of Cancer Research, London where he is Medical Director for the Rare Cancers Division and Head of the Melanoma Unit. His main interests are melanoma, renal cell cancer and ovarian cancer, and he is Chairman of the NCRI Melanoma Clinical Studies Group. Over the last 15 years Martin has continued to develop his interests in drug development particularly in the field of biological therapies and gene therapy. Martin is Vice Chairman of GTAC and SACGM(CU). He chaired the Committee for Clinical Research at the Royal Marsden Hospital and Institute of Cancer for 10 years. Martin also co-chairs the Joint Subcommittee on the Retroviral Safety and the Gene Therapy Working Party, and is on the Editorial Board of a number of journals. He is a Fellow of the Royal College of Physicians, and has published over 300 articles and has edited 6 textbooks.

**Professor Ernest Gould**  
**Assistant Director**  
**Centre for Ecology and Hydrology, Oxford**

Professor Ernest Gould has been a virologist for approximately 35 years, studying in Liverpool, moving to Birmingham, Belfast, London and finally, Oxford. He originally worked with orthomyxoviruses and paramyxoviruses, such as influenza and measles but for the past 25 years his interests have

focused on the arboviruses, with emphasis on the flaviviruses such as Yellow fever, Japanese encephalitis, Tick-borne encephalitis virus. He has also worked with alphaviruses and bunyaviruses as well as with non-arboviruses such as the rabbit caliciviruses all of which have become more prominent with the increasing interest in emerging viruses. His group recently demonstrated that African viruses such as West Nile, Usutu and Sindbis virus are being introduced into the UK via migratory birds. Ernest's areas of research cover virus epidemiology, pathogenesis, evolution, diagnosis and control. In 2002, he retired as the Director of CEH Oxford (formerly the Institute of Virology and Environmental Microbiology) and is now a Senior Research Fellow in the Institute. He has been a member of several advisory committees including, ACDP, ACZOO, and is currently a member of the University of Oxford Safety Committee and the equivalent committees in CEH. Ernest also advises on the CL4 laboratory in Lyon, France. He has published approximately 150 peer-reviewed papers and written many reviews and book chapters.

**Dr Penny Hirsch**  
**Principal Research Scientist**  
**Rothamsted Research Centre, Harpenden**

Dr Penny Hirsch is a Principal Research Scientist at Rothamstead Research Centre, where she is the leader of the Soil Microbial Ecology Group. Her main interests are in soil microbial ecology and microbial gene transfer, including the survival of laboratory grown bacteria and fungi in the environment; the ecology of microbes involved in nutrient cycling in soil; bacterial plasmids and bacteriophages, and soil as a reservoir of genes and of potential pathogens. Penny has been a member of the ACRE since 1999, and was a member of the ACGM and associated TSC, until it's replacement by SACGM(CU). She was biological safety officer at Rothamstead between 1986 and 1996.

**Dr Keith Howard**  
**Head of Molecular Virology and Vector Development**  
**Oxxon Therapeutics Ltd, Oxford**

Dr Keith Howard completed his PhD at the London School of Hygiene and Tropical Medicine after a study of changes in gene expression during the life cycle of the parasitic trypanosome, *Leishmania donovani*. Following six years postdoctoral work on *in vitro* models of herpes simplex virus (HSV) latency and development of HSV vectors in the group of Professor David Latchman at University College London, Keith joined Cantab Pharmaceuticals Ltd (now Xenova Plc) where he adapted the company's DISC HSV vaccine for use in the treatment of neurological disease. Since 2002 he has been Head of Molecular Virology and Vector Development at Oxxon Therapeutics Ltd, (formerly Oxxon Pharmaccines Ltd), directing the development of innovative recombinant poxvirus vectors for the treatment of chronic infections and cancer.

