



**Specialist  
Pharmacy  
Service**

**Pan UK Pharmacy Working  
Group for ATMPs**

# **Gene Therapy Medicinal Products**

## **Governance and Preparation Requirements**

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## Contents

Reference	Title	Page
1.0	Executive Summary	3
Figure 1	Pharmacy process for initiating GTMP	4
<b>Part 1</b>	<b>Governance</b>	5
2.0	What is Gene Therapy?	5
2.1	“In vivo” (Non-Cellular) vs “Ex vivo” (Cellular) Gene Therapy	5
Figure 2	In Vivo vs Ex Vivo GTMP	6
3.0	What legislation governs gene therapy?	7
Table 1	GTMP legislation and guidance documentation	7
3.1	Classification of containment levels for Gene Therapies	7
4.0	What Governance is required?	9
Figure 3	Local Governance Recommendations	9
4.1	Genetic Modification Safety Committee (GMSC)	10
4.1.1	HSE GMSC requirements for clinical trial gene therapy medicines	10
4.1.2	GMSC Membership	11
4.1.3	Establishing a GMSC	12
4.1.4	GMSC Terms of Reference	12
4.1.5	GMSC responsibilities	12
5.0	GMSC Risk assessments	13
5.1	General information	13
6.0	Notifications	14
<b>Part 2</b>	<b>Operational</b>	16
7.0	Receipt and storage	16
7.1	In vivo (non-cellular) GTMP	16
7.2	Ex vivo (cellular) GTMP	16
8.0	Gene Therapy Medicinal Product Preparation	17
Figure 4	Technical Feasibility Process	17
8.1	Preparation and handling of in vivo (non-cellular) GTMP	18
Figure 5	Gene Therapy Preparation Location – Non Cellular	18
8.2	Preparation and handling of ex vivo (cellular) GTMP	19
Figure 6	Gene Therapy Preparation Location –Cellular	19
8.3	Preparation of GTMP within aseptic facilities	20
8.3.1	Operator protection	20
8.3.2	Preparation process	20
8.3.3	Isolator/Biological Cleaning Considerations	20
8.3.4	Waste management	21
8.3.5	Transport	21
8.4	Preparation of GTMP medicines within a clinical setting	21
9.0	Glossary	22
10.	References	23
Appendix 1	Regulations	24
Appendix 2	Example of a GMSC Risk Assessment	25
Appendix 3	GMSC Terms of Reference	33

## Foreword

The PAN UK Pharmacy Working Group for Advanced Therapy Medicinal Products aims to facilitate the implementation of ATMPs into practice. Gene Therapy Medicinal Products (GTMPs) are a sub-category of ATMPs which are showing great promise to the benefit of patients. As such, access to GTMPs, whether in Clinical Trials or in routine implementation of medicines holding marketing authorisations, is increasing throughout the UK. A subgroup of the Pharmacy Working Group has produced the following guidance in response to increased numbers of enquiries from organisations naïve to Gene Therapy wishing to understand governance and preparation requirements for these innovative medicines.

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## 1.0 Executive Summary

This document has been produced to facilitate the introduction of gene therapy medicinal products (GTMPs) into healthcare organisations. It outlines the governance requirements and facility requirements for GTMPs and provides useful guidance for sites wishing to undertake clinical trials involving GTMP investigational medicinal products, and for sites wishing to implement the use of GTMP holding marketing authorisations.

As GTMPs develop and are used with increasing frequency in clinical and pharmacy practice, it is essential that standards are set and guidance produced for the safe and secure handling and preparation of GTMPs.

The following process flow chart outlines the stages which require Pharmacy consideration when an organisation wishes to use a GTMP.

