

The SACGM Compendium of guidance

Part 6: Guidance on the use of genetically modified
microorganisms in a clinical setting

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6.1 Guidance on the use of genetically modified microorganisms in a clinical setting

Overview

1. The Health and Safety Executive (HSE) has prepared the following guidance in association with the Department for the Environment, Food and Rural Affairs (Defra) with the advice of the Scientific Advisory Committee on Genetic Modification (SACGM), and its clinical research studies working group, together with the Advisory Committee for Releases to the Environment (ACRE). The guidance should help applicants and the clinical study host organisation to choose the most appropriate regulatory procedure, particularly those wishing to undertake studies involving the administration to humans of substances based upon genetically modified microorganisms (GMMs). The term 'clinical research studies' refers to all human-based experimentation and includes clinical trials as defined under the Medicines for Human Use (Clinical Trials) Regulations 2004 and will be used throughout the guidance. It is primarily intended to cover the pre-marketing phase of the development of GM-based therapies.
2. It is likely that the majority of GMMs entering clinical research studies in the UK will fall into the lowest hazard categories, that is Class 1 and 2. Most previous studies have been Class 1 activities, which represent negligible risks to both human health and the environment. Conventional hospital facilities, good practice and implementation of the standard principles for preventing hospital-acquired infection will generally be adequate for the management of the risks associated with these GMMs. Therefore, it is anticipated that most clinical centres will be able to undertake such studies. The hazards associated with many non-GM vaccines, pharmaceuticals or molecular agents could be seen as representing equivalent or higher risks and centres that can gain regulatory approval for studies involving such therapies should, in principle, be adequate for GM studies.
3. However, it should be recognised that the physical facilities are only a part of the overall regulatory control system, and studies are likely to be limited to centres that have appropriate systems in place to ensure good research governance. Furthermore, as the technology advances, it is possible that GMMs that require more specific control measures may enter the clinic, necessitating a centre with more specialised facilities.
4. All centres wishing to undertake clinical research studies with GMMs should have acceptable standards of fabric and cleanliness and the requirements of the relevant GM

Regulations must be met. This document offers guidance and advice to ensure compliance.

Scope

5. This guidance covers all clinical research studies carried out under the Genetically Modified Organisms (Contained Use) Regulations 2000 enforced by HSE, and the Genetically Modified Organisms (Deliberate Release) Regulations 2002 enforced by Defra. It should be highlighted that whichever route applicants submit their clinical study application; both HSE and Defra are jointly involved in the evaluation of risk assessments. This guidance is primarily intended to cover the use of GMMs in the pre-marketing phases of product development. Guidance on the application to market products containing GMMs is under development by the European Medicines Evaluation Agency (EMA).
6. These pieces of legislation apply to the UK but exclude Northern Ireland, where distinct parallel legislation exists. Furthermore, there are differences in approach between European countries and those wishing to conduct trials in different member states are advised to seek advice from the appropriate national competent authorities.
7. The two sets of UK GM Regulations deal with protection of both human health and the environment, but exclude product and patient safety. These aspects are covered by specific medicines legislation. For example, drug characterisation studies are covered by the Medicines for Human Use (Clinical Trials) Regulations, which are enforced in the UK by the Medicines and Healthcare Products Regulatory Agency (MHRA). Some studies involving GMMs may fall outside of the Medicines for Human Use (Clinical Trials) Regulations where they are patient characterisation studies; for instance where the GMM is used to provoke a physiological response within a subject for analytical purposes, rather than to characterise the broad effects and efficacy of a therapeutic product.
8. To date, most clinical research studies involving GMMs in the UK have been carried out under the Contained Use Regulations. A small number of studies with GM bacterial vaccines have been carried out as so-called 'Part B deliberate release' research trials. This guidance will explain why one or other of these two sets of regulations covers clinical research studies, and how those involved in planning and running studies must decide upon the most appropriate legal path for their particular trial. It also offers advice on the assessment and management of the risks to human health and the environment with a brief description of appropriate controls in Section 6.4.

9. This guidance primarily covers any activity in which viable GMMs are administered to humans. The use of nucleic acids (eg plasmid DNA, antisense or siRNA) is excluded from the scope of both the Contained Use Regulations and the Deliberate Release Regulations, except where it is vectored by a GMM or can give rise to an infectious agent (for example, siRNA delivered by retroviral vector or use of a viral cDNA). Consequently, such use is not covered in detail in this guidance. Furthermore, this guidance does not cover the use of products derived from GMMs, such as recombinant proteins.
10. Finally, detailed guidance on the safety of different types of GMM vector systems and therapeutic genes is not covered in this section. However, this can be found in Part 2 of the Compendium.

Definitions

11. A genetically modified organism is defined as an organism (with the exception of humans) in which 'the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination' using 'recombinant nucleic acid techniques involving the formation of new combinations of genetic material by the insertion of nucleic acid molecules, produced by whatever means outside an organism, into any virus, bacterial plasmid or other vector system and their incorporation into a host organism in which they do not naturally occur but in which they are capable of continued propagation'.
12. 'Contained use' is defined as: 'Any activity ...in which genetically modified organisms are cultured, stored, transported, destroyed, disposed of or used in any other way and for which physical, chemical or biological barriers, or a combination of such barriers, are used to limit their contact with, and to provide a high level of protection for, humans and the environment'.
13. A deliberate release is defined as: 'An organism under a person's control is "released" if he deliberately causes or permits it to cease to be under his control or the control of any other person and to enter the environment'.
14. Organisms are considered to be under a person's control where he or she: '...keeps them contained by any system of physical, chemical or biological barriers (or combination of such barriers)...ensuring that the organisms do not enter the environment or produce descendants which are not so contained; or that any of the organisms which do enter the environment, or any descendants of the organisms which are not so contained, are harmless'.

Medicines legislation regulatory approval

15. Drug characterisation studies carried out under the Medicines for Human Use (Clinical Trials) Regulations require a clinical trials authorisation (CTA) from MHRA and approval by the by an appropriate research ethics committee, which may be the Gene Therapy Advisory Committee (GTAC; a multi-centre research ethics committee). Compliance with the good clinical practice (GCP) and quality control (QC) requirements set out by MHRA/EMA is mandatory in these cases, including the generation of source material and preparation of therapeutic product in accordance with the principles of good manufacturing practice (GMP). Patient characterisation studies that fall outside of the Medicines for Human Use (Clinical Trials) Regulations do not need a CTA and are therefore exempt from these requirements. Those wishing to undertake any form of clinical research studies should seek advice from MHRA and the research ethics service to ascertain the regulatory requirements in this regard.

16. Before clinical research studies involving GMMs can commence, compliance with either the Contained Use Regulations or the Deliberate Release Regulations must be ensured. The requirements of the two sets of regulations differ considerably and therefore a choice must be made by those proposing the clinical trial as to which set of regulations apply. This choice will be largely dependent on the nature of the GMM, and the trial protocol. It is important that the appropriate legislation is identified and adhered to, and guidance to inform the decision-making process is given below, and schematically in Figure 6.1.1.

Contained use or deliberate release?

17. The Contained Use Regulations (Directive, 90/219/EC, amended by Directive 98/81/EC) cover all contained activities involving the use of GMMs. The definition of 'contained use' is wide ranging, and the term 'any activity' means that clinical research studies involving the use of GMMs fall within the scope, providing that appropriate containment measures are implemented. These measures are 'chemical or physical or biological barriers, or any combination of these', designed to minimise contact with humans and release into the environment. In principle, most clinical procedures can be carried out in a contained manner, however, some GMMs might be difficult to contain after administration to humans. For example, if subjects were expected to shed viable GMMs into the wider environment, then Contained Use Regulations may be inappropriate, and the study might have to be considered as a deliberate release activity.

18. The Deliberate Release Regulations (Directive 2001/18/EC) and the Environmental Protection Act (EPA) regulate activities where GMOs are intentionally released from someone's control into the environment.
19. The essential difference between the two sets of regulations is whether there is intention to release a GMO (or if the action is expected to cause a GMO to be released into the environment) or the intention is to keep the organisms contained using a combination of chemical, physical or biological barriers.
20. The clinical research studies that have been deemed to be deliberate releases in the UK have involved the administering of certain genetically modified enteric bacterial pathogens as putative vaccines to human volunteers. In these particular cases it was expected and accepted that the organisms were likely to be shed in significant numbers into the wider environment, and as the risk assessment was that they were unlikely to cause harm to human health or the environment, deliberate release consent was given for the clinical study.
21. Most clinical research studies will be undertaken in hospitals or specialist research centres and, by their nature, the activities involved in preparation and administration of the organism will be carried out under 'contained use' conditions. It is what happens after administration of the GMM to the patient/volunteer that determines whether or not the trial is considered to be 'contained use' or 'deliberate release'. This decision will often depend upon whether or not there are any anticipated routes through which the environment could be exposed to the organism post administration.
22. If the environment could be exposed to a GMM, this may be deemed to be a 'deliberate release' although the final decision will depend upon the characteristics of the GMMs being used. For example, the GMM may be biologically contained. A GMM would be regarded as being biologically contained if it is endowed with inherent or engineered characteristics resulting in sufficient attenuation, disablement or auxotrophy to impair its ability to infect, replicate or survive outside of a specialised environment.
23. Issues relating to whether a GMM is biologically contained have led to a perceived 'grey area' between the two sets of regulations. However, administration of a highly biologically contained GMM could be regarded as a contained use activity irrespective of the nature of the trial if attenuation and disablement of the GMM is intended to provide control even when the subject/volunteer goes out into the community and beyond the physical confines of a hospital/clinic. Conversely, a GMM with an excellent safety profile but that is less impaired biologically would require consent under Deliberate Release Regulations before it is released in the absence of physical or chemical barriers.

