

**Scientific Advisory Committee on Genetic
Modification (Contained Use)**

Annual Report

January to December 2008

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Foreword

It gives me great pleasure once again, after another very busy year, to introduce the 2008 Annual Report of the Scientific Advisory Committee on Genetic Modification (Contained Use) (SACGM(CU)).

The Committee was established in July 2004 and meets three times a year, with **ad hoc** meetings and specialist sub-groups set up as required. Our work is varied but the role of the Committee can be summarised as:

- Providing advice to the Competent Authority on technical issues arising from activities notified under the Genetically Modified Organisms (Contained Use) regulations 2000.
- Providing advice on risk assessments for contained use activities involving GMO's (this covers >99% GM activities in the UK).
- Development and updating of guidance on all aspects of contained use of GMOs.

The underpinning science is constantly advancing and becoming increasingly complex. To help us deliver robust risk assessments and recommendations to HSE covering this diverse knowledge base, we work closely with other Advisory Committees and Government departments who attend our meetings. In addition, we often invite scientists working on a particular notification or in a field of interest to attend, deliver presentations and answer Committee queries. Thus we can reassure ourselves that our advice is supported by the best possible evidence base.

We could not operate effectively without the expertise, professionalism and integrity of our Committee members. They are all leaders in their field and generously give their time to Committee meetings and working groups; their input is recognised and valued.

We are all committed to openness, all minutes and agendas are placed upon the website and I encourage you to look at them to see the breadth and depth of our activities.

Finally, I must express gratitude to our expert and professional secretariat. They work hard not only to service meetings, but form a necessary bridge across to our own stakeholder community and to other Government departments. We simply could not operate without them. Their esteem is demonstrated by their success in gaining internal promotion and I congratulate those who have moved on to new roles during the year.

A handwritten signature in black ink, appearing to read 'Janet Bainbridge', with a stylized flourish at the end.

Professor Janet Bainbridge, OBE
February 2009

Introduction

Established in 2004 in accordance with the Office of Science and Technology's Code of Practice for Scientific Advisory Committees (CoPSAC), the SACGM(CU) (hereafter referred to as the Committee) is a non-statutory scientific advisory committee. The Committee provides scientific advice to the UK Competent Authority (CA) on the contained use of genetically modified organisms, particularly in respect of hazard identification and risk assessment.

The Health and Safety Executive (HSE) provides the Secretariat for the Committee. The Secretariat liaises closely with the Chair, other members of the CA and prepares papers, organises and hosts the Committee's meetings. The Secretariat also prepares reports from the Committee and draft guidance arising from advice of the Committee. The Secretariat also maintains the [SACGM\(CU\) website](#), where information about the Committee, its members, as well as meeting agendas and minutes may be downloaded.

In 2008, the Committee held three main meetings:

- 21 April 2008 – [13th meeting](#)
- 10 July 2008 – [14th meeting](#)
- 20 November 2008 – [15th meeting](#)

In addition to these meetings, the Committee's Viruses Working Group reconvened to update and amend the part of the Compendium of Guidance relating to retroviruses.

[The Compendium of Guidance](#) represents what the Committee considers to be safe and good practice when working with genetically modified organisms (GMOs) in a contained use setting. Whilst it is not mandatory to follow this guidance, doing so will almost certainly ensure that workers are complying with the health and safety law that governs laboratory work with GMOs. The guidance is widely used by the research community.

Terms of Reference

SACGM(CU) provides scientific and technical advice to the UK CA on the risks posed to human health and to the environment from the contained use of genetically modified organisms. In particular the Committee:

- provides advice on the technical issues of individual activities notified under the Genetically Modified Organisms (Contained Use) Regulations 2000 (as amended in 2005) – (GMO(CU));
- provides advice on risk assessments for contained use activities involving GMOs; and
- develops and updates guidance on all aspects of contained use of GMOs including the SACGM Compendium of Guidance.