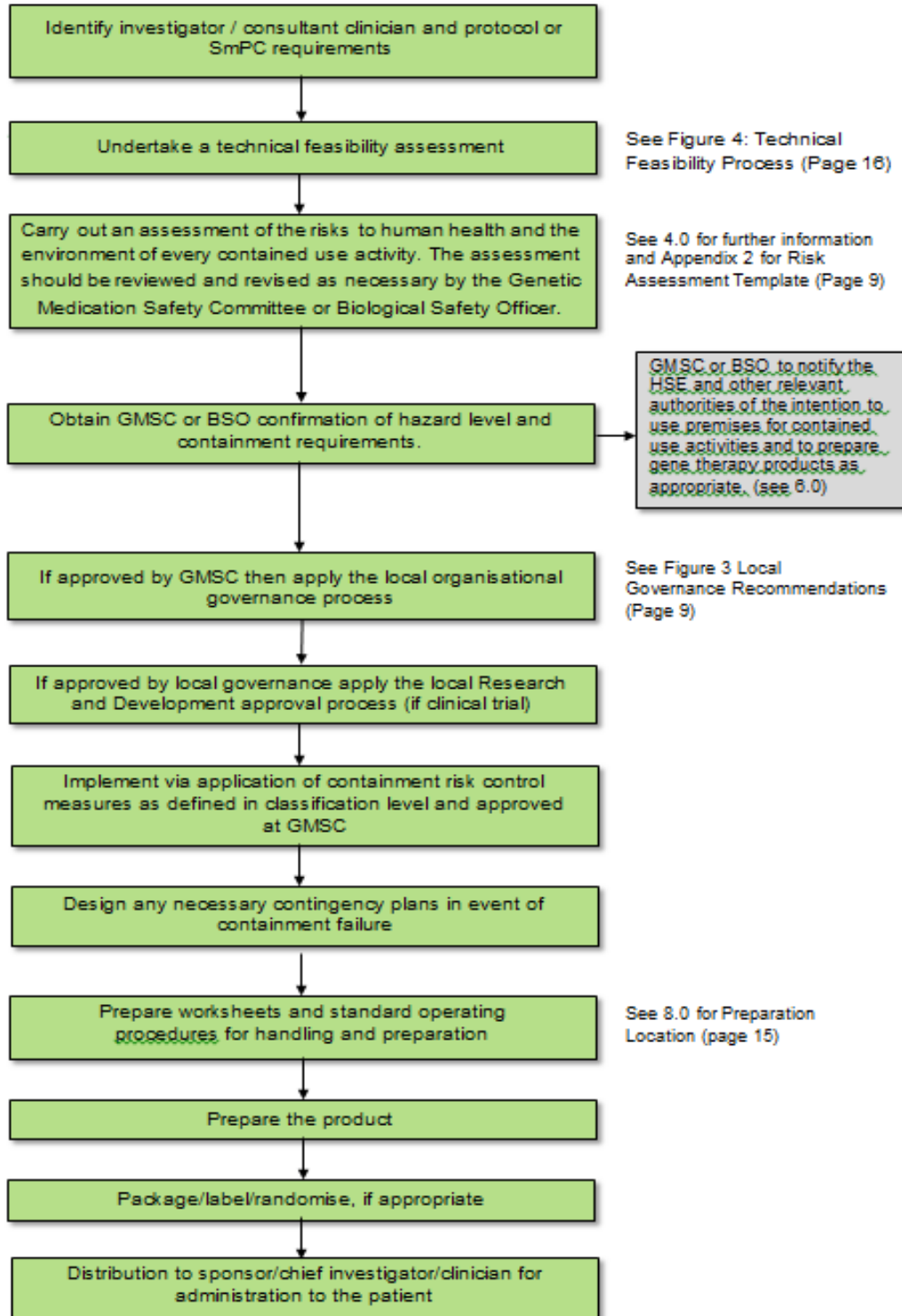


Figure 1: Pharmacy process for initiating GTMP

## Part 1 Governance

### 2.0 What is Gene Therapy?

GTMPs are advanced therapy medicinal products (ATMPs)<sup>[1]</sup>.

Gene therapy medicinal products (GTMPs) are defined as a biological medicinal product which has the following characteristics:

- a. It contains an active substance which contains or consists of a recombinant nucleic acid used in or administered to human beings with a view to regulating, repairing, replacing, adding or deleting a genetic sequence.
- b. It's therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence.

Most GTMPs are used in clinical trials<sup>[2]</sup> although there are GTMPs with marketing authorisations (e.g. Talimogene Laherparepvec) and horizon scanning would predict that this trend is likely to increase.

On occasion a gene therapy may be given as an unlicensed medicine (i.e. an import or a manufactured special). Organisations should ensure that any use of unlicensed GTMPs complies with their local unlicensed medicine policies.

GTMP modes of action are well documented<sup>[3]</sup>. They are designed to introduce genetic material into cells to compensate for abnormal genes or to make a beneficial protein which then multiplies and exerts a positive effect. Another mode of action is in place where a mutated gene causes a necessary protein to be faulty or missing, the GTMP may be able to introduce a normal copy of the gene to restore the function of the protein.

The manufacture of GTMPs is complex as a carrier called a viral vector is required to deliver the gene to the cell. Certain viruses are often used as vectors because they can deliver the new gene by infecting the cell. The viruses are genetically modified to ensure that they can't cause disease when used in people. Retroviruses integrate their genetic material (including the new gene) into a chromosome in the human cell whereas adenoviruses, introduce their DNA into the nucleus of the cell, but the DNA is not integrated into a chromosome.

### 2.1 “In vivo” (Non-Cellular) vs “Ex vivo” (Cellular) GTMP

GTMP is classified as ‘in vivo’ where the GTMP is injected directly into a specific tissue in the body and it is then taken up by individual cells, or where the GTMP is administered intravenously (IV). An example of ‘in vivo’ GTMP is Talimogene Laherparepvec.

Alternatively, a sample of the patient's cells can be removed and used as the starting material. This is an autologous therapy where the viral vector is used to introduce the gene to the starting material cells. The engineered cell is then incubated and expands to form the medicinal product. The genetically modified cells, now classed as a medicine, are then returned to the patient. This is called 'ex vivo' GTMP e.g. CAR-T cell therapy.