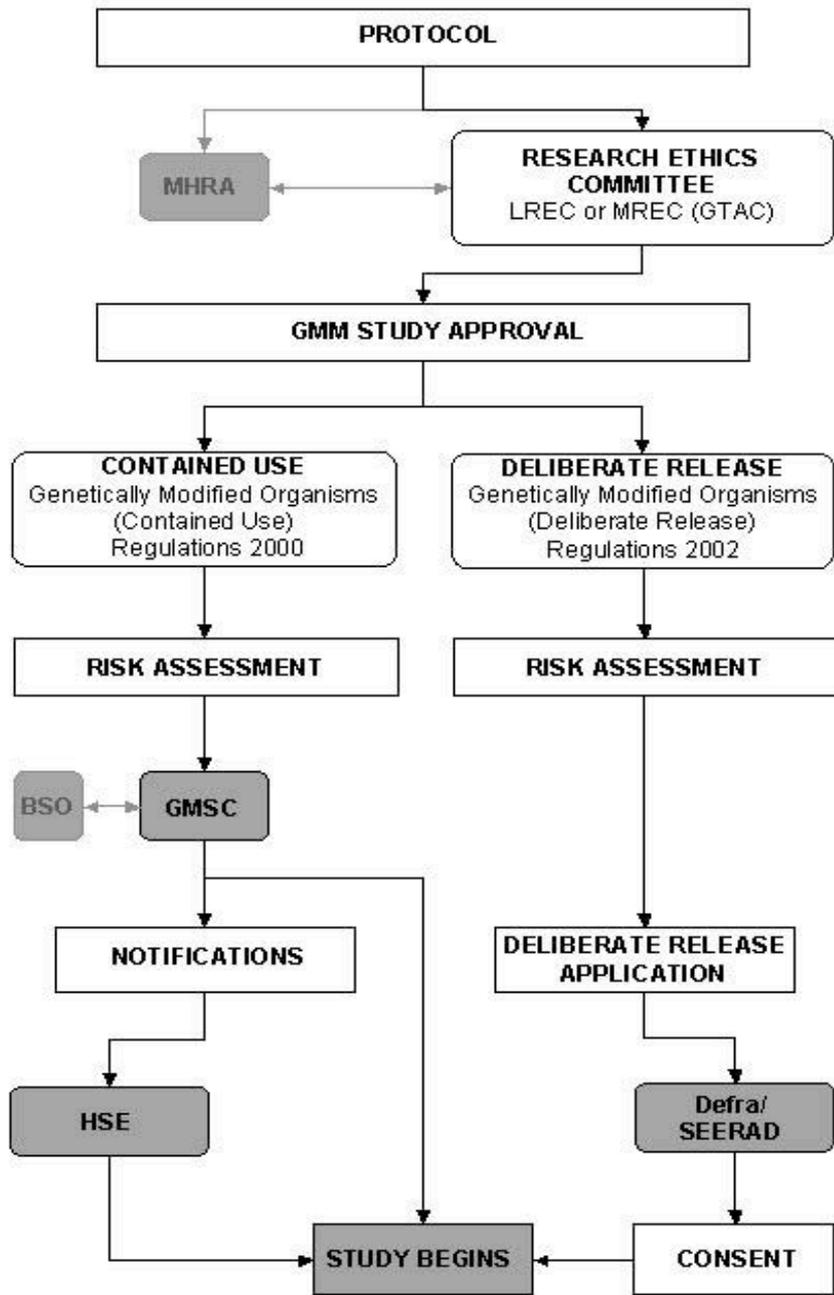


Figure 6.1.1 Diagram showing the principle steps required to gain regulatory approval for clinical research studies involving a GMM. Key: MHRA – Medicines and Healthcare Regulatory Authority; LREC – Local research ethics committee; GTAC – Gene Therapy Advisory Committee; MREC – Multi-centre research ethics committee; GMSC – Genetic Modification Safety Committee; BSO – biological safety officer; HSE – Health and Safety Executive; Defra – Department for the Environment, Food and Rural Affairs; SEERAD - Scottish Executive Environment and Rural Affairs Department.

24. Take for example a study where volunteers/patients are administered a GM vaccinia virus on an outpatient basis. The regulatory issues may vary depending on the nature of the vaccinia strain being used. Certain strains of vaccinia have been administered to humans for many years and have an excellent safety profile.
25. The use of a disabled/highly attenuated GM vaccinia, such as modified vaccinia ankara (MVA), could be considered sufficiently biologically contained so as to always be classified as a contained use activity.
26. However, use of a fully replicative GM vaccinia (eg one based on Western Reserve or Lister strains) could also be considered a contained use if specific measures were employed to control the shedding of virus, for example, through the use of occlusive bandages that are appropriately managed and disposed of. In the absence of such measures, the study would be considered to constitute a deliberate release, as shedding can be predicted, and consent would be required.
27. Use of a partially attenuated vaccinia (such as one based on the Lister-derived LC17m8 strain), however, could be considered under either set of regulations depending on the characteristics of the virus and subsequent management of the trial. If it was thought to be sufficiently biologically contained then it could be considered as a contained use activity, however, a rigorous assessment of the risks to wider human health and the environment is required under both sets of regulations and this should highlight the relevant properties of the GMM and guide the decision as to which legal path to take.
28. Consider another example where volunteers are being administered with a GM enteric pathogen, such as an attenuated strain of *Salmonella typhi*. If shedding of the organism in faeces were predicted, this would be considered to be a deliberate release unless specific measures are taken to minimise the release into the environment.
29. In such cases the early studies may be carried out in containment, and therefore notified as a contained use activity, with volunteers remaining in specialised facilities until either shedding has ceased, or they are dosed with an appropriate broad-spectrum antibiotic and discharged. Subsequent trials are often carried out on an outpatient basis, and in the absence of control measures post-administration of the GM organism, the trial would be considered a deliberate release activity.
30. The only exceptions would be where data accrued from earlier studies had shown limited shedding, and the organisms were sufficiently attenuated to ensure they would not survive

and replicate in the environment. In such cases the studies could be considered to be contained use activities.

31. It may therefore be necessary for some phases of the clinical study to be considered as a contained use activity while others are considered to be deliberate releases. For example, it may be possible to conduct a Phase I trial involving a relatively small number of subjects on an in-patient basis under tightly controlled conditions and hence satisfy the requirements of Contained Use Regulations. However, the same GMM used in a larger Phase III trial might necessitate an outpatient approach where it may not be possible to employ sufficient physical or chemical barriers limiting contact with humans and the environment. Thus, such studies might have to be considered as a deliberate release and the requirements of Deliberate Release Regulations be met.
32. Data accrued from the earlier study phases may be informative and the risk assessment should be updated in the light of study findings. Such data may demonstrate that, in practice, the GMM is sufficiently contained (for example, is not shed in significant numbers) and can be handled under Contained Use Regulations where it would otherwise require consent under Deliberate Release Regulations. Therefore, accurate risk assessments can make the decision clearer and there is a need for extensive data collection when the study is of a scale that makes it feasible.
33. It is important to note that under EC Medicines Regulations (Council Regulation (EEC) No 2309/93, as amended by regulation EC/726/2004), applications for authorisation to market products containing or consisting of GMOs must include an environmental risk assessment (ERA) for the purposes of deliberate release. This will be irrespective of the nature of the GMM and any inherent properties or biological control mechanisms. This risk assessment must include data gathered from earlier trials, and this re-emphasises the need to update risk assessments and accrue data on shedding and monitoring as work progresses (see *Shedding and monitoring*).
34. All applications, irrespective of which regulatory route taken, will be evaluated for risks to human health and the environment on a case-by-case basis. Applicants who remain uncertain for their particular case can contact the following competent authorities directly:
35. Under Contained Use Regulations, information and guidance may be found at:
www.hse.gov.uk/biosafety/gmo.

Applicants can also contact the Biological Agents Unit in HSE at:

Biological Agents Unit
Health and Safety Executive

1.2 Redgrave Court
Merton Road
Bootle
Merseyside L20 7HS

E-mail: SACGM@hse.gsi.gov.uk

36. Under Deliberate Release Regulations, information and notes on the application format and procedures can be found at:

www.defra.gov.uk/environment/gm/regulation/applications.htm.

37. Applicants can also contact the GM Science, Policy and Regulation Team in Defra at:

GM Controls and ACRE Secretariat
Department for Environment, Food and Rural Affairs
Zone 4/F6,
Ashdown House,
123 Victoria Street
London, SW1E 6DE

Email: gm-regulation@defra.gsi.gov.uk

6.2 Preparing for studies under the contained use and deliberate release regimes

Overview

1. The Contained Use Regulations establish a regulatory system that requires anyone intending to use GMMs in any way to ensure that risks to human health or the environment are minimised through the application of appropriate control measures. Users are required to undertake a number of steps, as shown below. Where appropriate, the equivalent requirements under the Deliberate Release Regulations are given. Each step is expanded upon in the following guidance, under the headings:
 - carrying out a risk assessment for both human health and the environment;
 - assignment of containment and control measures and classification of the activity;
 - the establishment of a genetic modification safety committee (GMSC) to review any risk assessment carried out;
 - notification of first use of premises; and
 - notification of certain individual activities.

