Technical guidance for GMM assessments

NB: This guidance reproduces the information available in the various "hover-over" information buttons on the on-line assessment template

1. Initial assessment (for Activity Class 1-3 activities)

1.1. Overview of the GMM(s) that will be constructed:

Recipient organism(s) to be used: Give the name of the organism(s) to be used including strain, the name of the wild-type organism from which it is derived, and give ACDP Hazard Group, if relevant, and the degree of disablement/attenuation. Any relevant literature/guidance which provides evidence of the degree of disablement should be cited.

Vector(s): List names of vectors, and indicate any disabling mutations including the extent to which they can be mobilized (if relevant). Any relevant literature/guidance which provides evidence of the degree of disablement should be cited.

Inserted genetic material: List names of genes/genetic material to be inserted (give meaningful names where possible not codes). Describe the function of the inserted material (if not known, consider likely effects by comparison with homologues if available) and the source of the genetic material ie is it sourced from a wild-type organism, generated artificially or altered in anyway before insertion. If you are looking at groups/families of genes, list all to be used but a description of the function(s) of the gene family is sufficient.

1.2. An indication of the most hazardous GMM to be constructed:

Taking into account both hazards to human health and the environment identify the most hazardous GMM that will be constructed ie the most hazards combination of recipient, vector and insert of those listed. If it is not clear that any one combination will be more hazardous than the others, then indicate this on the assessment, and give an example combination as evidence. Issues to consider when making this assessment include:

- If the agent has been disabled, consider how likely it is to revert to wild-type, eg is it a single point mutation or multiple? The type of mutation can affect the likelihood of reversion, for example deletion mutants are less likely to revert to wild-type than point mutations or conditional-lethal mutants.
- Will the gene product will be expressed, over-expressed, under any means of control eg inducible or not expressed in a biologically active form. But note that even "normal" human genes may be harmful if over-expressed, especially if expression occurs in tissues that do not normally express the protein.
- As well as causing harm by infection, consider also whether the GMM could be toxigenic, allergenic or can cause harm by other means, eg oncogenic.
- Could the insert could be disseminated and maintained in the outside environment in the event of a breach of containment via recombination or gene transfer to a wild-type organism. If so, consider whether the GMM could survive long enough for gene transfer/recombination to take place.

2. Comprehensive assessment (for Class 2 and 3 activities only)

2.1. Assessment of risks to human health and safety:

a) **Recipient micro-organism**: The recipient micro-organism may be both recipient and vector eg you modify a virus which is then used to transfect a cell line, delivering your gene(s) of interest. Make this clear when describing the hazards. You should consider the following issues:

- If the agent is listed in the Approved List of Biological Agents, then use a disabled or attenuated strain rather than wild-type if possible.
- If cell lines are used, the nature and source eg primary cell lines vs authenticated lines from cell banks , human vs non-human should be addressed, as well as considering the likelihood of the cells harbouring adventitious agents.
- As well as the risk of infection, consider also whether the agent produces toxin(s), is allergenic or can cause harm by other means.
- If the agent has been disabled, consider how likely is would be to revert to wild-type, eg is it a single point mutation or multiple? The type of mutation can affect the likelihood of reversion, for example deletion mutants are less likely to revert to wild-type than point mutations or conditional-lethal mutants. One means of minimizing the consequences of any reversion is to insert your gene of interest into the site of a disabling mutation so even if reversion occurs, the worst case will only be reversion to wild-type ie inserted sequence is lost and not expressed.

b) **Inserted genetic material**: Describe the function of the inserted material (if not known, consider likely effects by comparison with homologues if available) and the source of the genetic material ie is it sourced from a wild-type organism, generated artificially or altered in anyway before insertion. If you are looking at groups/families of genes, list all to be used but a description of the function(s) of the gene family is sufficient. Consider the following:

Direct effects	Is the inserted material known to code for any proteins with known harmful effects eg toxic, immunogenic, oncogenic, or able to modulate cell growth or differentiation eg a cytokine or hormone. If harmful effects are known, indicate whether the gene product will be expressed, over-expressed, under any means of control eg inducible or not expressed in a biologically active form. But note that even “normal” human genes may be harmful if over expressed, especially if expression occurs in tissues that do not normally express the protein
Indirect effects	If the inserted material can alter the properties of the host organism in such a way as to change its pathogenicity, immunogenicity, host range, tissue tropism or means of transmission. For example, does it encode a pathogenicity determinant such as an adhesion, a penetration factor or a surface component that provides resistance to host defences? Or does it code for a surface component, envelope protein or capsid protein that might bind to a different receptor to that normally used by the recipient. If the inserted material encodes for drug or antibiotic resistance, especially those currently used for medical treatment.
Gene transfer	If the insert could be disseminated and maintained in the outside environment in the event of a breach of containment via recombination or gene transfer to a wild-type organism. If so, consider whether the GMM could survive long enough for gene transfer/recombination to take place. One means of minimizing the consequences of any recombination is to insert your gene of interest into the site of a disabling mutation so even if recombination occurs, the insert will be lost.