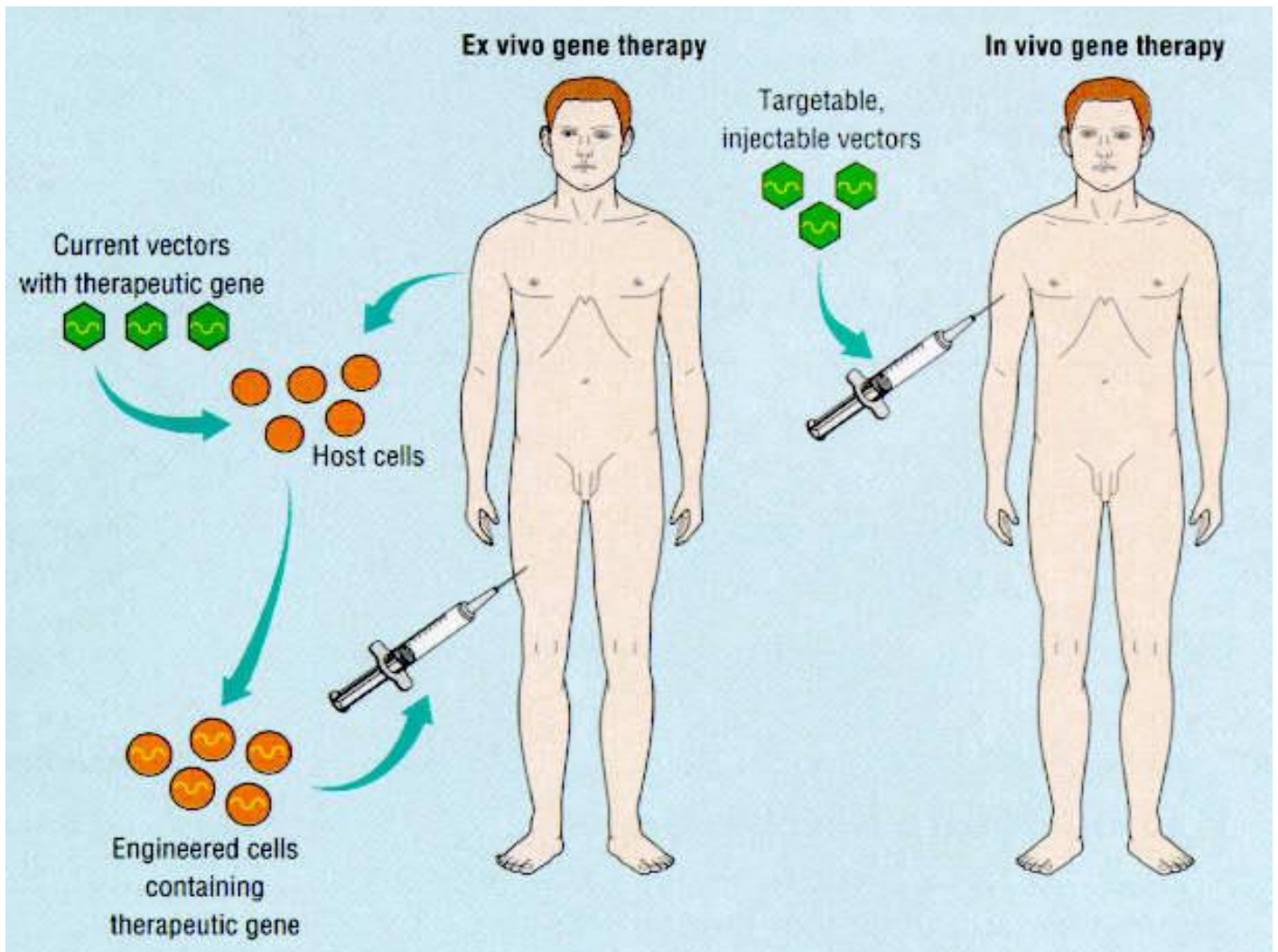


Figure 2: In Vivo vs Ex Vivo GTMP<sup>[4]</sup>

### 3.0 What Legislation Governs Gene Therapy?

The following legislation should be consulted. Investigational Medicinal Product (IMP) GTMPs are regulated by the MHRA and HSE. Licensed GTMPs are governed by the medicines regulators only.

Human Medicines Regulations 2012 SI: 2012 - No. 1916
Regulation (EC) NO 1394/2007 On Advanced Therapy Medicinal Products (“The ATMP Regulation”)
Health and Safety Executive (HSE) Genetically Modified Organisms (Contained Use) Regulations 2014
The Medicines for Human Use (Clinical Trials) Regulations 2004
If the gene therapy product is being used in a clinical trial reference should be made to the following :-
Clinical Trials Directive 2001/20/EC
Medicines for Human Use (Clinical Trials) 2004 SI: 2004- No.1031 as amended

Table 1 GTMP legislation and guidance documentation

### 3.1 Classification and Containment Levels for GTMP

If the GTMP has been genetically modified, the Genetically Modified Organisms (Contained Use) Regulations 2014 will apply. There are four classes of activities according to the regulations<sup>[5]</sup>. The classification is based on the level of risk to humans and the environment.

**Class 1** – activity of no or negligible risk for which containment level 1 is appropriate to protect human health and the environment

**Class 2** – activity of low risk for which containment level 2 is appropriate to protect human health and the environment

**Class 3** – activity of moderate risk for which containment level 3 is appropriate to protect human health and the environment

**Class 4** – activity of high risk for which containment level 4 is appropriate to protect human health and the environment

The classification of the activity involving the genetically modified organism (GMO) is determined by the containment and control measures identified as necessary via the risk assessment. Containment measures are detailed in Schedule 8 of the Genetically Modified Organisms (Contained Use) Regulations 2014 available at:

<http://www.hse.gov.uk/pubns/priced/l29.pdf>

In reality, most activities involving GTMP that are currently in clinical trials and in development will be class 1 or 2.

For example: Containment level 1 is suitable for class 1 activities involving GTMPs such as replication incompetent adeno-associated viruses. Containment level 2 is required for class 2 activities such as the use of conditionally replicating virus vectors. However, the classification for each individual activity must be determined by the risk assessment process that identifies necessary control measures from Schedule 8. Control measures identified from the highest containment level determine the class of the activity. For further details on risk assessment of GMOs see the HSE Compendium of guidance Part 2 <http://www.hse.gov.uk/biosafety/GMO/acgm/acgmcomp/part2.pdf>



#### 4.0 What Governance Is Required?

As GTMPs are ATMPs it is important that organisations that wish to introduce a gene therapy for use either in a trial or as a licensed medicine have a defined organisational governance process in place. This is recommended in Advice for Chief Pharmacists on Advanced Therapy Medicinal Products (February 2017)<sup>[6]</sup> (See Figure 3)