UK Competent Authorities for Genetic Modification (Contained Use) Activities

The Health and Safety Executive and the Secretary of State for the Department for Environment, Food and Rural Affairs (Defra) form the Competent Authority in England and Wales. 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 Government. Although not part of the Competent Authority, the National Assemblies for Wales and Northern Ireland are included in all UK CA considerations.

The roles and responsibilities of the different members of the UK CA are set out in [Appendix 1](#).

Genetically Modified Organisms

Genetic engineering is different from traditional breeding methods in that the organism's genes are manipulated directly. A multicellular organism that has been modified in this way is referred to as a genetically modified organism (GMO). Similarly, modified micro-organisms are referred to as GMMs (genetically modified micro-organisms).

Contained use (CU) is where control measures are used to limit contact between GMOs, humans and the environment. In practice, this involves work in laboratories, animal houses, indoor plant growth facilities and large-scale production facilities on industrial sites. The vast majority of GM work includes strategies that severely incapacitate the organism so that it is unable to survive or proliferate outside of the laboratory without specified 'artificial' growth requirements. For the smaller number of activities involving organisms still capable of growth outside of the laboratory, a robust risk assessment must be submitted for scrutiny by the CA with identified appropriate and proportionate containment measures to prevent release, before work may commence. The safety record in this sector is therefore extremely good.

During 2008, a total of 181 notified GM activities were received by the CA. 1 derogation request was received:

Class of Activity	Number Received
1 (New premises)	25
2	138
3	13
4	0
Significant change to work	4
Accident	1

The majority of notified activities involved the use of replication defective viral vectors (either adenovirus or retrovirus based systems) for expression of transgenes in mammalian cells. A breakdown of work by organism type may be found in [Appendix 2](#). Details of all GM work notified to HSE may be found on the electronic [GM Public Register](#).

Membership

The Committee has expertise/representation in the following areas:

- Molecular virology
- Molecular bacteriology
- Clinical applications (i.e. gene therapy, vaccine development, clinical virology, molecular oncology)
- Molecular plant biology
- Environmental microbiology
- Biological safety
- Trades Union Representative

The Committee comprises a Chair, Vice Chair and 14 members as follows:

- Professor Janet Bainbridge, OBE (Chair)
- Professor Martin Gore (Vice Chair), Royal Marsden Hospital, London
- Dr Gary Burns, MBE, AstraZeneca Ltd, Macclesfield
- Dr John Carr, University of Cambridge
- Dr Martin Carrier, Queen Mary College, London
- Dr Peter Coyle, Regional Virology Laboratory, Belfast
- Professor Ernest Gould, Centre for Hydrology and Ecology, Oxford
- Dr Penny Hirsch, Rothamsted Research, Harpenden
- Dr Keith Howard, Baxter Vaccines, AG, Austria
- Professor David Lewis, St George's Hospital, London
- Dr Philip Minor, National Institute for Biological Standards and Control
- Mr Robert Osborne, University of Glasgow
- Dr Brian Robertson, Imperial College, London
- Dr Peter Searle, University of Birmingham
- Dr Michael Skinner, Imperial College, London

Members' biographies and interests may be found on the [SACGM\(CU\) website](#).

Although there have been no changes in membership in 2008, there are a number of vacancies on the Committee, which will need to be filled in the coming workplan for 2009.

Interactions with other committees

The Secretariat maintains strong links with a number of other scientific advisory committees. Furthermore, several members also sit on these committees, namely:

- The Advisory Committee on Dangerous Pathogens ([ACDP](#))
- The Advisory Committee on Releases to the Environment ([ACRE](#))
- The Gene Therapy Advisory Committee ([GTAC](#))

The Committee frequently invites members from these committees to its meetings in order to inform their discussions on relevant and some of the more contentious agenda items. This has been built upon this by including updates from cross-representing Committee members as part of the Secretariat Report. It should be noted that the Vice Chair of the Committee is also the Chair of GTAC.