2.1.1. Summary of risks to human health

Given the hazards identified, summarise the risks to human health. This should take into account:

- the consequences of exposure ie how severe the response might be;
- the likelihood of any exposure occurring in a laboratory setting; and
- any uncertainties that have been identified .

2.2. Assessment of risks to the environment

a) **Recipient micro-organism -** In addition to risks to humans, consider also:

- whether agent is a plant or animal pathogen controlled under animal/plant health legislation
- if any adventitious agents that might be present could cause harm to animals or plants
- the agent infect or colonize plants or animals

b) **Inserted genetic material**

Direct effects	In addition to human health risks, consider whether the inserted material codes for an animal or insect toxin or another product that could silence a gene encoding an crucial metabolic enzyme in susceptible hosts
Indirect effects	If the inserted material can alter the properties of the host organism in such a way as to change its pathogenicity, immunogenicity, host range, tissue tropism or means of transmission. For example, does it encode a pathogenicity determinant such as an adhesion, a penetration factor or a surface component that provides resistance to host defences. Or does it code for a surface component, envelope protein or capsid protein that might bind to a different receptor to that normally used by the recipient. If the inserted material encodes for drug or antibiotic resistance, especially those currently used for medical treatment (including animals when considering environmental hazards).
Gene transfer	If the insert could be disseminated and maintained in the outside environment in the event of a breach of containment via recombination or gene transfer to a wild-type organism. If so, consider whether the GMM could survive long enough for gene transfer/recombination to take place. One means of minimizing the consequences of any recombination is to insert your gene of interest into the site of a disabling mutation so even if recombination occurs, the insert will be lost.

2.2.1. Summary of risks to the environment

Given the hazards identified, summarise the risks to the environment. This should take into account:

- the consequences of exposure ie how severe the response might be;
- the likelihood of any breach of containment; and
- any uncertainties that have been identified

3. Nature of the work to be carried out and review of control measures

Generation of aerosol and splashes - Think about procedures such as centrifugation, sonication, homogenization and vigorous mixing (eg using a vortexer).

Means of containment - Give detail of the class of microbiological safety cabinet to be used, and any other means of containment eg sealed buckets in centrifuges or lidded containers when mixing.

Sharps - This includes the use of needles, scalpels, knives and laboratory glassware such as Pasteur pipettes. If needles are required eg for inoculation of animals, then consideration should be given to the use of safer needle devices where possible.

Scale of activity - Give an indication of the maximum volume likely to be cultured and the concentration/titre expected. Indicate the frequency of culture if possible eg one-off *vs* once a week etc. If a viral vector is to be used *in vivo*, indicate maximum volume to be injected at any one time

Other biological risks - This includes the use of blood, other body fluids/tissues, and cells lines/cultures, both human and animal. When deciding the likelihood of contamination, consider the source of the material and whether it has undergone any pre-screening or characterization elsewhere. If you need to use specific containment measures or work at a particular Containment Level because of these risks, indicate as such as this will not drive the final Activity Class for the GM activity ie you can assess an activity as Class 1 on the basis of the risks from the GMM, but have to work at CL2 because you are handling unscreened human blood. In addition to infection risks, you should also consider whether any of the biological material to be used can cause harm by other means, ie is allergenic or toxigenic or otherwise harmful such as prions.

Occupational health considerations - Certain medical conditions may make individuals more susceptible to infection or ill health eg because their immune system is not functioning correctly. If the work being undertaken could pose a risk to such individuals you should seek further advice from the Occupational Health Service before work starts as a fitness for work assessment or other screening may be required on a case by case basis. Anyone working with human blood and unfixed tissues should be offered hepatitis B immunization. Other vaccines exist for agents used in the laboratory but you should seek advice from the Occupational Health Service about the risks and benefits of these before starting work.