Risk assessment

Carrying out a risk assessment for both human health and the environment

2. Irrespective of whether the activity is a contained use or a deliberate release an assessment of the risks to human health and the environment must be carried out. A good risk assessment is crucial to ensure that a trial is conducted and managed appropriately, and consequently this is a pivotal step in both the contained use and the deliberate release regulatory processes.
3. It is probable that a full risk assessment will have been carried out for the development and production of the trial material. This will be an important source of information and can be used as a basis for the risk assessment required for the clinical research study. It will still be important, however, to generate a suitable and sufficient risk assessment specifically for the clinical research study.
4. It should be emphasised that, in most cases, the hazards posed by infectious non-GM organisms that may be encountered in a clinical setting, for example blood-borne pathogens, are considerably greater than those posed by GM organisms being used in

the clinic. While it is a regulatory requirement to assess the risks and employ measures to minimise the chances of exposure, in practice these organisms should be handled in a way that is commensurate with the actual hazards posed. The need is for an informed and pragmatic approach rather than overcomplicated procedures, specialised facilities or unnecessary protective equipment.

5. It is often helpful when considering work with GMMs to relate them to familiar or routine clinical situations. Often, individuals focus on the GM aspects of the study and can over emphasise the risks. Drawing staff attention to comparisons with the hazards associated with non-GM infectious agents encountered regularly in hospitals can serve to achieve perspective. The standard principles for preventing hospital-acquired infection will be adequate in most instances.
6. The risk assessment should identify if there are any steps or procedures that could lead to exposure of other patients, staff, visitors or members of the public, or to contamination of wards, theatres, or corridors of the hospital, as well as wider environmental exposure. Measures designed to manage or control these risks should then be implemented. Users should note that applications to market a GMM for therapeutic purposes will need to include a full ERA (see paragraph 33). This ERA is required to cover all aspects of the use of the product in a clinical setting except direct patient effects. This will include storage, transport and use of the material and exposure of staff, as well as the wider environment (ie beyond the confines of the administering establishment). Many of these aspects are covered under human health risk assessments for the purposes of the Contained Use Regulations, which highlights the importance of a robust approach at the pre-marketing phase.
7. Users of GMMs in a clinical setting have a number of advantages over colleagues working in research laboratories who have to carry out assessments prior to the construction of the organism. By the time a GMM reaches the clinic, its properties should be well understood *in vitro* and often *in vivo*. What may not be known in early stage Phase I studies is how the GMM behaves in humans. However, all initial safety data, including data from cell culture, toxicological assays and animal experimentation should be available to those carrying out the risk assessment. Indeed, for studies that fall under the Medicines for Human Use (Clinical Trials) Regulations, all toxicological and safety data are required by the MHRA in order for a CTA to be issued.
8. However, what will be different is the nature of the activity. This includes the preparation and handling of the GMM, the deliberate exposure of people, and the subsequent fate of the GMM. Laboratory workers usually handle GMMs in a microbiological safety cabinet, whereas they are handled in the open in many clinical environments by staff who are not

necessarily trained microbiologists. These factors potentially increase the risk of occupational exposure and it is these areas that the risk assessment should concentrate on. The assessment should consider each stage of the trial and identify any risks to human health or the hospital and surrounding environment. A trial may consist of a number of steps and it may be convenient to consider these in three separate, but overlapping, pathways:

GMM pathway – considers all aspects relating to the GMM, including:

- the properties of GMM;
- receipt and storage of the GMM;
- preparation of GMM for administration;
- disposal of excess GMM;
- transport and containment of the GMM;
- criteria for patient discharge post-trial;
- GMM tracking system – from receipt through to destruction.

Subject pathway – considers all procedures involving the subject, including:

- administering the GMM;
- patient handling and emergency procedures;
- sampling and monitoring of shedding (if required);
- interactions with other patients and staff, visitors and family.

Waste pathway – considers all GMM-contaminated waste, including:

- stages at which contaminated waste is generated;
- transport and containment of waste;
- inactivation and disposal.

9. This approach allows the specification of hazards associated with certain activities, who is at risk at each step and the necessary measures required to minimise the risks for a particular procedure. This approach has been used successfully at a major gene therapy centre in the UK (as summarised in Figure 6.2.1) and can aid the identification of areas where new standard operating procedures (SOPs) and new local rules may be needed.
10. It is important to stress the need for SOPs, not only to ensure proper handling of treated patients, but also to minimise any risks posed by GMM contaminated material. It is recommended that SOPs be drawn up for all procedures involving GMM-treated patients as well as activities involving the GMM itself, and adherence to these SOPs is both monitored and enforced by an appropriate member of staff. SOPs should be reviewed regularly and updated in the light of new operational considerations or exposed shortcomings. A risk assessment, administration protocols and SOPs may be provided by

a trial sponsor, with the expectation that they be adopted by the organisations participating in the trial. In these situations, the risk assessment and administration protocols would remain the same at any site, although the SOPs may need to be adapted to meet local needs. Further details are provided in paragraphs 23-30.

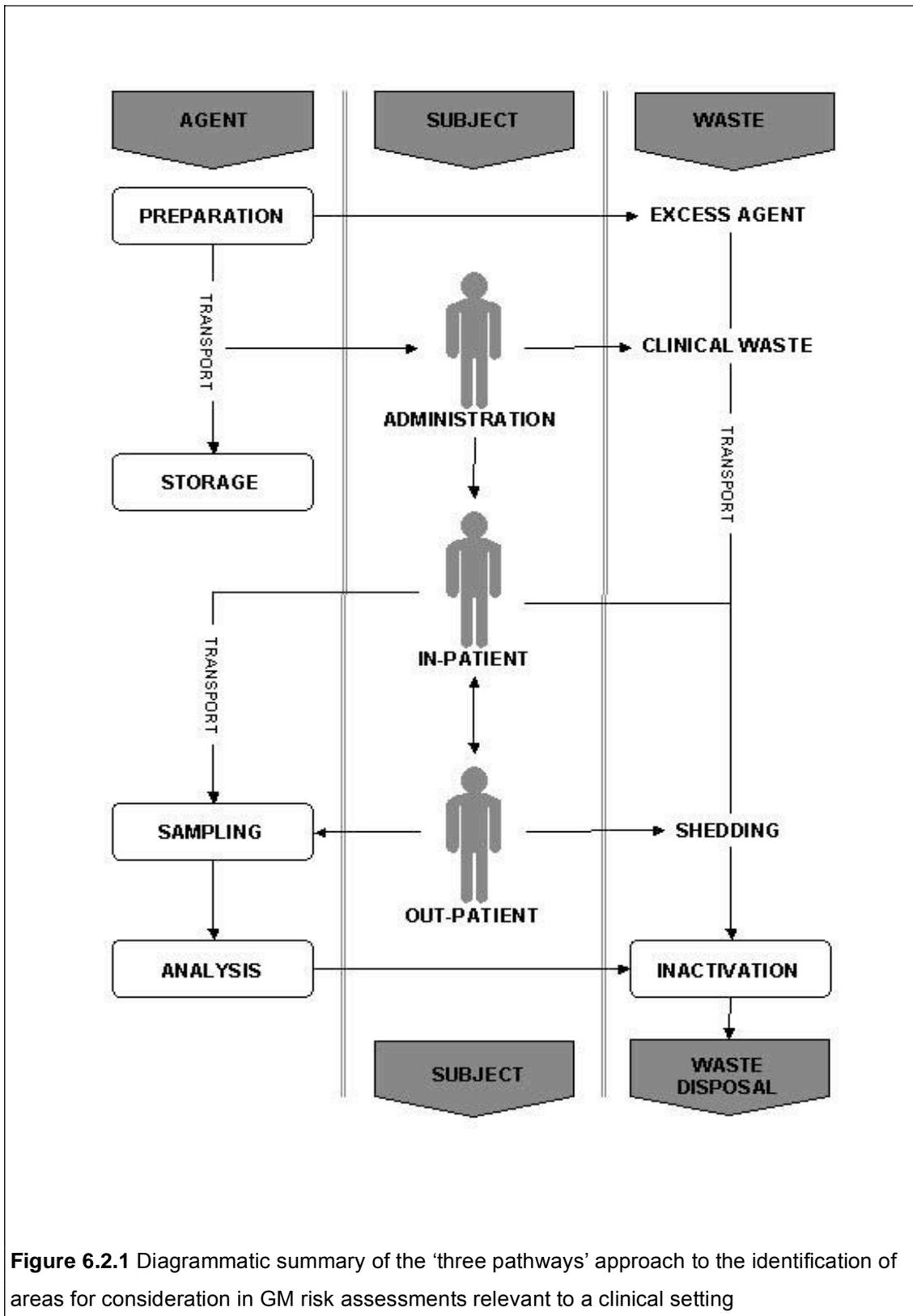


Figure 6.2.1 Diagrammatic summary of the 'three pathways' approach to the identification of areas for consideration in GM risk assessments relevant to a clinical setting

Risk assessment for human health (applicable for both contained use and deliberate release activities)

11. Schedule 3 of the Contained Use Regulations establishes a number of steps that must be followed when carrying out a risk assessment for human health (other than the subjects/volunteers directly involved in the trial). When doing so it can be useful to consider the properties of the GMM and what effects it may have in normal, healthy individuals and then to determine the control procedures needed to prevent, or reduce, the risk of exposure.