**Dr David Lewis**  
**Senior Lecturer and Honorary Consultant Physician**  
**Division of Infectious Diseases**

## **St. Georges Hospital, London**

Dr David Lewis is a Consultant Physician and Senior lecturer in the Medical School at St. Georges Hospital, London, specializing in infectious diseases, and the development of novel vaccines. After qualifying in medicine from the University of Wales, David obtained an MSc in medical microbiology, and a PhD for his research on HIV in infected patients. He was awarded an MD in 1994, and became a Fellow of the Royal College of Physicians in 1998. Much of David's research has focused on the development of vaccines, and he has conducted a number of clinical trials with recombinant enteric bacteria, including Shigella and Salmonella. David has carried out a number of phase 1 clinical trials using live bacterial vaccines, and is the clinical trials coordinator of the EC 6<sup>th</sup> Framework programme 'MUVAPRED' which is evaluating novel mucosal vaccines. David is the Deputy Director of the St George's Vaccine Institute, and is responsible for day to day running of the facilities including clinical isolation rooms and containment laboratories. David is currently on a Working Party of the Academy of Medical Sciences, drawing up guidelines for researchers involved in human challenge studies using pathogens.

### **Dr Sue Mayer Director GeneWatch UK**

Dr Sue Mayer is the Director of GeneWatch UK, a Non-Governmental Organisation, which monitors developments in genetic technologies from a public interest, environmental protection and animal welfare perspective. Sue has a first degree in Pharmacology, and a PhD in veterinary cell biology, as well as a degree in veterinary science. Her career has been varied as she has worked as a veterinary surgeon, a research scientist, a University lecturer, and as Director of Science, Greenpeace UK, before her current position as Director of GeneWatch UK. Sue is a member of the Government appointed Agriculture and Environment Biotechnology Commission, and was formerly a member of the ACGM's TSC. She is currently a Board member of Greenpeace UK, and Chair of the Board of Trustees of Vetwork UK, an animal welfare charity.

### **Dr Philip Minor Head of Division of Virology National Institute for Biological Standards and Control**

After obtaining his degree in Biochemistry from Oxford, Dr Philip Minor studied for a PhD at the ICRF in London, before undertaking post-doctoral research on influenza virus at the University of Warwick. He joined NIBSC as a virologist where he has worked for over 25 years. Philip has been Head of the Division of Virology for the last 15 years. During this time he has worked on vaccine development and its regulation, both nationally and internationally through the World Health Organisation. He has extensive experience of the application of molecular biology to virology regulation and pathogenesis, particularly working on poliovirus virulence, attenuation, epidemiology, antigenic structure and receptor sites. Philip has extensive experience of

working on a wide range of committees, including the ACDP, various WHO expert committees, and the UK Committee on Adverse Reactions to Vaccination and Immunisation. He is a former editor of the Journal of General Virology, and is currently the editor of Biologicals. Philip has over 180 publications.

**Mr Robert Osborne**  
**Biological Safety Adviser,**  
**University of Glasgow**

After obtaining a BSc in Chemistry and Zoology from the University of London, and an MSc in Applied Immunology from Brunel, Robert Osborne spent 16 years working at the Animal Virus Research Institute at Pirbright. After leaving Pirbright he moved to the University of Glasgow to work as a Research Fellow in the MRC Retrovirus research laboratory in the Department of Veterinary Pathology. Since 1994 Robert has worked as the University Biological Safety Adviser, responsible for all aspects of biosafety management within the University, encompassing all aspects of working with pathogenic agents and genetically modified organisms. He was formerly a member of the ACGM and is an active member of the European Biosafety Association.

**Dr Brian Robertson**  
**Senior Lecturer**  
**Centre for Molecular Microbiology & Infection**  
**Imperial College, London**

Brian Robertson studied Zoology at the University of Edinburgh, before undertaking a PhD in Parasitology at Imperial College London. He then switched to molecular microbiology and worked on *Neisseria gonorrhoeae* for 5 years at the Max-Planck-Institut in Germany. On returning to the UK he worked on both *Neisseria* and *Mycobacterium tuberculosis* at Imperial College London, where he is now a Senior Lecturer in the Department of Infectious Diseases and Microbiology in the Faculty of Medicine. His main interest is pathogen biology and the interaction with the host organism. He served as chair of the local GMSC and on the ACGM for two years.