Key business during 2008

During the three business meetings in 2008, the Committee were asked to advise on several recurrent issues including:

- Revision of the SACGM(CU) Compendium of Guidance – Retrovirology Section
- Updates on the implementation of the Callaghan review recommendations for animal and human pathogens

13th Meeting of SACGM(CU) on 21 April 2008

Eleven out of a total fifteen members were in attendance. At the 13th meeting, members advised upon a number of matters including:

- a proposal to conduct clinical studies with a measles vaccine carrying an HIV derived insert;
- classification of new strains for poliovirus vaccine production;
- clarification on guidance for lentiviral vectors;

Proposals to conduct clinical studies with a measles virus vaccine carrying an HIV derived insert

An international consortium was invited to present to the committee on its proposal to conduct clinical trials with a novel system employing a measles virus vector delivering an HIV antigen gene. In this instance, the UKCA required confirmation that the properties of the construct meant that the study could be safely carried out under the Contained Use Regulations and that the classification assigned to the construct was correct.

The Committee was content that the evidence presented supported the class assigned to the construct. However, based on the data presented on viral shedding, the committee was unable to advise the UKCA that the construct could be considered to be biologically contained. The consortium was

therefore asked to return to present to a future meeting at such a time when more data were available from planned further studies.

Classification of new strains for poliovirus vaccine production

The Committee was invited to advise on the classification of a vaccine strain of poliovirus engineered with attenuating modifications and selected to avoid reversion of the attenuating mutations. At the time of the meeting, the WHO global polio eradication programme had been achieving great success and all three wild-type serotypes of the virus were on course for eradication by the end of 2012. Post-eradication, the only source of virus would therefore be from laboratories or vaccine production facilities and as such, stringent biosecurity would be required to minimise the potential for release from these facilities with a consequent re-emergence of the disease.

Whilst the Committee appreciated the rational design of the vaccine strains, the Committee was concerned that rates of reversion may increase during large scale production and therefore further data were required before it could give an opinion on the classification of the strain.

Classification of lentiviral vectors – request for clarification of guidance

The Committee was invited to advise on the suitability of its guidance with regard to risk assessment of retroviral and lentiviral vectors. A number of duty holders had raised their difficulty in interpreting the Compendium's guidance on lentiviral and retroviral vectors with HSE, with consequent over classification of the work. The uncertainty appeared to surround the inherent hazard associated with the use of lentiviral vectors and potential for induction of insertional mutagenesis.

The Committee agreed that clarification was necessary and decided to reconvene its Viruses Working Group (which had originally advised on the guidance). The Secretary obtained support to also recruit for the purposes of the meeting, additional pertinent expertise (See virology working group).

14th Meeting of SACGM(CU) on 10 July 2008

Twelve out of a total fifteen members were in attendance. At the 14th meeting, members advised upon a number of matters including:

- Research on insertional mutagenesis by lentiviral and retroviral vectors
- regulation of synthetic biology as an emerging technology

HSE commissioned research – insertional mutagenesis in lentiviral vectors

Given the concern raised by a number of studies in animals and people, on the inherent risks of lentiviral and retroviral vectors, HSE commissioned a research project through Prof Mary Collins at University College London, to

look at safety aspects of these retroviral and lentiviral vectors. The research has developed a rapid and quantitative assay for insertional mutagenesis by retroviral vectors and lentiviral vectors in cell culture. In this way it is possible to identify components that contribute to mutagenesis and implement design features that will make safer viral vectors for use in the laboratory and clinic.

Members were supportive of the research and the funding of such work that can contribute to addressing safety issues related to genetically modified organisms. The research findings have direct relevance to the guidance that can be given in the SACGM(CU) Compendium.

Synthetic Biology – emerging technology and its regulation

The emerging field of synthetic biology aspires to use the disciplines of chemistry, engineering and computing to design and synthesise biological systems and networks that are predictable, simple, robust and efficient. The Committee discussed the emerging field with input from Professor Paul Freemont (Imperial College, London).

The Compendium of Guidance provides brief guidance on the field, which the Committee felt was still current and sufficient until further progress technological advances had been realised. However members raised the question of whether the existing definitions within the GMO(CU) regulations, would encompass some of the proposed activities in the field of synthetic biology. One aspect in particular related to the generation of artificial cells. Further legal interpretation was deemed necessary although it was recognised that the realisation of this activity was still some way off.