12. The following prompt questions may help:

- What is the normal mode of transmission of the GMM?
- What other routes of transmission are possible, eg needlestick injuries?
- What are the possible consequences of an accidental exposure?
- What are the consequences for other body systems (ie non-target tissues) from the systemic administration of the GMM?

13. These aspects should be covered by the risk assessment prepared by those who generated and tested the GMM, for example, the biotechnology company sponsoring the trial. The GM trial risk assessment will need to consider these aspects in relation to the health and safety of staff handling the GMM as well as other staff, visitors and patients, ie:

- all health-care workers who could be involved in patient care;
- pharmacy staff;
- ancillary staff (eg cleaners, maintenance and waste contractors);
- the patient/volunteer's family, friends and other contacts;
- other patients not directly involved in the trial;
- vulnerable groups (eg the elderly, children, pregnant women and those who have compromised immune systems).

Risk assessment for the environment (applicable for both contained use and deliberate release activities)

14. Rigorous environmental risk assessments (ERAs) are required for all contained use and deliberate release activities. Clearly, if the GMM is to be released into the environment under Deliberate Release Regulations, then a more detailed ERA will be required. Once again, the sponsoring organisation providing the GMM for the study should have carried out an ERA, and this can form the basis of the assessment relating to the trial.

Consideration should be given to any aspects of the trial which differ from the original assessment and which could lead to environmental exposure. Useful questions for the sponsor or investigator to consider include, for example:

- By what mechanisms could the hospital environment be contaminated (eg beds, wards, corridors, drains)?
- What is the host range of the parental organism, and could the modification alter this?
- Could the GMM contaminate or spread in the hospital or into the wider environment?
- What could be the effects if the GMM escaped into the hospital or wider environment?
- Could the genetic insert be transferred to another organism?
- Could the GMM pose a threat to human health in the wider community and to other non-target organisms?
- What procedures can be employed to prevent contamination of the hospital or wider environment?

15. When formulating an ERA, answering questions such as those above can highlight to the applicant which is the most appropriate regulatory route to choose.

16. The ERA should consider the possibility of genetic exchange between GMMs and other microorganisms. For example, the bacterium *Shigella dysenteriae* is restricted to the human gut and there is no other animal reservoir. The possibility of environmental colonisation and spread of an attenuated GM strain is therefore minimal. However, genetic information (for example, antibiotic resistance) could be transferred via interaction with commensal organisms in the gut, which may pose a risk to human health, if not to the subject then perhaps to the community. Moreover, replication-defective adenoviruses or conditionally replicative herpes viruses may undergo recombination with their wild-type counterparts that could reverse attenuating genetic lesions. The risks associated with these possibilities need to be considered in terms of both human health and environmental risks. For highly disabled, non-replicating GMMs with a narrow host range, the environmental risk assessment may be more straightforward, however, justification for that conclusion must be provided.

17. Users should note that, under the Genetically Modified Organisms (Deliberate Release) Regulations 2002, the use of antibiotic resistance marker genes must be totally phased out by October 2008 (2004 for marketing applications, and 2008 for experimental releases).

Containment and control

Assignment of containment and control measures and classification of the activity (contained use only)

18. The Contained Use Regulations require users to implement appropriate control measures from tables in Schedule 8 and to use these to establish the containment level and final classification. This poses a difficulty for users working with GMMs in a clinical setting, as the tables only cover laboratories, animal houses, glasshouses and industrial production. For further information on containment and classification under the Contained Use Regulations, see Section 6.4.
19. Four levels of containment are identified, with Level 1 being the lowest and Level 4 the highest. Whichever containment level is deemed appropriate effectively sets the class of the activity that in turn determines the notification requirements (see *Notification of certain individual activities* and Figure 6.2.2). The GM risk assessment carried out by the organisation supplying the GMM should have identified the necessary controls and set a GM Activity Class.
20. The majority of GMMs going into human studies have fallen into the lowest level of activity classification, ie Class 1. This is likely to continue to be the case as GMMs have been designed and engineered for safe administration to humans. There have, however, been a small number of GM studies that have been classified as Class 2 (including some GM vaccine trials), and the move towards replication competent/replication conditional vectors or those with altered tropism is likely to increase the numbers being classified as Class 2. It is unlikely that many gene therapy trials will be classified as Class 3, although there have been a small number of studies with GM vaccines based on ACDP Hazard Group 3 enteric pathogens, such as *Salmonella typhi*, which have been classified as requiring Containment Level 3. In these cases the lack of a suitable small animal model for these organisms meant that studies had to go straight into human volunteers under contained conditions. Thus, although attenuation was predicted following targeted multiple gene deletions, a containment level appropriate for the unmodified pathogen was used until attenuation in humans was established.
21. If the production of a GMM involves an activity that has been classified as a Class 1 activity then by definition it represents negligible risk to human health and the environment, and the containment requirements in the clinic are likely to be minimal. Indeed in most cases, standard hospital procedures and protective measures should suffice. These procedures are deemed suitable to protect staff from pathogens that

patients may be carrying, including blood-borne viruses, and will consequently be expected to provide more than adequate protection against any GM organisms used in the clinic.

22. Under the Deliberate Release Regulations, written consent from the Secretary of State is required prior to the release of GMOs into the environment in Great Britain. There are no levels of classification. A GMO can only be released if it is considered to pose no or negligible risks to human health and the environment.

Other requirements

Role of the principal investigator (PI)

23. The PI has a pivotal role in ensuring that all aspects of the proposed study comply with the relevant trust's research governance framework, including the legal obligations essential for the use of GMMs. The PI should consult the trust research documentation for work that falls within the Contained Use and Deliberate Release Regulations. While the PI is required to be suitably qualified to carry out the clinical research study under the good clinical practice guidelines, they may not always be qualified to handle the GM aspects of a study. The PI should still take responsibility for ensuring that appropriate expertise is available and co-opted where necessary. This may require the establishment of a GMSC (or ensuring that they have access to one) or the appointment of a suitably qualified biological safety officer.

The establishment of a genetic modification safety committee (GMSC) to review any risk assessments carried out (contained use only)

24. Health-care organisations wishing to use GMMs in human studies, and ultimately in the clinical setting, should comply with good practice in order to provide a high degree of management oversight and audit control on research activities. Organisations involved in research that fall within the responsibilities of the Secretary of State for Health must comply with the Research Governance Framework for Health and Social Care. Those wishing to do research studies that fall outside these responsibilities should also seek to observe the principles of the Research Governance Framework.
25. In addition to this, the Contained Use Regulations (regulation 16) requires that anyone (ie any organisation) who carries out a risk assessment under regulation 6 must establish a genetic modification safety committee (GMSC) to advise them in relation to that

assessment. There is no legal requirement for any GMSC involvement for applicants with deliberate release consent.

26. The sole statutory purpose of the GMSC is to advise the management of the notifying organisation on the adequacy of any risk assessments undertaken relating to GM activities.
27. Where health-care organisations are going to carry out clinical research studies on behalf of, for example, a pharmaceutical company, the risk assessment may be provided by that organisation and the trust would not need its own GMSC. For instance, where an organisation intends to carry out a multi-centre study, it is possible for that organisation to notify, as a connected programme of work, its intention to carry out a single activity at a number of different premises. To ensure sufficient enrolment, subjects/volunteers may need to be recruited from a wide range of hospitals. Regulation 13(2) allows for a 'connected programme of work' to cover a single activity carried out at a number of different premises. Protocols and SOPs would be provided by the managing centre and adopted by the hospitals participating in the trial. In these situations, the managing centre would establish a central GMSC and the participating hospitals would not need to establish their own. The risk assessment would remain the same for each hospital, although, the SOPs may need to be adapted to meet local needs. The health-care organisation will have to judge whether to use or have reviewed the company risk assessment or undertake one of its own.
28. This scenario only applies to the legal requirement to establish a GMSC, which has a very specific remit under law, ie to review any risk assessments. If a centre chooses to go down the route described above, it should be recognised that at a local level they would still need some mechanism to ensure that the local management is aware of the trial, as would be the case for any drug trials. All clinical research studies involving human volunteers needs to be considered by a research ethics committee. Furthermore, the person responsible for the trial on site needs to ensure that management and other staff are aware of the risk assessments, and are involved in drawing up the necessary SOPs, including those covering emergency procedures.
29. If health-care organisations are notifying their own research, and do not have GMSCs in place, they may need to either establish one or have access to one. For example, hospitals that have active research departments often have established GMSCs. Teaching hospitals often have access to a GMSC operating in one of the university departments (although there may be contractual implications for a trust using a university committee to assess a protocol to be used in a clinical trial). However, although such committees can provide useful advice to those wishing to carry out GM clinical research

studies, many lack members with the appropriate expertise, for example, on clinical issues and infection control. To overcome this, individuals with relevant expertise should be co-opted onto the committee.

30. Depending on the nature of the planned trial it may be necessary to have a range of representatives such as management, trial nurses, pharmacists, infection control staff, virologists, microbiologists, employee representatives (eg union representatives), health and safety advisors (such as a biological safety officer, see below) and clinicians. It is important to have employee representation since, for many staff, such studies may be their first encounter with GM. All concerns should be acknowledged and dealt with constructively by providing information so that informed judgments can be made. Consideration should also be given to using other established trust committees for evaluation of the introduction of GM work (eg trust health and safety or infection control committees). However, where opinion and technical support is required it would be less fragmentary to pull the appropriate personnel onto the GMSC to allow all aspects of the study to be discussed and agreed.
31. While it is important to have the correct representation on the GMSC, centres should avoid having unnecessarily large and unwieldy committees. The composition can be tailored for different GM studies and outside expertise can be drafted in where necessary.