**Dr Mike Skinner**  
**Principal Research Scientist**  
**Avipox Group Leader**  
**Institute for Animal Health, Compton**

Dr Mike Skinner studied Microbiology at the University of Leeds, followed by bacterial genetics and biochemistry for his PhD at the University of Leicester. He moved into the molecular biology of viruses, with postdoctoral positions on coronaviruses (Würzburg, Germany), poliovirus (Leicester and Reading) and HIV (MRC-LMB, Cambridge) before joining the Institute for Animal Health as a group leader to work on avian poxviruses. Since then he has also worked on avian leukosis virus and a birnavirus. His scientific interests are virus-host interactions and vaccines. At the IAH, Mike is a long-serving member of the local GMSC, having also served as chairman and Biological Safety Officer.

**Dr Peter Searle**  
**Cancer Research UK Institute for Cancer Studies**  
**University of Birmingham**

Dr Peter Searle is currently a Senior Lecturer at the Cancer Research UK Institute for Cancer Studies, University of Birmingham. He has over 20 years research experience with genetic modification techniques. For the last 10 years he has worked on cancer gene therapy, using retrovirus and adenovirus vectors. He has been the Biological Safety Officer for the Institute for over 10 years, and is also Biological Safety Officer for the University Hospital Birmingham NHS Trust, where he guided the establishment of gene therapy clinical trials.

**Professor Peter Williams**  
**Department of Microbiology and Immunology**  
**University of Leicester**

After completing his degree at Imperial College, Professor Peter Williams obtained his PhD in bacterial genetics from the University of East Anglia. He went on to carry out post-doctoral research positions before moving to a lectureship in genetics at the University of Leicester, where Peter is currently the Professor of Microbiology and Head of the Department of Microbiology and Immunology. His research background is in microbial molecular genetics, which he has applied to the study of the regulation of bacterial virulence factors, particularly in relation to diseases of the gastrointestinal tract. He is especially interested in the role of iron uptake and metabolism in the pathogenesis of infection.

### Annex 3 Register Of SACGM(CU) Members' Interests

SACGM(CU) members have declared the following commercial and non-commercial interests deemed relevant to their appointment to the SACGM(CU).

**Note:** Share holdings only declared if over £25,000.

Member's Name	Interest
Professor Janet Bainbridge (Chair)	<b>Employer:</b> University of Teeside (on external secondment) <b>Commercial Interests:</b> None <b>Non-commercial Interests:</b> None
Professor David Baulcombe	<b>Employer:</b> The Sainsbury Laboratory/University of East Anglia joint appointment. <b>Commercial Interests:</b> Participant in Sainsbury Laboratory "returns to inventors scheme". This scheme remunerates SL scientists with a fraction of license revenue from inventions made in the course of their employment. <b>Non-commercial Interests:</b> Research funded by BBSRC, Gatsby Charitable Foundation, EU framework V programmes
Dr Gary Burns	<b>Employer:</b> AstraZeneca <b>Commercial Interests:</b> Company shares <b>Non-commercial Interests:</b> None
Dr John Carr	<b>Employer:</b> Cambridge University <b>Commercial Interests:</b> None <b>Non-commercial Interests:</b> Research grants received from various sources incl. BBSRC, Leverhulme Trust, Royal Society, Defra
Dr Martin Carrier	<b>Employer:</b> Queen Mary, University of London <b>Commercial Interests:</b> None <b>Non-commercial Interests:</b> None
Dr Peter Coyle	<b>Employer:</b> Royal Group of Hospital Trust, Belfast. <b>Commercial Interests:</b> None <b>Non-commercial Interests:</b> None