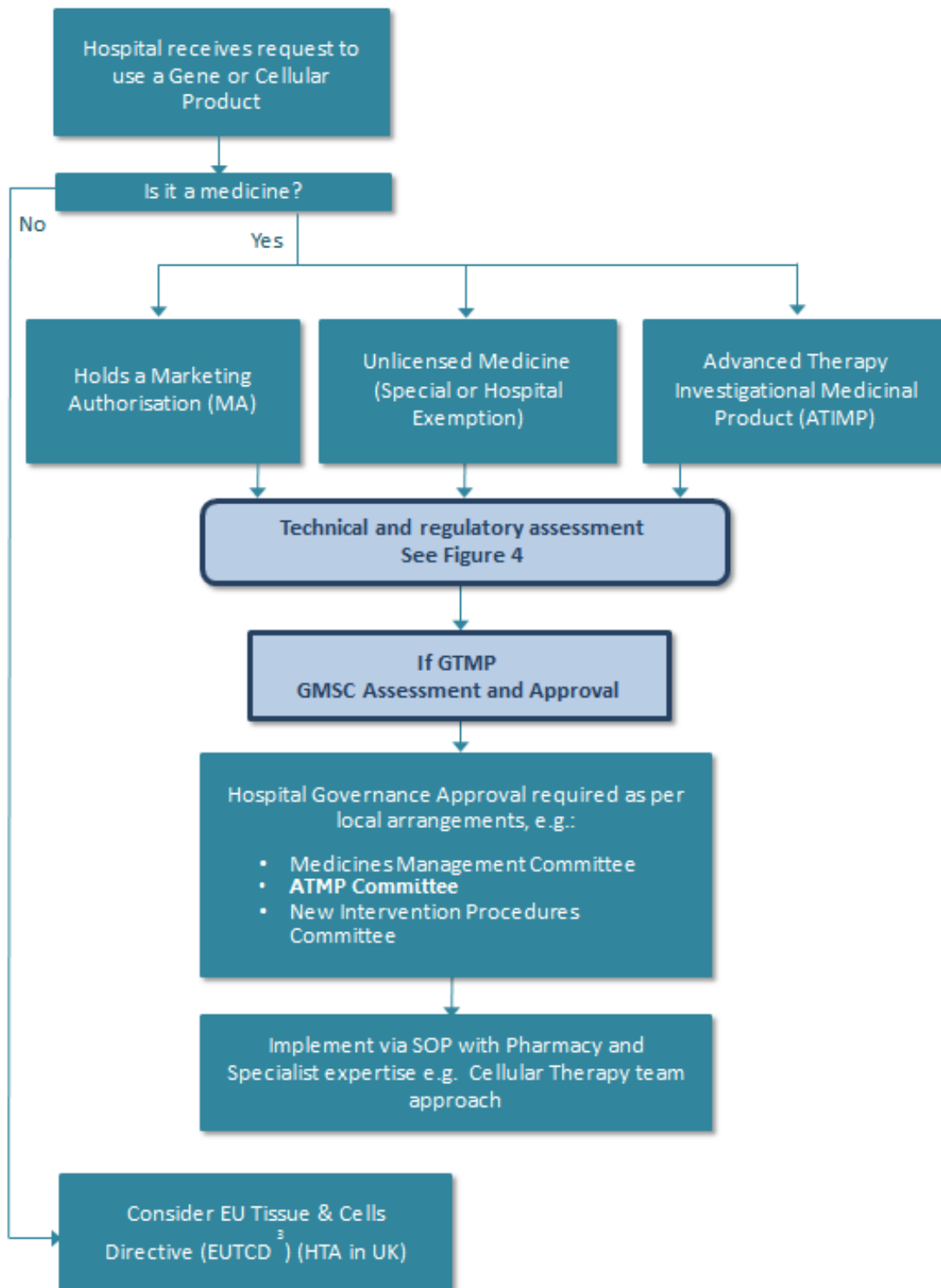


Figure 3 Local Governance Recommendations

**The Pan UK Pharmacy Working Group for ATMPs recommends that for introduction of any GTMP, a risk assessment and evaluation by a GMSC is the preferred organisational governance route.** However, the mandatory requirements, in practice, apply only to clinical trials. These are laid out in Genetically Modified Organisms (Contained Use) Regulations 2014 Regulation 8. Risk assessment is technically only required for any GTMP that is also a GMO and who can perform the risk assessment differs depending on the classification of the GMO. For class 1 activities, the regulations allow risk assessment evaluation from a competent individual e.g. a Biological Safety Officer, or by a GMSC. For class 2 activities, a GMSC is required. However the Pan UK Pharmacy Working Group for ATMPs recommends that any GTMP is assessed by a GMSC regardless of the GMO status of the medicine.

Additionally, there is no absolute regulatory requirement for a GTMP holding a marketing authorisation to be approved by a GMSC. However, in order for any GTMP to be appropriately assessed, it is recommended by the Pan UK Pharmacy Working Group for ATMPs that best practice is to ensure that licensed products are risk assessed by the local GMSC to confirm operational procedures.

The expertise of the GMSC is beneficial for licensed medicines and non GMO investigational GTMPs, as traditional access to new drugs systems (e.g. medicines management committees) and Research and Development committees may not include specific GTMP handling expertise and therefore will benefit from having input from the GMSC when applying organisational medicines governance.

#### **4.1 Genetic Modification Safety Committee (GMSC)**

##### **4.1.1 *Requirements and Recommendations For GMSC involvement with Clinical Trial Investigational GTMP***

- There is a requirement to obtain independent competent advice on the risk assessment for GMOs. For class 1 activities competent advice can be gained from a person e.g. BSO or from the local GMSC. Class 2 activities involving GMOs require the competent advice to be gained from the local GMSC.
- Where a clinical trial involves an investigational GTMP the Pan UK Pharmacy Working Group for ATMPs recommends that an organisation sets up a GMSC regardless of the class. This recommendation is in line with HSE Genetically Modified Organisms (Contained Use) Regulations 2014 and will ensure that the organisational governance infrastructure is in place for all GTMPs which may require future assessment.
- In order to provide the competent advice required, it is recommended that the GMSC undertake the following:
  - To carry out assessment of risks to human health and the environment – the product, the patient and the waste pathways must be risk assessed.

- To formulate local policy in consideration of working with GTMPs, including dealing with accidents, spillages and other incidents.
- To obtain advice on the risk assessment prior to contained use commencing from the organisation's biological safety officer (if one is appointed), or designated 'competent persons'. Some organisations may delegate BSO duties to the committee as a whole via the representation of staff appointed to the GMSC.
- To notify HSE before starting a contained use with GMOs, as appropriate.
- To ensure adherence to safety principles and application of appropriate containment and control measures.
- To ensure HSE are notified when accidents/incidents occur.
- If the product is a licenced medicinal product within the EU, then the product is exempt from the majority of Genetically Modified Organisms (Contained Use) Regulations 2014, other than Regulation 18 (principles of occupational and environmental safety).

#### **4.1.2 GMSC Membership**

The suggested GMSC membership includes the following groups:

- Representation from management and employees.
- Representatives of various technical disciplines, representing management and employees, health and safety advisor(s) such as a BSO and, if necessary, input from clinicians.
- Suggested membership:
  - Trust biological safety officer (if appointed)
  - Local biological safety officers (if appointed)
  - NHS Health and Safety Lead
  - Research Governance Representative
  - Staff representatives (can be local biological safety officers)
  - Consultant Microbiologist
  - Consultant Virologist (suggested Chair)
  - Consultant in Infectious diseases
  - Consultant in Occupational Health
  - Senior Pharmacist
  - Senior Nurse
  - Infection Control representative
  - Management representative
  - Technical expert
  - Aseptic Accountable Pharmacist
  - Clinical trial pharmacist
  - Estates representative

#### **4.1.3 *Establishing a GMSC***

Organisations should set up a GMSC in line with the HSE GMO guidance to fulfil the HSE<sup>[7]</sup> and pharmacy governance requirements<sup>[6]</sup> to advise the medicine management and therapeutics committees on the implementation of GTMPs.