Biological safety officer (BSO)

32. The hospital may need to appoint a BSO to advise management or to assist the GMSC in undertaking the actions required to comply with statutory obligations. The BSO would ensure that any measures required by the risk assessment are properly applied, and advise management/GMSC on matters of safety. In practice, the BSO often plays a pivotal role as a co-ordinator and interface between researchers/clinicians and the GMSC. There is no statutory requirement for a BSO, although it is recommended that a suitably qualified individual be appointed or identified within the trust. They should possess good communication skills, have an appropriate understanding of GM issues and have experience or training relevant to the clinical environment. The BSO should also be familiar with infection control procedures, and either be a part of, or have good links to, the infection control team.
33. The BSO could be an internal appointment, or co-opted from an allied research facility/university department. If the BSO is required to have contact with patients, they will probably need to be given an honorary contract in order to do so.

Notification of first use of premises (contained use only)

34. Regulation 9 of Contained Use Regulations requires that the competent authority (HSE) be notified of the intention to begin work with GMOs on the premises. If a hospital incorporates a medical school or research department that has already notified HSE of work with GMOs, it is often possible to simply 'extend' the notification (under regulation 15(2)) to include the hospital by contacting HSE. Otherwise, a premises notification must be submitted, along with the risk assessment for the proposed activity. Provided the study has been assigned as a Class 1 activity (see *Assignment of containment and control measures...*) the trial may start upon receipt of acknowledgement from HSE. This is not the case for notifications made under Deliberate Release Regulations, where written consent is required prior to the start of the clinical study.
35. For multi-centre studies, a single notification is required from the managing centre under regulation 9(1). In such cases the managing centre would be considered to be the 'person' responsible for the work. In many cases, this may be a clinical research organisation (CRO). The names and addresses of the participating centres are required and any additional premises that are selected subsequent to the initial notification can be added by providing details to the competent authority at the appropriate time for addition to the notification database. However, the notification is only relevant to the connected programme of work and the managing centre. If the participating centre resolves to undertake its own studies involving GMMs, then it must submit its own premises notification, along with the relevant risk assessments and activity notifications.
36. A fee is payable for premises notifications. For multi-centre trials a single fee is payable. No further fee is required if additional premises are added at a later date to the initial premises notification. A fee is payable for each individual notification made under Deliberate Release Regulations.

Notification of certain individual activities (contained use only)

37. Once the premises have been notified for Class 1 activities, all future Class 1 activities can proceed without further notification, however, they will be still subject to regulatory oversight through inspection programmes.
38. Regulation 10 stipulates that HSE must be notified of the intention to begin activities assigned as Class 2. This notification must be submitted in addition to any notification of premises but can be submitted simultaneously (and only one fee is payable). If submitted simultaneously with the premises notification, or if it is the first Class 2 activity undertaken at the site, then the trial may start 45 days after receipt of acknowledgement from HSE, or

sooner if agreed by the CA. Regulation 10 also stipulates that all subsequent Class 2 activity be notified; however in this case, the trial may start upon receipt of acknowledgement from HSE.

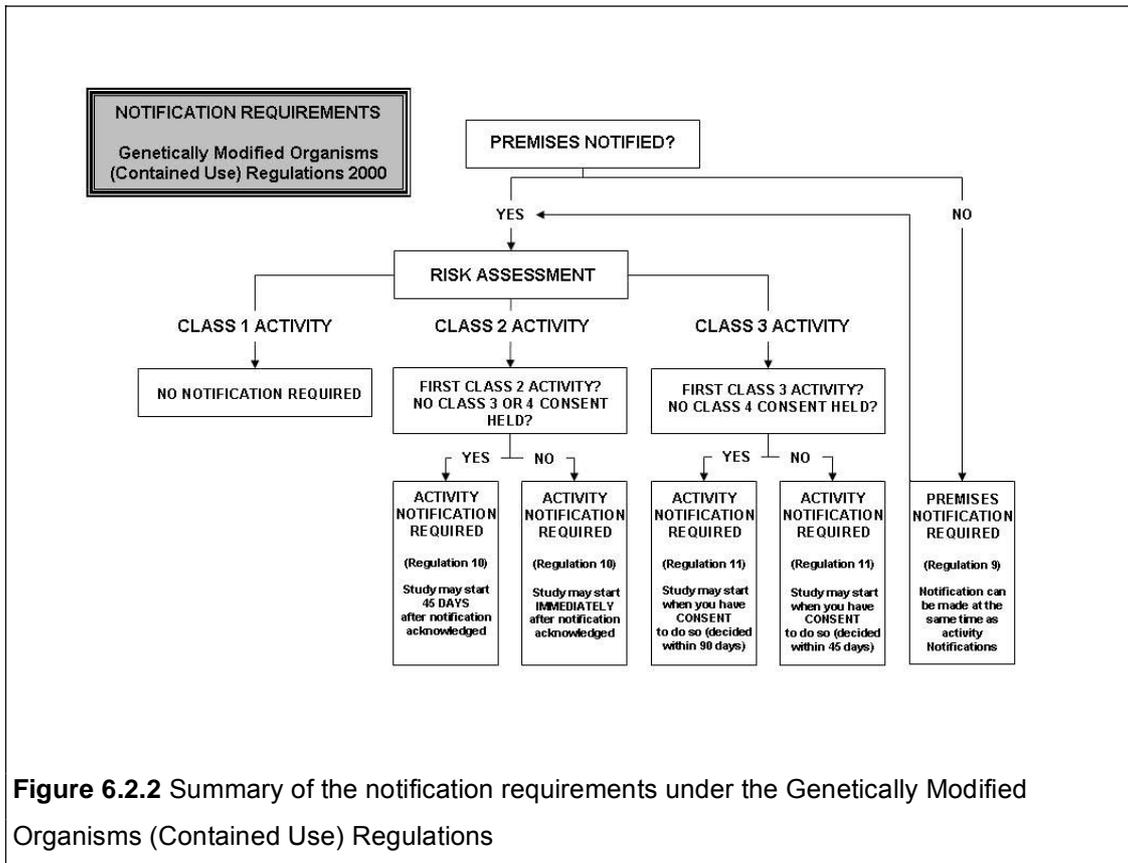


Figure 6.2.2 Summary of the notification requirements under the Genetically Modified Organisms (Contained Use) Regulations

39. Regulation 11 stipulates that written consent is required to begin activities assigned as Class 3 or Class 4. Notification must be submitted in addition to any notification of premises but can be submitted simultaneously, as described above.
40. Users may wish to note that under regulation 13(2), notifications may cover a single activity or a 'connected programme' of work, and should consider which is the most appropriate route to take. A connected programme of work is defined as 'a series of activities involving genetic modification which form a coherent and integrated programme'. It could be argued that many Class 2 clinical activities could well fall into this category. For example, if working on gene therapy approaches to the treatment of head and neck cancers using immunotherapy, researchers may wish to use a number of different vectors and therapeutic genes in a series of related studies. There will be a common goal: the treatment of head and neck cancer, and the connected programme would allow flexibility in the approach taken in light of clinical results, without the need for numerous repeat activity notifications each time there was a change in vector or insert. The notification should outline the types of vectors and immune modulating genes that are likely to be used in the course of the programme, and look at the worst-case scenario from the range

of vector/insert combinations listed. Under the Deliberate Release Regulations, the consent for release is specific and limited to the clinical study described in the notification, and further studies require new notifications.

41. Under regulation 13(3), a connected programme can also cover a single activity, for example, a Phase III trial, carried out by the 'same person' at a number of separate sites. This could include a multi-centre trial notified by a sponsoring organisation. For example, Company A might notify a Phase III trial to be carried out at ten separate centres across the country (which will have been listed in the premises notification). Provided that the notification covers a single activity, and is being carried out under the overall management of the notifier, it can be considered a connected programme. The notifier will provide a single risk assessment, and a single GMSC would be required. Day-to-day management of the study can be carried out by the different principal investigators (PIs) at each site, with the sponsoring company will have overall management responsibility.
42. Connected programmes only apply at Class 2, 3 and 4, as there are no 'activity notifications' required for Class 1 activities. For Class 1 activities, a multi-centre trial is notified as a premises notification listing the participating centres.
43. A summary of all the notification requirements under the Contained Use Regulations can be found in Figure 6.2.2. Notification forms are available from HSE or can be downloaded at: www.hse.gov.uk/biosafety/gmo/law.htm.