Member's Name	Interest
<p>Professor Martin Gore (Vice Chair)</p>	<p><b>Employer:</b> Royal Marsden Hospital</p> <p><b>Commercial Interests:</b> Funding including honorariums, expenses and financial support for clinical trials and research has been provided by: Alza, Antigenics, Astra Zeneca, Aventis, Bayer, Bristol Myers Squibb, Celgene, Centocor, Chiron, Cobra Therapeutics, Debiopharm, Genta Inc, Gilead, GlaxoSmithKline, Intermune, Johnson &amp; Johnson, Kendle, Lilly, Lippincott, Maxim Pharmaceuticals, Merck, ML Labs, Novartis, OSI Pharmaceuticals, Pharma Mar, Pierre Fabre, Progenics, Roche, Schering Plough, Servier, Telik, Wyeth, Xenova. Advisor to Cambridge Antibody Technology (including retainer for services); Member of Advisory Boards <i>i.e.</i> Bayer, Schering Plough, 3M, Centocor, Merck, Pfizer, GlaxoSmithKline, Novartis</p> <p><b>Non-commercial Interests:</b> Medical Director Rare Cancers Division. Head of Melanoma Unit. Vice-Chair of the Gene Therapy Advisory Committee. Co-chair of the sub committee on retroviral safety and the gene therapy working party. Member of the editorial board of a number of scientific journals</p>
<p>Professor Ernest Gould</p>	<p><b>Employer:</b> NERC</p> <p><b>Commercial Interests:</b> None</p> <p><b>Non-commercial Interests:</b> Holder of and collaborator in research funding from BBSRC, Wellcome Trust, Dstl, and several small drug companies.</p>
<p>Dr Penny Hirsch</p>	<p><b>Employer:</b> Rothamsted Research</p> <p><b>Commercial Interests:</b> None</p> <p><b>Non-commercial Interests:</b> BBSRC - CASE studentship; industrial sponsor Syngenta, 2001-4 (Syngenta give some support to the student, none to Rothamsted or Dr Hirsch).</p>
<p>Dr Keith Howard</p>	<p><b>Employer:</b> Oxxon Therapeutics Ltd</p> <p><b>Commercial Interests:</b> None</p> <p><b>Non-commercial Interests:</b> None</p>
<p>Dr David Lewis</p>	<p><b>Employer:</b> St George's Hospital Medical School</p> <p><b>Commercial Interests:</b> None</p> <p><b>Non-commercial Interests:</b> Most current research funded by European Commission 6th Framework: one grant to test vaccines/antibodies from transgenic plants (approx £410k), second to develop live mucosal vaccines (approx £750k). One current grant involving GMOs funded by Institute Pasteur Paris (£120k); two previously from Microscience (approx £335k); and one each from Wellcome Trust, MRC and WHO (approx £470k total). Occasional adviser to FAP (Brazilian League Against Tuberculosis) on recombinant BCG.</p>

Member's Name	Interest
Dr Sue Mayer	<p><b>Employer:</b> GeneWatch UK</p> <p><b>Commercial Interests:</b> Board Member of Greenpeace UK</p> <p><b>Non-commercial Interests:</b> Agriculture and Environment Biotechnology Commission – member Five Year Freeze – steering board Vetwork UK – trustee Lancaster University - Honorary Research Fellow Green Alliance - member GeneWatch UK has undertaken research for: Friends of the Earth, The Guardian, Unilever, Royal Society for the Protection of Birds, Action Aid, Greenpeace, Consumers' Association, WHO.</p>
Dr Philip Minor	<p><b>Employer:</b> NIBSC</p> <p><b>Commercial Interests:</b> None</p> <p><b>Non-commercial Interests:</b> None</p>
Mr Bob Osborne	<p><b>Employer:</b> University of Glasgow</p> <p><b>Commercial Interests:</b> None</p> <p><b>Non-commercial Interests:</b> None</p>
Dr Brian D. Robertson	<p><b>Employer:</b> Imperial College London</p> <p><b>Commercial Interests:</b> None</p> <p><b>Non-commercial Interests:</b> None</p>
Dr Peter Searle	<p><b>Employer:</b> University of Birmingham</p> <p><b>Commercial Interests:</b> None</p> <p><b>Non-commercial Interests:</b> Biological Safety Officer at the Institute for Cancer Studies, and the University Hospital Birmingham NHS Trust. Collaborative relationship (unpaid) with ML Laboratories, which has involved funding a research project in my laboratory. Research funding currently from MRC.</p>
Dr Michael Skinner	<p><b>Employer:</b> Institute for Animal Health</p> <p><b>Commercial Interests:</b> I am a co-inventor on patents relating to genetically modified vaccines for poliovirus and for a fowlpox virus recombinant vaccine vector. The latter is being actively pursued and has been commercially licensed by Oxxon Pharmaccines. I receive patent income via the BBSRC's 'rewards for inventors' scheme.</p> <p><b>Non-commercial Interests:</b> Most research in my lab is funded by the BBSRC (occasionally, but not presently, by the EC). Currently a project on recombinant fowlpox vectors is funded by Oxxon Pharmaccines (c. £75k pa). I have acted as a WHO special advisor on recombinant vaccines. I act as external PhD examiner to various Universities.</p>