The following needs to be considered when setting up a GMSC:

- Membership
- Chair
- Deputy Chair
- Terms of Reference
- Statutory notification of premises to HSE first use of premises for genetic modification activities
- Subsequent notification of projects to HSE as appropriate (class 2 or above)
- Risk assessment documentation
- Regular meetings, agendas, minutes
- Organisational structure and governance e.g. subcommittee of clinical governance or health and safety committees.

#### **4.1.4 *GMSC Terms of Reference***

The GMSC needs to have Terms of Reference (ToR). An example can be found in Appendix 3. The ToR must state the institutions that the GMSC advises. There can be a written agreement in place to confirm that arrangements are in place for one organisation to advise another organisation using a shared committee.

#### **4.1.5 *GMSC Responsibilities***

The GMSC has the following roles and responsibilities. These need to be documented in the local Terms of Reference:

- Coordinate communication with HSE for GMO activities
- Risk assessment review for gene therapy studies:
  - Assess risk to human health and safety to environment
  - Containment and control measures
  - Classification of organism
  - Ensure written SOPs in place
- Approval of premises as being suitable for the proposed activities
- Review of facilities for preparation, handling and administration
- Approval of SOPs and training
- Approval of projects e.g. clinical trials or studies with appropriate controls in place
- Advise Medicine Management Committee on licensed GTMPs

## 5.0 GMSC Risk Assessments

The documentation of the risk assessment should be co-ordinated by the local clinical trial principal investigator prior to presentation for review by the GMSC. Information to support the risk assessment will involve other healthcare professionals depending on the nature of the GTMP.

If as recommended by the Pan UK Pharmacy Working Group for ATMPs, the organisation decides to use the GMSC as part of their licensed medicine governance process (see Section 4.0) the risk assessment should be co-ordinated by the treating consultant clinician.

An example of a risk assessment template can be found in Appendix 2.

## 5.1 General Information

Regulation 5 of the Genetically Modified Organisms (Contained Use) Regulations 2014 requires that suitable and sufficient assessment of the risks to human health and the environment be carried out prior to any activity involving genetic modification of micro-organisms taking place. A full risk assessment may have been carried out for the development and production of the material by the manufacturer. This will be an important source of information and should be used as a basis for the risk assessment required for the local activities. It will still be important, however, to generate a suitable and sufficient local risk assessment. Those members of staff completing risk assessments should have the appropriate knowledge of processes involved to be able to correctly classify the activity. The aim of a risk assessment is thus to identify the hazards, to estimate the severity and likelihood that the hazards will lead to actual harm, identify control measures required and how they should be implemented to mitigate any hazards and assign an activity classification. Through the risk assessment, the risks to human health and the environment from an occupational and environmental safety perspective can be established.

The risk assessment should be divided into the three separate, but overlapping, pathways<sup>[8]</sup>:

- The product pathway:
  - the properties of the GTMP
  - receipt and storage of the GTMP
  - preparation of the GTMP for administration
  - transport and containment of the GTMP
  - criteria for patient discharge post-trial
  - GTMP tracking system – from receipt through to destruction
- The patient pathway:
  - administering the GTMP
  - patient handling and emergency procedures
  - sampling and monitoring of shedding (if required)

- interactions with other patients and staff, visitors and family
- The waste pathway:
  - stages at which contaminated waste is generated
  - transport and containment of waste
  - inactivation and disposal

In completing the risk assessment, it is recommended that the following areas are considered and it may be useful to refer to Schedule 8 of the Genetically Modified Organisms (Contained Use) Regulations 2014:

- Spillage
- Staff training and competence

A person responsible for contained use should retain the risk assessment for at least 10 years from the date the contained use stops. There should be review of the risk assessment after implementation and in the event of significant change to any of the processes covered. Therefore the assessment should be considered as a living document which requires to be kept up-to-date and contains sufficient information for people involved in the activity regarding risks and controlled measures required.

There is no statutory format for the risk assessment as each occasion may require modification to ensure all relevant data is gathered. However, the guidance provides an example of a template that is suitable to guide the applicants and wider team through the thought process required to complete the form. (see Appendix 2)

As the HSE do not review individual product risk assessments, granting authorisation falls to the local GMSC. In completion of the risk assessment, the applicant should avoid one word answers e.g. “yes” or “no”, lack of justification, explanation or detail. Failure to adequately assess the impact on staff or the environment is a common issue that will result in a delay in granting authorisation by the local GMSC to handle GTMPs.

## 6.0 Notifications

It is recommended that the Chair of the GMSC prepares the notification to the HSE.

On the first occasion that any organisation uses a GTMP that is a GMO, the HSE premises notification form - notification of intention to use premises for contained use *activities*, should be completed.

The GMSC Chair must receive an acknowledgement of receipt of the notification from the HSE prior to any GTMP work commencing in the organisation. This is usually available within 10 days of receipt of the notification.

If the GMSC has deemed that the first contained use does not require HSE notification via the premises notification form (this could be because it is non-notifiable<sup>[7]</sup> due to the activity having class 1 status only), then a summary of the risk assessment should be

submitted along with information on waste management and details of any expert advice received.

Subsequent notifications:

**Class 1** activities – do not require notification

**Class 2** activities – Regulation 10 requires that all class 2 contained uses are notified to the HSE prior to commencement of the activity. The information requested in Schedule 6 should be provided. Where notification of the premises has not been carried out previously, the user can undertake class 2 contained use if 45 days have elapsed since acknowledgement of receipt of the notification. If the premises have been previously notified or if granted for class 3/4 contained use then the user may undertake class 2 contained work upon notification of receipt.

**Class 3** activities - Regulation 11 states that a user cannot undertake Class 3 activities unless written consent has been granted by the competent authority. The information requested in Schedule 6 should be provided. The competent authority must provide its decision to grant or refuse consent within 90 days of the submission, if there has been no previous notification of the premises. Where previous notification has been granted the HSE must review and reply within 45 days prior to commencement of any subsequent work activities.