The Committee requested that they be kept abreast of developments in this field.

15th Meeting of SACGM(CU) on 20 November 2008

Eight out of a total fifteen members were in attendance. At the 15th meeting, members advised upon a number of matters including:

- modification of virulence genes in *Burkholderia mallei*
- respiratory viral disease vaccine
- reverse genetics seasonal influenza virus vaccine

Genetic modification of bacterial regulatory systems – alteration of virulence in *Burkholderia mallei*

The Committee's opinion was sought on whether it was the feasible to provide some generic guidance on the approach to risk assessment for activities involving the alteration of bacterial regulatory genes. A recent publication on the modification of a global regulatory gene of ***Burkholderia mallei*** was presented as an example of work in this area.

Members felt that alteration of bacterial regulatory systems generally result in a reduction in fitness given the need to control protein expression in different environments. There are several well documented cases of virulence being increased when regulatory genes have been altered. The impact of modifying a global regulatory gene, which might control expression of up to 50 downstream effector molecules, was deemed to be complex and necessitate a comprehensive assessment of the risks. With this in mind, the committee was of the opinion that such risk assessments challenging and may present unique properties and as such, advised that each needs to be considered on a case-by-case basis.

Attenuated inhalation vaccine for respiratory viral disease

A proposed clinical trial in infants and children involving a live attenuated bovine parainfluenza virus (bPIV) expressing human PIV and respiratory syncytial virus (RSV) proteins, was discussed. The committee raised a number of issues in relation to:

- the need to monitor for enhanced respiratory disease;
- potential for virus shedding from naive volunteers – related to location of trial and staff involved;
- relevance of the proposed sampling time points for virus detection;
- potential for residual virus infectivity in cattle

As this clinical trial was being undertaken a deliberate release activity, the views of SACGM(CU) were raised with the Defra secretariat and discussed at the ACRE meeting on Dec 4th and the applicants asked to provide additional information before consent for the experimental release could be given.

Seasonal influenza virus vaccine – use of reverse genetics approach

Reverse genetics technology offers an opportunity to efficiently and rapidly produce accurate, targeted vaccine seed virus strains in comparison to traditional reassortment methodology. The Committee was invited to advise on the risks of this technology in comparison to established reassortment methods and on the classification on seasonal influenza strains derived from the technology.

The Committee agreed that strains produced by reverse genetics posed no greater risks than those produced by traditional methods and indeed were of the view that there were significant advantages in using the reverse genetics approach. Members felt that no additional control measures would be necessary above those used for vaccine seed virus made by traditional methods. However, the Committee felt that further information on infectivity and residual pathogenicity in animals would be required before it would be appropriate to classify this work as Class 1.

Working Groups

The Committee is sub-divided into a number of working groups (see [Appendix 3](#)) the Competent Authority is able to call upon their specific expertise as and when required. For example, during 2008, it had become evident that there may be some confusion in the way that the Compendium's retrovirus guidance was being interpreted.

Meeting of the Viruses Working Group on 27 June 2008

HSE sought advice from SACGM(CU) and it was decided that the Viruses Working Group be reconvened to redraft the retrovirology part of the compendium of guidance. Additional members with experience in retrovirology were recruited as external experts, namely Professor Mary Collins (University College London) and Dr Jonathan Stoye (National Institute for Medical Research).

The working group met on 27th June 2008, to consider the inherent risks to human health from retroviral (including lentiviral) vectors, in light of the latest scientific data and developments in vector technology. Based on the best available science, the relevant section of the Compendium was redrafted to reflect a proportionate approach to containment and classification based on the activity being undertaken.

For example, members were in agreement that the built-in safety features of many commercially available retroviral vectors used by the majority of researchers, posed a minimal inherent risk in themselves. Consequently, provided a non-harmful insert was being expressed using such a vector, it may be appropriate to assign the activity the lowest classification. The working group felt that where the activity involved the use of sharps or aerosol generating procedures, then the likelihood of exposure to a significant quantity of virus increased consequently the work should be classified as Class 2.