Member's Name	Interest
Professor Peter Williams	<p><b>Employer:</b> University of Leicester</p> <p><b>Commercial Interests:</b> None</p> <p><b>Non-commercial Interests:</b> Research funded by BBSRC, Wellcome Trust and EU. Editor of international peer reviewed journals 'FEMS Microbiology Letters' and 'Immunobiology'. Member of the MRC Advisory Board, and of the Scientific Advisory Board of the Meningitis Research Foundation.</p>



## Annex 4 SACGM(CU) Information Note On Lentiviral Vectors

### SACGM Information Note

#### Concerns about the safety of some viral vectors

This note is intended to inform GM Centres on preliminary research results that may have safety implications for work involving lentiviral vectors or vectors containing the “WPRE sequence”. It includes interim advice on containment measures and consequences for notifications.

HSE is aware of reports of the unexpected development of liver tumours in mice in a pre-clinical study using lentiviral vectors. The Gene Therapy Advisory Committee (GTAC) on 5 November issued an Open Letter to professional bodies, the UK gene therapy research community and GTAC’s equivalents abroad, alerting them to these findings. A copy of the letter is attached. GTAC is the national ethics committee for gene therapy research, and is primarily concerned with patient safety. Although no gene therapy trials are ongoing with this type of vector in the UK, the purpose of the letter was to alert those who may be planning trials and regulatory bodies in other countries.

HSE’s interest is focused on the developers and users of such vectors for whom the safety considerations are very different. The Scientific Advisory Committee on Genetic Modification (Contained Use) – SACGM – has met to consider the preliminary research and its interim advice is incorporated below.

#### The Research Observations

The unpublished research (due to be submitted for publication shortly) shows that most of the tumours occurred in a group of mice that had been inoculated *in utero* with lentiviral vectors carrying the factor IX gene. A small number of tumours were also observed in animals that had been treated neonatally or had received vectors carrying only marker genes.

The mechanism of induction of tumour formation is not clear, and may be due to insertional mutagenesis and/or to expression of proteins encoded by the vector itself. Experiments are ongoing to investigate the precise nature of the tumours and the mechanism of induction. Although the number of mice involved is small and the wider implications are not yet clear, SACGM and HSE considers that the research community should be alerted to these observations so that they can be considered as part of risk assessments of activities with this type of vector.

The vectors used in the animal studies contained an enhancer of gene expression derived from woodchuck hepatitis virus (WHV) called the woodchuck post-transcriptional regulatory element, WPRE. This element is capable of expressing part of the X protein from WHV. A number of

publications have suggested that truncated hepadna virus X-proteins may have oncogenic properties (Tu *et al* 2001 *Cancer research* 61, 7803; Sirma *et al* 1999, *Oncogene* 18, 4848). A short communication detailing concerns about WPRE has recently been published in *Gene Therapy* (*Gene Therapy* advance online publication 28 October 2004).

### **Interim Advice**

The risks considered by GTAC are different from those considered by SACGM. Clinical use involves the intentional introduction of a vector into patients; workplace exposure is unlikely to involve the same doses of virus. However, until the mechanism of induction of tumours is established, SACGM and HSE are recommending a precautionary approach to laboratory work with some of these vectors.