**Class 4** activities – as Class 3. The HSE must receive notification of an intention to handle class 4 GMMs 90 days before work is due to begin and at least 45 days prior to commencement of any subsequent work activities.

## Part 2 Operational

The following guidance should be applied once governance approval has been granted for the implementation of a GTMP within the organisation.

### 7.0 Receipt and storage

#### 7.1 In vivo (non-cellular) GTMP

Operators should always wear appropriate personal protective clothing when removing the GTMP from the container in which it is delivered. In case of damage to the product integrity action to be taken should be defined locally for each product in line with the GMSC waste management risk assessment.

GTMPs should be stored correctly and securely at an appropriate temperature. This temperature should be monitored at least on a daily basis and the readings recorded.

Where cold storage at -80 degrees centigrade is required, it is recommended that the in vivo GTMP should be stored within a freezer in the pharmacy department. A dedicated locked freezer is the preferred arrangement however a separate shelf within a designated freezer may be acceptable. Appropriate temperature monitoring systems with audible and visual alarms to alert staff of out-of-specification situations and accompanying monitoring procedures should be implemented.

If the product is stored outside of pharmacy (e.g. if in liquid nitrogen tanks or clinical areas), it is recommended that a risk assessment is carried out to ensure that the same standard of storage and temperature monitoring is carried out. Storage locations should be inaccessible to unauthorised personnel and should not pose a risk of undue exposure.

#### 7.2 Ex vivo (cellular) GTMP

Where cellular GTMP are provided ready to administer or simply requiring a thaw, then pharmacies may be the most appropriate location to receive, thaw and issue where stability allows, or to receive and issue prior to thaw in the clinical area.

Where more complex preparation steps are required this will require the most appropriate local aseptic facilities to be decided upon. (see Figure 8)



## 8.0 Gene Therapy Medicinal Product Preparation

The Advice for Chief Pharmacists on Advanced Therapy Medicinal Products (February 2017) stated that the decision tree below should be used to establish location for ATMP preparation.

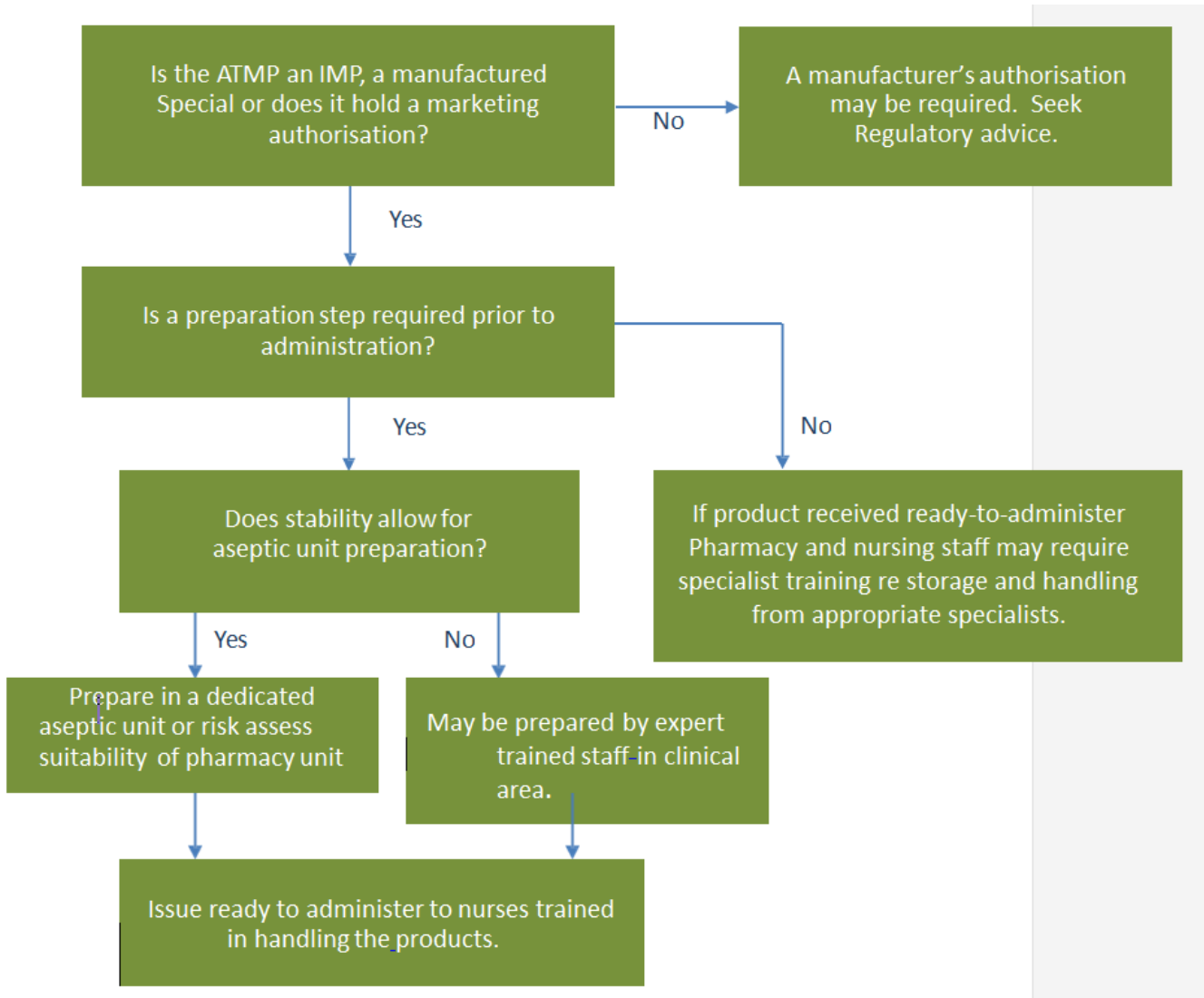


Figure 4 Technical Feasibility Process<sup>[6]</sup>

When specifically considering GTMPs it is important to supplement the general principles above with further detail, including an understanding of the definition of “preparation”.

- Preparation is the process of making the product ready-to-administer.
- Often referred to reconstitution activity.
- Reconstitution can occur either in a clinical area or in aseptic facilities.