The revised guidance was published in December 2008.

ACDP working group on common containment measures

Following the outbreak of foot and mouth disease from Pirbright in August 2007, several Government sponsored reviews took place. One of those led by Sir Bill Callaghan, proposed several recommendations to improve the way animal pathogens are regulated; all of these recommendations were accepted by Government. The recommendations included the development of a single regulatory framework for human, animal and genetically modified pathogens, broadly utilising the risk-based framework of the Genetically Modified Organisms (Contained Use) regulations.

As part of this process, the Advisory Committee for dangerous Pathogens (ACDP) were tasked with formulating a set of common containment measures for these pathogens. Two Members of SACGM(CU), namely Dr Gary Burns and Dr Mike Skinner, were co-opted to the ACDP Common Containment Measures Working Group. The working group met initially in September and November 2008, with further meetings planned in January, March and May

2009. Considerable progress has been made in this respect and the working group is expected to deliver a finalised containment table with supporting guidance in May 2009.

Future Work

In addition to the normal 'reactive' business of the Committee, the plan of work for 2009/10 will include the following topics:

- Contribution to the formulation of a common set of containment measures for human and animal pathogens;
- Input into the development of a single regulatory framework for human, animal and genetically modified pathogens;
- Emerging topic of 'Synthetic Biology' will be advised upon from a risk assessment perspective;
- Contribution to the European Commission working group on new techniques;
- Development of simplified procedure for the exemption of safe organisms from the GMO(CU) regulations;
- Recruitment of new Committee members to restore the membership to full cadre.

Appendix 1: United Kingdom Competent Authority Role

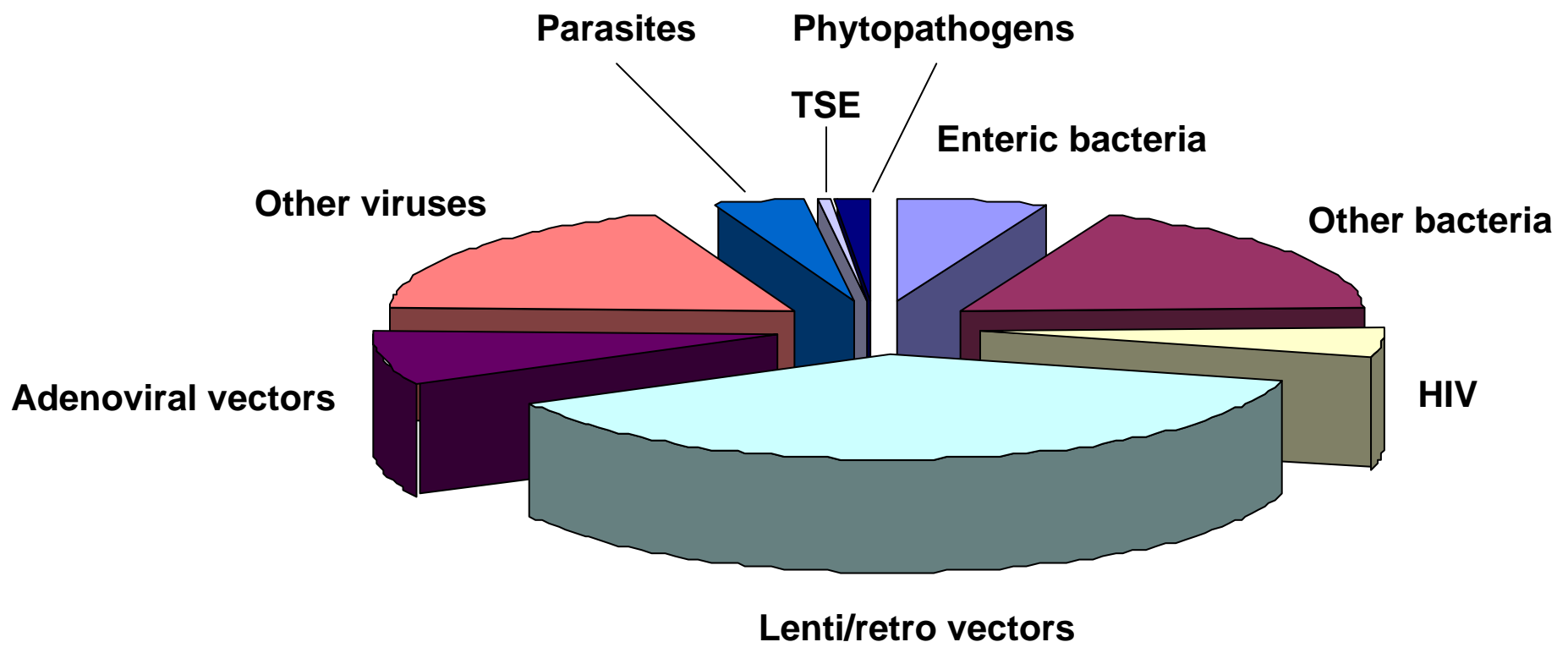
Health and Safety Executive (HSE): HSE has lead responsibility for human health and safety throughout Great Britain. HSE administers the permissioning process for the whole of the competent authority, and its Biological Agents Unit (BAU) maintains the Public Register and provides technical comment on the notifications. HSE's BAU undertakes inspections of notified premises and activities to check compliance and 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 Government (SG): 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 Government in Scotland. This means that they have a legal responsibility to comment on environmental aspects of contained use activities involving GM animals and plants.