Although GTAC have highlighted lentiviral vectors we are aware that the WPRE sequence is used in a range of other vectors, including retroviral, adenoviral, and adeno-associated virus based systems. GM Centres should establish whether vectors, and in particular lentiviral vectors, they use contain the WPRE sequence. Where using:

- any lentiviral vectors, or
- vectors containing WPRE,

risk assessments should be reviewed to consider whether the containment being used for the work is appropriate. It is recommended that containment level 2 be used for work with all lentiviral vectors or viral vectors containing wild-type WPRE, or truncated forms of WPRE, unless the X-protein promoter and start codon have been truncated. This is because it is not clear whether truncated forms of WPRE are safer than wild type, although ongoing experiments should cast further light on this issue. Viral properties, such as the route of transmission or viral tropism, are unlikely to be altered by the presence of WPRE.

Researchers in the laboratory will be working in a manner that is intended to minimise or prevent exposure to the vector. Good microbiological practice, and the fact that most work with viruses is carried out in microbiological safety cabinets, should minimise exposure. However, work with animals, which involves direct injection of the vector, requires particular caution. Accidental injection could lead to exposure to high levels of the virus.

It is recommended that measures are taken to:

- eliminate the use of sharps unless absolutely necessary;
- adopt procedures that reduce the likelihood of exposure, such as wearing gloves, and minimising aerosol formation.

### **Notification under the Genetically Modified Organisms (Contained Use) Regulations 2000**

Some work involving lentiviral vectors or other vectors carrying the WPRE sequences may currently be classified as a 'class 1' activity. Other activities are classified as 'class 2'. Although we are recommending that containment level 2 be used, we are not expecting centres that have currently classified their activities as class 1 to notify HSE until further information on the mechanism of tumour formation is available.

For activities currently classified as class 2, users should amend their risk assessments, and ensure that the new information is cascaded to those working with lentiviral vectors or vectors carrying the WPRE sequences. Once again centres are not required to notify the change in risk assessment to HSE.

### **Next Steps**

We understand that further studies are ongoing which should cast further light on these issues. Once this further information becomes available we will update this advice as appropriate.

### **Contact**

If you have any specific questions or concerns please contact the SACGM Secretariat at: [SACGM@hse.gsi.gov.uk](mailto:SACGM@hse.gsi.gov.uk)

**SACGM Secretariat. 19 November 2004**

## Annex 5 Sources Of Information

Further information can be obtained at the following sources:

- The SACGM(CU) related information including minutes and agendas is available at <http://www.hse.gov.uk/aboutus/meetings/sacgmcu/>
- Further information on GMOs and the Regulator (HSE) is available at <http://www.hse.gov.uk/biosafety/gmo/index.htm>
- The Public Register of GM notifications made under GMO(CU) 2000 is planned to be available electronically. In the interim, a paper Public Record is held by the Notifications Officer, HID SI4, Bootle and HD, Rose Court. Information on notifications made in Scotland is also available in Belford House, Edinburgh. In addition, main Local Area HSE Offices will hold information on notifications of Contained Use work taking place in their area.
- Compendium of Guidance: provides guidance on risk assessment, control and containment measures and other aspects of GMO contained use activities and is available at
- <http://www.hse.gov.uk/biosafety/gmo/acgm/acgmcomp/index.htm>
- A guide to the GMO (Contained Use) Regulations 2000, ISBN 0-7176-1758-0 is available from HSE books, £13.50.
- GMO (Contained Use) Regulations 2000, INDG86(rev2) leaflet is available free from HMSO website at [www.hmso.gov.uk](http://www.hmso.gov.uk) or the HSE website (address above).
- ACGM Newsletters 29 onwards (prior to this, they relate to the '92 Regs), available on the website at <http://www.hse.gov.uk/biosafety/gmo/information.htm>
- Deliberate release of GMOs into the environment is covered by Genetically Modified Organisms (Deliberate Release) Regulations) – further information on this can be obtained through the Advisory Committee on Releases into the Environment (ACRE) at **(DN: website address)**
- Food safety aspects – further information on this can be obtained through the Food Standards Agency (FSA) at **(DN: website address)**
- Product approval/marketing approval for medicines – further information on this can be obtained through Medicines & Healthcare Regulatory Authority (MHRA) at **(DN: website address)**
- Gene therapy trials – further information on ethical considerations and patient safety can be obtained through GTAC at **(DN: website address)**