6.3 Conducting studies under the contained use and deliberate release regimes

GMM preparation and handling

(applicable for both contained use and deliberate release activities)

1. The preparation of products that are to be administered to patients raises considerable concern among practitioners. GMM trial material that is considered an investigational medicinal product (IMP) must be manufactured and prepared to the same standards as other licensed or experimental medicines. Its manufacture and preparation should conform to good manufacturing practice (GMP) of investigational products (InP) under the Clinical Trials Directive and quality control/assurance (QC/QA) requirements. Most clinicians argue that all products that are to be administered to patients should be prepared in a similar manner, ie within the pharmacy, or by pharmacy staff. However, there has been a reluctance to allow the preparation of products containing microorganisms to take place within the centralised facility due to concerns regarding possible cross-contamination, which could be either way, ie the GMM contaminating other pharmacy products or becoming contaminated by pharmacy products. Although such scenarios are unlikely in a professionally run pharmacy, they need to be considered and appropriate measures and procedures adopted.
2. There is clearly a tension between the requirement to protect the quality of the GMM product and the need to prevent contamination of other medicines. There may be a number of ways in which GMM products can be dispensed safely, without compromising either the pharmacy or the product. For example, some centres have opted for the use of a dedicated isolator, or a side room, within the pharmacy, to allow sufficient separation of work activities. Others have used the pharmacy outside normal working hours. Alternatively, there may be a need for a satellite facility dedicated for the use of GMMs to be set up. Pharmacy departments are accredited and highly regulated for medicine preparation and therefore it would be prudent for them to oversee the operation of a satellite facility of this type with pharmacy staff trained to handle the products. No accreditation would be required, provided that only basic reconstitution or dilution of the product takes place. If any further manipulations of the product are foreseen, then this may require an application for a license followed by inspection and accreditation by the MHRA.
3. **Health-care organisations need to be proactive about getting involved with biological therapies of this type, in the same way they are required to be proactive about declaring themselves research active under research governance. If they are**

unwilling or unable to fund changes to allow the safe handling and administration of GMM vectors then they should reconsider their suitability for enrolling subjects on to gene therapy studies.

4. In many cases, the trial material will arrive on site from a pharmaceutical or contract bio-manufacturing company in a form that is ready for administration. Some pre-administration manipulation may be required, however, which will necessitate working in a manner that keeps the GMM free of contaminants to ensure patient safety and a high-level of asepsis will be required. The material should also be handled in a way that affords sufficient protection to the operator and those in surrounding areas. Preparation of a GMM for administration may, therefore, have to be carried out in a microbiological safety cabinet or isolator. The handling of GMMs designated as Class 1 would not require the use of a cabinet for the purposes of operator protection, however, it is standard practice to utilise a microbiological safety cabinet to safeguard product purity. It is important to consider how the preparation area and equipment will be decontaminated after use, and indeed may be a condition of a deliberate release consent. Decontamination should be monitored where possible, however, as there is no validated means of actively monitoring for the presence of viruses, a means of disinfection that is known to effectively destroy the organism should be employed.
5. Decontamination is particularly important in the event that the same equipment is to be used for different organisms, and a suitable period of time should elapse between uses.
6. It should be noted that bedside or ready-for-use reconstitution is permissible in certain circumstances. Reconstitution is not covered in the Medicines for Human Use (Clinical Trials) Regulations 2004, however, it is referred to specifically in the MHRA guidance/consultation note MLX328, which states that 'a hospital or health centre does not need to hold a manufacturing authorisation for the packaging and labelling of medicines for use in a clinical trial'. For this exemption to apply the activity must be carried out by specified people and the repackaged or labelled medicinal product must be used exclusively in that hospital or health centre or any other site which is participating in the clinical trial. Furthermore the guidance states 'reconstitution of medicinal products used for clinical trials does not fall within the scope of manufacture'. Consequently bedside reconstitution will often be permissible, and practitioners are advised to discuss this with their pharmacist.

Safe storage

(applicable for both contained use and deliberate release activities)

7. The Contained Use Regulations require appropriate safe storage for the GMM. Most will require refrigeration or freezing upon arrival at the study centre and, in most cases, a designated refrigerator or freezer/freezer compartment within the pharmacy or secondary preparation facility will be adequate. There should be separation for individual products either by the use of separate refrigeration units or by clear internal divisions. Furthermore, there should be separation of GM trial samples from other GMM-contaminated materials, particularly tissue and blood samples taken for monitoring purposes. Although there is no formal requirement below level 4, it would be good practice to lock the storage unit and restrict access to trial materials. Consideration should also be made to other aspects of product storage, for example a contingency plan should be in place to safely resite the GMM materials in the event that the refrigerator or freezer fails.

Safe transport

(applicable for both contained use and deliberate release activities)

8. The risk assessment should consider the hazards associated with moving GMM samples between different areas or facilities (for example from pharmacy to theatre), particularly the consequences of accidental releases in areas where individuals not involved in the trial might be exposed. However, the use of appropriate packaging should make the likelihood of an accidental spillage negligible. Once again it should be remembered that clinical specimens are routinely transported safely through the hospital. However, so as to avoid any potential mishaps, some centres have adopted the approach of 'walking' the routes through which the GMM sample will be transported prior to the trial commencing, so that any additional hazards can be identified. The use of suitable secondary containment for the transportation of GMM material would minimise the consequences of accidental spillage since the GMM would be contained and, if necessary, could be opened in a safety cabinet before deciding on a suitable course of action. The use of secondary containment during movement of GMM material in a positive air pressure environment is particularly important as the ambient pressure could disseminate the GMM from the site of the incident.

Spillages and accidental contamination

(applicable for both contained use and deliberate release activities)

9. As previously stated, most GMMs used in clinical research studies pose negligible or low risk to humans or the wider environment. Nevertheless, an accidental spillage could contaminate public areas, operating theatres etc, and needs to be addressed appropriately.

10. The risk assessment should consider any hazards associated with accidental spillages or contamination, and these should be addressed by assigning control procedures and drawing-up contingency plans. The appropriate action will be dependent on the nature of the GMM, the site of the spill and the severity of the accident. For example, where the GMM is not aerosol-borne, thorough disinfection of the incident site is likely to be sufficient. If an aerosol-borne GMM is released, then more serious action may be necessary, such as the evacuation of the area for an appropriate amount of time to allow the aerosol to subside and the use of a respiratory mask during disinfection of the area. Such action will be dependent on the nature of the organism, as well on factors such as volume and concentration of virus in the spilled material. Where air handling is in operation, consideration should be made to having access to an emergency shut-off facility, unless it is able to contain the organism or clear the aerosol (eg negative pressure or appropriate filtration system). The use of secondary containment during movement of GMM material would minimise the consequences of accidental spillage, however, suitable emergency procedures must exist and an appropriate disinfectant or decontamination agent be readily available. Regulation 21 of Contained Use Regulations requires that any accidents involving a GM organism be reported to HSE.
11. Further information regarding the appropriate disinfection and decontamination procedures can be found in: in Appendix 3 of the ACDP publication *The management, design and operation of microbiological containment laboratories* and in Part 3 of the Compendium.

Disposal of GMM contaminated waste

(applicable for both contained use and deliberate release activities)

12. The inactivation of waste is another area that causes concern among GM users, as the requirement to inactivate GMMs in contaminated waste under the Contained Use Regulations is interpreted as being more onerous than the steps taken when dealing with normal clinical waste. This is not necessarily the case and GM clinical waste should be dealt with in a pragmatic way.
13. Both the form of contaminated material generated and the procedure for dealing with it should be described in the risk assessment. As there is no formal definition of 'waste' in Contained Use Regulations, the risk assessment should identify all types of material that could be regarded as GMM contaminated.

14. The intention of the Regulations is to limit contact with the environment and people, as opposed to preventing all contact. In practice, there may be a need for specific inactivation procedures to limit contact, although the approach taken should be commensurate with the risk. For example, the needle and syringe used to withdraw blood samples following patient treatment can be disposed of as any other contaminated sharps. Used vials containing the inoculated material could be treated with a chemical disinfectant or autoclaved prior to disposal.
15. Dirty bedlinen should be cleaned using routine procedures unless gross contamination is suspected, in which case, the normal procedures for handling such bedding (eg with blood or faecal contamination) should be implemented. This would normally involve a high temperature wash (eg 65 °C), and as the procedures are considered sufficient to deal with blood-borne viruses or enteric pathogens, they should be sufficient for GMMs used in hospitals. Similarly, surgical equipment should be cleaned in the standard way, which has been proven to be effective at preventing cross-contamination.
16. Unused or excess clinical materials containing viable GMMs may be returned to the trial sponsor, or inactivated on site through disinfection or autoclaving, prior to disposal in the clinical waste stream.

Shedding and monitoring

(applicable for both contained use and deliberate release activities)

17. This is an area that often causes difficulty in risk assessments and is an important factor in determining whether a clinical activity can be considered a 'contained use' or a 'deliberate release'. Where it is known that persistent long term shedding is likely (for example, following administration of a vaccine derived from an enteric pathogen) the activity may need to be considered as a deliberate release. The distinction will be based on a number of factors, including the degree of biological containment and on the safety of the GMM as discussed in *Contained use or deliberate release?*
18. For studies carried out under Deliberate Release Regulations there will be a requirement that releases of GMMs are accompanied by a monitoring plan. A description of the monitoring plan and techniques to be used must be supplied with the application for consent.
19. The purpose of post-release monitoring is to identify any effects of the GMO on human health and the environment. The plan should include specific methods for tracing and monitoring the effects of the GMOs in the volunteers and any other media in which GMOs

may be released into. The plan should also indicate the duration and frequency of the monitoring.