Appendix 2: Breakdown of GM activities by organism type



Appendix 3: SACGM Working Groups

Clinical Trials Working Group

Dr Martin Carrier
Dr Peter Coyle
Professor Martin Gore
Dr Peter Searle

Containment and Control Working Group

Professor Janet Bainbridge
Dr Gary Burns
Dr Martin Carrier
Mr Robert Osborne
Dr Brian Robertson

GM Risk Assessment Working Group

Professor Janet Bainbridge
Dr Gary Burns
Dr Martin Carrier
Dr Brian Robertson

Plants Working Group

Dr John Carr
Professor David Baulcombe (External member)
Dr Penny Hirsch
Professor James Dunwell (co-opted from ACRE)

Viruses Working Group

Dr Martin Carrier
Prof. Mary Collins (external member)
Dr Peter Coyle
Dr Ernest Gould
Dr Keith Howard
Dr Philip Minor
Mr Robert Osborne
Dr Peter Searle
Dr Michael Skinner
Dr Jonathan Stoye (external member)

Abbreviations

ACDP	Advisory Committee on Dangerous Pathogens
ACRE	Advisory Committee on Releases to the Environment
ATCSA	Anti-Terrorism, Crime and Security Act 2001
BAU	Biological Agents Unit
CA	Competent Authority
CL	Containment Level
CoPSAC	Code of Practice for Scientific Advisory Committees
COSHH	Control of Substances Hazardous to Health
Defra	Department for Environment, Food and Rural Affairs
DH	Department of Health
DSTL	Defence, Science and Technology Laboratory
EA	Environment Agency
EC	European Commission
GM	Genetic Modification
GMM	Genetically Modified Micro-organism
GMO	Genetically Modified Organism
GMO(CU)	Genetically Modified Organisms (Contained Use) Regulations
GTAC	Gene Therapy Advisory Committee
HG	Hazard Group
HID SI4	Hazardous Installations Directorate, Specialised Industries Division 4
HPA	Health Protection Agency
HPAI	Highly Pathogenic Avian Influenza
HSE	Health and Safety Executive
HSENI	Health and Safety Executive Northern Ireland
HSL	Health and Safety Laboratory
MHRA	Medicines and Healthcare Products Regulatory Agency
NGO	Non-Governmental Organisation
NIBSC	National Institute of Biological Standards and Control
SACGM(CU)	Scientific Advisory Committee on Genetic Modification (Contained Use)
SG	Scottish Government
siRNA	small interfering ribonucleic acid
SRF	Single Regulatory Framework
NAW	National Assembly for Wales
WHO	World Health Organisation