Further specific advice is found below in relation to GTMP.

**In VIVO** – non cellular preparation GTMPs can be reconstituted within pharmacy. Facility requirements are described in Section 8.0

**Ex VIVO** – i.e. cellular GTMPs require preparation by operators skilled in handling cellular products. The existing pharmacy aseptic workforce will not be able to handle these products. Facility requirements are described below.

It is recommended that, where possible, a dedicated cleanroom within an aseptic unit or a separate modular unit is used for the manipulation of ex vivo GTMP. However, in the absence of such a facility, the flow charts below provide pragmatic guidance on an acceptable approach to the suitability of available locations.

### 8.1 Preparation and handling of in vivo (non-cellular) GTMP

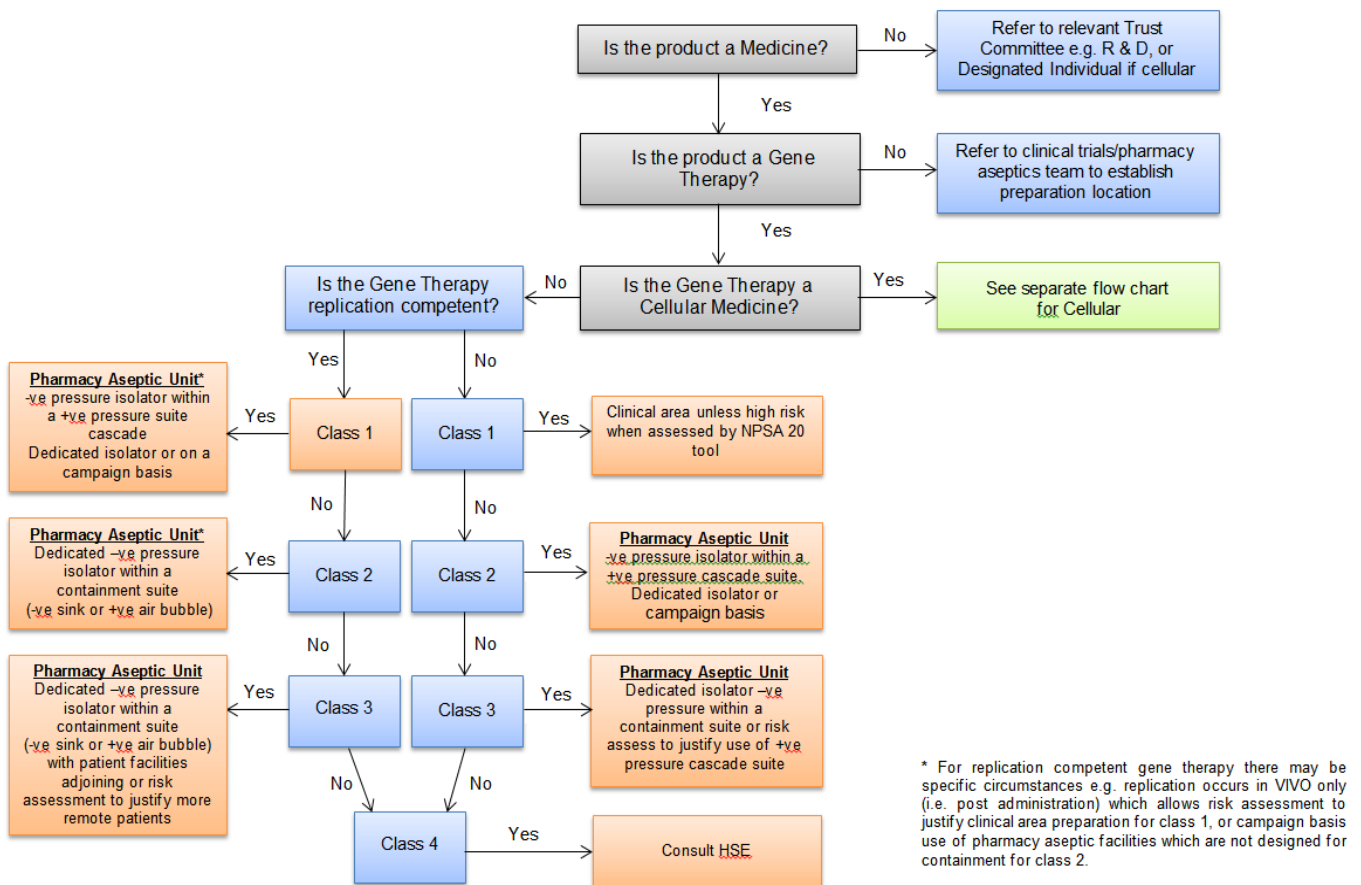


Figure 5 Gene Therapy Preparation Location – Non Cellular

It is recommended that where possible an in vivo GTMP is handled and prepared in pharmacy departments to minimise the risk of environmental contamination, product microbial contamination and also medication errors.

If pharmacy facilities are not available to handle GTMPs, consideration can be given to handling them in the clinical setting with appropriate SOPs in place and approval by appropriate pharmacy staff in line with recommendations above.