20. Information supplied by applicants with regard to the treatment of human waste that is destined to enter directly into the sewage system has often assumed that the GM microorganisms will be inactivated by the sewage treatment process and subsequent water purification, eg chlorination, and hence will not present a risk. This has generally not been accepted as a sufficient argument and in such cases applicants may be required to demonstrate that the shed GM will be inactivated in the medium into which it is released and, where appropriate, may have to be supported by evidence gained through laboratory studies. It should be noted that normal sewage treatment is not designed to inactivate microorganisms, except where specific treatments, eg UV, are used.
21. Details of the monitoring requirements will be written in to the consent, and are determined on a case-by-case basis. For example, if persistent long-term shedding was expected then post-release monitoring would include the detection of the GMM in excreta to confirm extent (quantity, quality and length of time) of shedding of the GMO.
22. Although it is guidance to applicants on best practice in the design of **post-market** monitoring plans, the document published by ACRE may still be informative and can be found at: www.defra.gov.uk/environment/acre/postmarket/acre_postmarket/index.htm.
23. The following paragraphs assume that the trial is being carried out under the contained use regime and the intention is to control/contain the GMM.
24. The risk assessment needs to consider the human health and environmental risks from shed GMMs. Where there is likely to be significant shedding, it may be necessary for treatment to be on an in-patient basis until shedding is complete or at a level unlikely to pose a risk. Alternatively, treating subjects with an appropriate antibiotic or antiviral prior to discharge can also be used to reduce or prevent shedding. In some cases (for example when using vaccinia-based GMMs) the use of occlusive dressings can be used to limit the release of GMMs, provided appropriate management and disposal of the dressings can be ensured. If any such approaches are not practical, the activity may have to be considered as a deliberate release activity.
25. An evaluation of the likely routes and the duration of shedding should be included in the risk assessment. Furthermore, the significance of the shedding in terms of risk management needs to be carefully considered. It is important that historical data from pre-clinical or other clinical research studies is used to evaluate the risks. Equally, for Phase I studies it is important to gather as much data as possible regarding the behaviour of the

GMM in humans while the scale of the study is small enough for this to be feasible. Where possible, data regarding the levels, routes and duration of GMM shedding should be gathered.

26. Consideration should therefore be made as to the best methods for detecting the GMM. For example, direct plating of bacterial vaccines with or without enrichment may be possible and appropriate. For viral GMMs, similar direct methods may not be applicable therefore indirect monitoring techniques such as PCR may be required. These techniques should be used with caution, as they may merely determine whether the GMM nucleic acids are present and not necessarily indicate the presence of an infectious organism or viable GMM. Quantitative PCR methods could be used to demonstrate that the amount of GMM nucleic acid was changing over time. For example, a rise in copy-number of a GMM genome might indicate a productive infection whereas static or decreasing copy-numbers would confirm that no replication was taking place. Molecular methods of detection should be validated, quality controlled and compared against appropriate standards. It is important that molecular data of this type is used in concert with the known biological properties of the organism (reinforcing the importance to obtain information during early studies when subjects can be more closely monitored) as well as consideration of other factors, such as:

- the infectious dose of the GMM;
- the host-range of the GMM;
- the likelihood of exposure of staff, patients and other contacts;
- the likelihood of expression of the insert DNA.

Training

(applicable for both contained use and deliberate release activities)

27. There is a requirement under the Contained Use Regulations (regulation 17) to provide appropriate training for staff and health-care organisations should ensure they have suitably qualified personnel to undertake this function. This training should cover the general principles of good microbiological practice and of good occupational safety and hygiene, which are set out in Schedule 7. It is generally considered good practice to keep written records of staff training, although there is no formal requirement to do so. The exception to this is where a Class 3 GMM is to be used, in which case formal training records must be kept. For the purposes of good clinical practice (GCP), there is a formal requirement for staff training, and records must be kept as part of the GCP induction process.

28. Prior to the commencement of a trial, all staff should be given clear instruction on:
- training for those who are going to carry out trials – carry out local assessments;
 - possible routes of exposure or infection;
 - recognition of the symptoms (if any) associated with infection with the GMM;
 - what to do in the event of accidental infection or exposure.
29. The primary role of staff training is to ensure the correct use of equipment, the safe handling of concentrated GMMs and adherence to SOPs. Hospital staff are often accustomed to handling material contaminated with infectious agents and used to employing 'standard precautions' (formerly known as 'universal precautions') to prevent exposure. This will lessen the amount of time needed for formal health and safety training.
30. However, even though GMMs will often be less infectious than natural organisms encountered on a day-to-day basis, the 'GM label' may create a perception that the hazards are greater than they really are. Appropriate training can help to reassure staff. In particular, occupational health staff, who may need to advise colleagues on GM risks associated with the trial, should be adequately briefed. The risks should have been thoroughly assessed and appropriate protective measures put in place. By effectively communicating this information, training can be utilised to demystify the GM organism and impart confidence to the staff.

Health surveillance

(applicable for both contained use and deliberate release activities)

31. There is no requirement for health surveillance under the Contained Use Regulations, however, where the trial involves a GMM classified as Class 2 or above, there may be a requirement to do so under COSHH. Since most clinical research studies have, so far, involved Class 1 activities, no specific procedures have been required to date. In practice, health surveillance is only worthwhile when the onset of damage to health can be reliably detected or is becoming more likely.
32. Although there is no specific legal requirement to carry out health surveillance, all good employers have occupational health services, which may be able to address any concerns staff may have about the trial, and provide help in the event of accidental exposure to the organisms in use.
33. In practice, the risks associated with the GMM are likely to be sufficiently low so as to negate the need for special health surveillance or monitoring. Some centres have adopted

the procedure of banking a baseline serum sample so that it can be determined if an incident has resulted in exposure to the GMM. This is generally considered to be unnecessary and, if such an approach is taken the purpose should be made clear. Furthermore, consideration should be made as to how long the sample should be kept, where and how it should be stored.

34. In some cases, staff may harbour persistent infections caused by microorganisms related to the GMM used in the trial. For example, since herpes simplex virus (HSV) persistently infects up to 90% of the population, there is a risk that genetic information could be transferred between HSV infecting a member of staff and an HSV-derived GMM used in a trial. Staff in this situation should be aware of these risks and assess their own health status. For example, should a staff member have an active herpetic cold sore or suspect they may be about to develop one, then they should raise this with the appropriate line manager. Their suitability for work with the GMM should be reviewed and their involvement in certain aspects of the trial be temporarily suspended, if deemed necessary.
35. In other cases, the trial may involve the use of a GMM delivering a gene that makes a molecule with a powerful biological function such as growth factors, immunomodulatory molecules or bacterial toxins. The risk assessment should consider whether there are any specific circumstances where accidental exposure could cause significant impact to health, for example by accelerating the growth of an underlying tumour or affecting the development of a foetus. Again, staff who are concerned about their own immune status or female staff suspecting they may be pregnant should make their line manager or occupational health professional aware, where this may be an issue with respect to the trial. These considerations should be made clear to staff prior to the trial commencing as part of their instruction and a culture of openness should be fostered between the trial staff and those with managerial responsibility.
36. Regulation 21 of the Contained Use Regulations requires that any accidents involving a GM organism be reported to HSE in addition to reporting serious incidents to HSE under RIDDOR. Furthermore, COSHH requires that records of anyone working with a Class 3 GMM should be kept in addition to other health records and should be stored for a period of 40 years.

Further information

37. Further information regarding the management of risks associated with all biological agents can be found in: the SACGM *Compendium of Guidance* and the ACDP publication

Biological agents: Managing the risks in laboratories and healthcare premises available from HSE Books, PO Box 1999, Sudbury, Suffolk CO10 2WA (Tel: 01787 881165).

6.4 Containment and classification under the Contained Use Regulations

Regulatory requirements

1. The overarching requirement of the Contained Use Regulations is that containment is applied to limit contact with, and provide a high level of protection for, humans and the environment and are relevant to all aspects of the activity, except those directly relating to the patient/volunteer. This general requirement is 'fleshed out' by two specific regulations – regulations 17 and 18 – and associated schedules, which prescribe the minimum containment for particular activities.
2. Regulation 17 sets out the 'principles of occupational and environmental safety', which aim to ensure that 'the exposure of humans and the environment to genetically modified micro-organisms is reduced to the lowest level that is reasonably practicable'. The 'principles', which are outlined in the associated schedule (Schedule 7), are described as the 'general principles of good microbiological practice and of good occupational safety and hygiene', and apply to any activity involving the use of GMMs.
3. Regulation 18 and its associated schedule (Schedule 8) require the application of containment measures from the tables given in Schedule 8. It is this aspect that causes many users the greatest difficulty, as the tables describe containment for laboratories, glasshouses, animal houses and 'other' settings, none of which are particularly appropriate for a clinical setting such as an outpatients clinic, a ward, or a procedures room ('other settings' describe containment in large-scale industrial research and production facilities). In practice this should not cause users any difficulty for the reasons outlined below.