## Abbreviations

List of abbreviations used in the Annual Report:

ACDP – Advisory Committee on Dangerous Pathogens  
ACRE – Advisory Committee on Releases into the Environment  
ACGM - Advisory Committee on Genetic Modification  
ACNFP - Advisory Committee on Novel Foods and Processes  
ACZOO – Advisory Committee on Zoonoses  
ATCSA - The Anti-terrorism, Crime and Security Act 2001  
BBSRC – Biotechnology and Biological Sciences Research Council  
BCG – Mycobacterium bovis  
DNA – Complementary Deoxyribonucleic acid  
Dstl – Defence Science Technology Laboratories  
CEH – Centre for Ecology and Hydrology  
CL – Containment Level  
DAP – Diaminopimelic acid  
Defra - Department for the Environment, Food and Rural Affairs  
DNA – Deoxyribonucleic acid  
EU – European Union  
EC – European Commission  
EPA - Environmental Protection Act 1990  
EPSRC - Engineering and Physical Sciences Research Council  
FMDV – Foot & Mouth Disease Virus  
FSA – Food Standards Agency  
GM – Genetic Modification  
GM-CSF – Granulocyte Made Colony Stimulating Factor  
GMM - Genetically Modified Microorganisms  
GMO - Genetically Modified Organisms  
GMO(CU) - Genetically Modified Organisms (Contained Use) Regulations 2000  
GMO(DR) - Genetically Modified Organisms (Deliberate Release) Regulations 200?  
GMSC - genetic modification safety committee  
GTAC – Gene Therapy Advisory Committee  
HA – Haemagglutinin  
HEPA – High Efficiency Particulate Absorption (Filter)  
HID SI4 – Hazardous Installations Directorate, Specialised Industries 4 (Biological Agents Unit)  
HIV – Human Immunodeficiency Virus  
HK – Hong Kong  
HPAI – Highly Pathogenic Avian Influenza  
HSE - Health and Safety Executive  
HSV1 – Herpes Simplex virus Type 1  
HSWA - Health and Safety at Work etc. Act 1974  
IAH – Institute for Animal Health  
ICRF – Imperial Cancer Research Fund  
MAFF – Ministry for Agriculture Fisheries and Food (replaced by Defra)  
MHRA – Medicines and Healthcare Regulatory Authority  
MRC – Medical Research Council

MRC LMB – Medical Research Council Laboratory for Molecular Biology  
MSC – Microbiological Safety Cabinet  
MUVAPRED – Mucosal Vaccines for Poverty Related Diseases  
NA – Neuraminidase  
NCRI – National Cancer Research Institute  
NERC – Nature and Environment Research Council  
NHS – National Health Service  
NIBSC – National Institute for Biological Standards and Control  
RARER - the Genetically Modified Organisms (Risk Assessment) (Records and Exemption) Regulations (RARER) 1996 (as amended)  
RNA - Ribonucleic acid  
RPE – Respiratory Protective Equipment  
SACGM - Scientific Advisory Committee on Genetic Modification  
SAPO – Specified Animal Pathogens Order  
SARS – Severe Acute Respiratory Syndrome  
SE - the Scottish Executive  
TSC – ACGM Technical Subcommittee  
UK CA - United Kingdom Competent Authority  
WA - Welsh Assembly  
WHV – Woodchuck Hepatitis Virus  
WHO – World Health Organisation  
WPRE – Woodchuck (Hepatitis Virus) Post-transcriptional Regulatory Element