Principles of occupational and environmental safety

4. The majority of clinical applications carried out with GMMs have involved the administration of organisms that have been severely disabled, and are therefore classified as being unlikely to cause disease or harm to humans or the environment, and require the lowest level of containment. Application of the appropriate measures from regulation 17 Schedule 7, combined with the appropriate measures used to protect the product from contamination, will provide sufficient containment for such organisms.
5. The principles in Schedule 7 are as follows:

- keeping workplace and environmental exposure to any genetically modified micro-organisms to the lowest reasonably practicable level;
 - exercising engineering control measures at source and supplementing these with appropriate personal protective clothing and equipment where necessary;
 - testing adequately and maintaining control measures and equipment;
 - testing, where necessary, for the presence of GMMs contaminating objects, equipment or working surfaces;
 - providing appropriate training of personnel;
 - formulating and implementing local codes of practice for the safety of personnel, as required;
 - displaying biohazard signs where appropriate;
 - providing washing and decontamination facilities for personnel;
 - keeping adequate records;
 - prohibiting in the work area eating, drinking, smoking, applying cosmetics or the storing of food for human consumption;
 - prohibiting mouth pipetting;
 - providing written standard operating procedures and risk assessments where appropriate to ensure safety;
 - having effective disinfectants and specified disinfection procedures available in case of spillage of genetically modified organisms; and
 - providing safe storage for contaminated laboratory equipment and materials where appropriate.
6. It should be noted that these apply to all activities in any setting, including work at high containment. Many of the measures are to be implemented 'where appropriate' or 'as necessary', and logically, are less appropriate when working with organisms that are unlikely to cause harm. For example, the use of 'engineering controls' and testing for process organisms outside of containment, are not required at Level 1, and often will not apply at Level 2. Such measures would apply in a laboratory setting at Level 2 if organisms are being cultured or concentrated, but are unlikely to apply in a clinical environment.
7. The use of a microbiological safety cabinet may be required when preparing material for administration; however, this will often be to protect the product rather than the operator. For certain organisms, such as those that can be transmitted by the airborne route (eg replication competent/conditional adenoviruses), the cabinets may be required to protect the operator from exposure.

8. 'Biohazard' signs should not be used for Class 1 organisms, and it is recommended that their use for Class 2 organisms is limited to the doors of laboratories where they are dispensed or stored. In practice, clinical interventions do not need biohazard signs as it is generally assumed that there may be hazardous microorganisms already present, that are handled in accordance with standard precautions.
9. The other measures listed are all required at the appropriate level, which will be dependent on the product and the setting for use. For example, training of staff will be required at all levels; however, the degree of training and instruction may vary considerably between activities. The appropriate level of training should be decided locally by the BSO or equivalent member of staff. Most clinical staff are familiar with procedures for taking and handling blood, or administering injections, and the procedures for administering GMMs should not be significantly different from these.
10. Local rules and codes of practice should again be drawn up 'appropriately', and should cover aspects such as training, disinfection, spillage procedures and disposal of contaminated waste.

Containment requirements – regulation 18

11. The full containment measures required by regulation 18, as described in Schedule 8 are outlined in Table 6.4.2, and look more daunting than they really are. In practice, the measures that are likely to be 'required' are shown in Table 6.4.1. At level 1 the only measures that are automatically required are the requirements to wear 'suitable protective clothing' and to 'inactivate GMMs in contaminated materials and waste by validated means'.
12. The use of 'suitable protective clothing' is normal practice, and 'waste inactivation' can normally use existing hospital waste procedures. Contaminated material such as swabs should be placed into the hospital 'yellow bag waste stream'. Contaminated sharps, such as syringes, glass vials etc, should be placed into sharps bins and disposed of as normal. Excess cultures or contaminated equipment can either be autoclaved or soaked in an effective disinfectant before disposal or washing.
13. For Class 2 projects, the containment requirements are not significantly greater than those previously described. However, as clinical staff routinely handle blood or tissue samples that could potentially harbour blood-borne viruses or other pathogens, they will be trained to avoid exposing either themselves or others. This degree of training should be sufficient for activities with GMMs.

14. Of the measures outlined in Table 6.4.1, only the need for an autoclave is related to equipment or the building fabric. The rest are procedural and describe 'systems of work'. Gloves are routinely worn in a clinical environment, and their use shouldn't be seen as automatically pushing work into Containment Level 2.
15. At Level 2 negative pressure is required if the risk assessment shows it is needed. For most clinical activities this will not be the case. Laboratories or pharmacies where clinical materials are prepared for patient administration will generally be under positive pressure to protect the product from contamination. A Class II microbiological safety cabinet can be used in such circumstances to protect the operator and the wider environment, without the need for the laboratory to be under negative pressure.
16. The normal waste management system should be used where appropriate. Sharps and other contaminated disposable equipment should be placed in appropriate containers (sharps bins) or yellow bags (swabs etc) for disposal. It is not considered necessary in such circumstances for the incinerator or waste contractor to be registered under the Contained Use Regulations.
17. Autoclaves are generally available in the microbiology department, however, if there is not one on site, alternative means of waste inactivation should be used, for example, the use of appropriate disinfection procedures.
18. In conclusion, it should be recognised that for most applications, normal routine clinical procedures for preparing, transporting, and administering products to patients should be sufficient to 'contain' GMMs. Similarly, the taking and processing of clinical samples should be carried out as normal, as these procedures are sufficient to protect against blood-borne viruses and other pathogens that may be present in clinical samples.
19. If it is suspected that a patient or volunteer may shed viable GMMs after administration, for example, from the site of inoculation, or in faeces or urine, appropriate measures should be taken to ensure that workers, the public or the wider environment are not exposed. This may be achieved by keeping patients in hospital until shedding ceases or use of occlusive bandages. This issue must be considered as part of the overall risk assessment, and advice should be sought from HSE if shedding is considered likely.

Containment measure	Level 1	Level 2
Autoclave	required on site	required in the building
Access restricted to authorised personnel only	not required	required
Specific measures to control aerosol dissemination	not required	required so as to minimise
Protective clothing	suitable protective clothing required	suitable protective clothing required
Gloves	not required	required where and to extent the risk assessment shows it is required
Specified disinfection procedures in place	required where and to extent the risk assessment shows it is required	required
Safe storage of GMMs	required where and to extent the risk assessment shows it is required	required
Inactivation of GMMs in contaminated material and waste	required by validated means	required by validated means

Table 6.4.1

Containment measures		Containment Levels			
		1	2	3	4
1	Laboratory suite: isolation (Note 1)	not required	not required	required	required
2	Laboratory: sealable for fumigation	not required	not required	required	required
Equipment					
3	Surfaces impervious to water and resistant to acids, alkalis, solvents, disinfectants, decontamination agents and easy to clean	required for bench	required for bench	required for bench and floor	required for bench, floor, ceiling and walls
4	Entry to laboratory via airlock (Note 2)	not required	not required	required where and to extent the risk assessment shows it is required	required
5	Negative pressure relative to the pressure of the immediate surroundings	not required	required where and to extent the risk assessment shows it is required	required	required
6	Extract and input air from the laboratory should be HEPA filtered	not required	not required	HEPA filters required for extract air	HEPA filters required for input and extract air (Note 3)
7	Micro biological safety cabinet/enclosure	not required	required where and to extent the risk assessment shows it is required	Required, and all procedures with infective materials required to be contained within a cabinet/enclosure	Class III cabinet required
8	Autoclave	required on site	required in the building	required in the laboratory suite (Note 4)	double ended autoclave required in laboratory
System of work					
9	Access restricted to authorised personnel only	not required	required	required	required via airlock key procedure
10	Specific measures to control aerosol dissemination	not required	required so as to minimise	required so as to prevent	required so as to prevent
11	Shower	not required	not required	required where and to extent the risk assessment shows it is required	required

Containment measures		Containment Levels			
		1	2	3	4
12	Protective clothing	suitable protective clothing required	suitable protective clothing required	suitable protective clothing required; footwear required where and to extent the risk assessment shows it is required	complete change of clothing and footwear required before entry and exit
13	Gloves	not required	required where and to extent the risk assessment shows it is required	required	required
14	Efficient control of disease vectors (eg for rodents and insects) which could disseminate the GMM	required where and to extent the risk assessment shows it is required	required	required	required
15	Specified disinfection procedures in place	required where and to extent the risk assessment shows it is required	required	required	required
Waste					
16	Inactivation of GMMs in effluent from handwashing sinks and showers and similar effluents	not required	not required	required where and to extent the risk assessment shows it is required	required
17	Inactivation of GMMs in contaminated material	required by validated means	required by validated means	required by validated means, with waste inactivated in the laboratory suite	required by validated means, with waste inactivated within the laboratory
Other measures					
18	Laboratory to contain its own equipment	not required	not required	required, so far as is reasonably practicable	required
19	An observation window or alternative is to be present so that occupants can be seen	required where and to extent the risk assessment shows it is required	required where and to extent the risk assessment shows it is required	required	required
20	Safe storage of GMMs	required where and to extent the risk assessment shows it is required	required	required	secure storage required

Containment measures		Containment Levels			
		1	2	3	4
21	Written records of staff training	not required	required where and to extent the risk assessment shows it is required	required	required

Table 6.4.2

Note 1 - In Table 6.4.2, 'isolation' means, in relation to a laboratory, separation of the laboratory from other areas in the same building, or being in a separate building.

Note 2 - Entry must be through an airlock which is a chamber isolated from the laboratory. The clean side of the airlock must be separated from the restricted side by changing or showering facilities and preferably by interlocking doors.

Note 3 - Where viruses are not retained by the HEPA filters, extra requirements will be necessary for extract air.

Note 4 - Where the autoclave is outside the laboratory in which the contained use activity is being undertaken, but within the laboratory suite, there shall be validated procedures for the safe transfer of material into that autoclave, which provide a level of protection equivalent to that which would be achieved by having an autoclave in that laboratory.

Further information

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This document contains notes on good practice which are not compulsory but which you may find helpful in considering what you need to do.

This document is available web only at: www.hse.gov.uk/biosafety/gmo/acgm/acgmcomp

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