## 8.2 Preparation and handling of ex vivo (cellular) GTMP

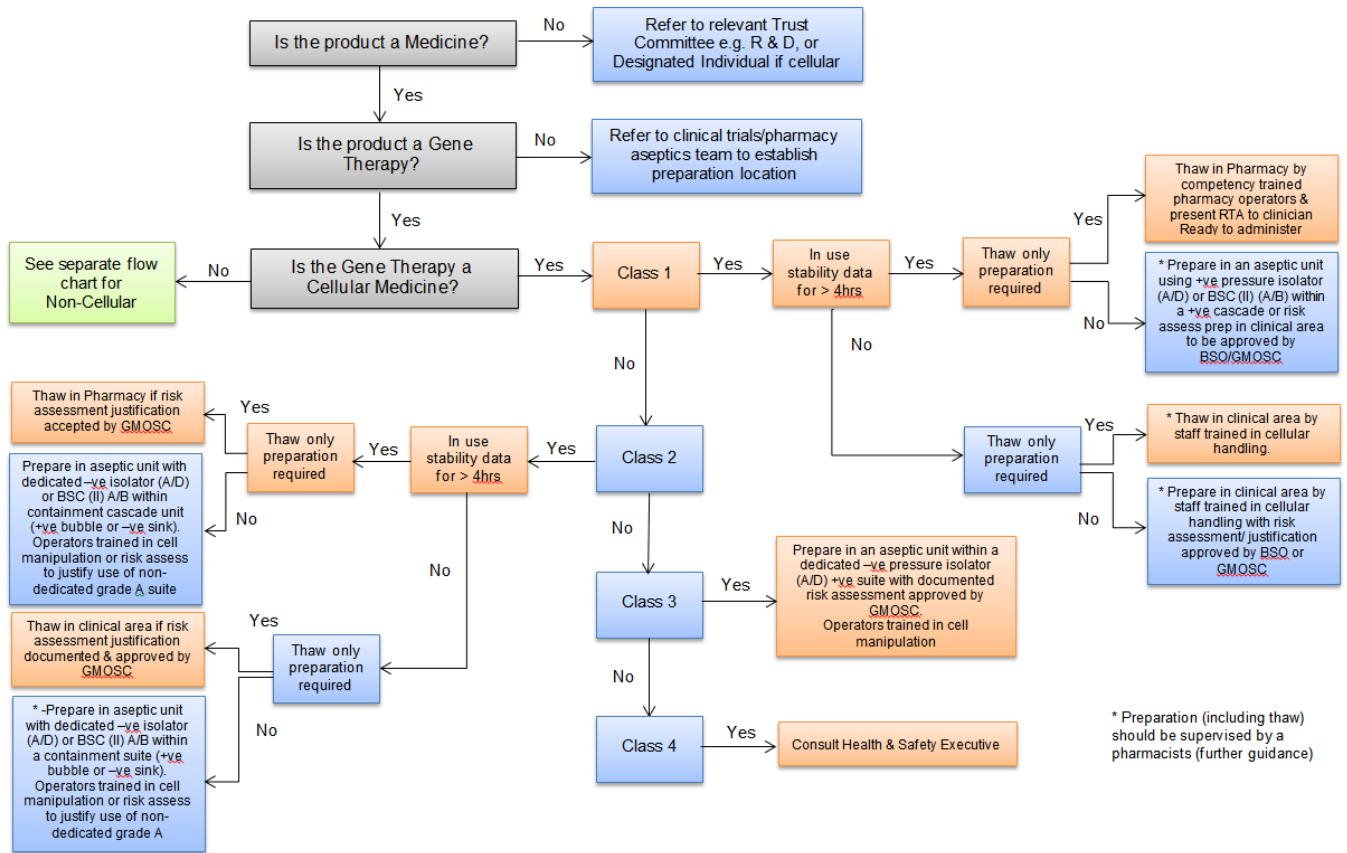


Figure 6 Gene Therapy Preparation Location – Cellular

The manipulation of cellular medicines requires skilled operators who are trained and understand the risks associated with handling a living product. It is therefore likely that the most appropriate operators will not be pharmacy aseptic operators. As advised in the Advice for Chief Pharmacists on Advanced Therapy Medicinal Products (February 2017)<sup>[6]</sup>, organisations should optimise the location preparation and this will be likely to involve the workforce from a stem cell laboratory or from specialist blood and transfusion services. Where the optimal location falls out-with Pharmacy, Pharmacist oversight of the preparation activity is required to ensure that all processing and handling is in line with SmPC or protocol requirements.

Where nurses are preparing cellular medicines, organisations should ensure that they are competent to do so. Training in cellular handling will be required.

### **8.3 Preparation of GTMPs within aseptic facilities**

Where Pharmacy aseptic units are employed to prepare GTMPs or where non-Pharmacy aseptic units e.g. Stem Cell Labs, have been identified as the optimal location for preparation (with Pharmacy oversight) the following good practice should be applied.

Where preparation occurs within a Pharmacy aseptic unit, the Accountable Pharmacist should assess the risks to their unit via a change control informed by the GMSC risk assessment. The following best practice guidance should be considered.

#### **8.3.1 Operator Protection**

- Personal protective clothing selected should be appropriate to the environmental grade of the room used to prepare the product. Garments should be sterile and disposable.
- In the event of accidental exposure, consult the relevant Summary of Product Characteristics or clinical trial protocol. If recommended, medical attention should be sought. Document the incident on the local clinical/health and safety incident reporting system and inform the Principal investigator if the GTMP is an investigational medicinal product.

#### **8.3.2 Preparation Process**

It is recommended that process maps be used as a tool to develop the aseptic preparation process. A risk assessment should be prepared which covers:-

- Transfer process in and out of the cleanroom and isolator
- Reconstitution process and procedures
- Consumables required
- Removal of components used in the preparation/ reconstitution of the gene therapy medicine
- Form of final packaging
- Transport Container Labelling – biohazard sign for class 2
- Stability, shelf life and storage requirements
- Development of worksheets
- Development of standard operating procedures
- Action to be taken in event of a spillage

This dedicated risk assessment will be used to inform the wider risk assessment used by the GMSC.

#### **8.3.3 Isolator/Biological Cleaning Considerations**

Antiviral cleaning agents should be used prior to preparation, in between patients and at the end of the session. Validation of surface sanitisation techniques should be carried out.

#### **8.3.4 Waste Management**

- Empty ampoules, vials and components used in the preparation of GTMPs, should be disposed of in accordance with local procedures and HSE requirements with regard to inactivation of waste (i.e. autoclaving and incineration) to ensure eradication of any remaining medicine.
- All materials used in the procedures should be sealed in biohazard containers.
- Non-disposable items should be cleaned with an appropriate anti-viral cleaning agent.

#### **8.3.5 Transport**

GTMPs should be transported from the aseptic unit to wards and departments in closed, labelled, leak-proof containers sealed in a plastic bag or secondary leak proof container. A spill kit to be available at all times.

Transport of GTMPs should be carried out directly to point of administration. The outer container should be labelled as “biohazard”

#### **8.4 Preparation of GTMPs within a clinical setting**

If pharmacy or non-pharmacy aseptic facilities are not available to handle GTMPs, or the shelf-life prevents aseptic unit handling, consideration can be given to handling them in the clinical setting with appropriate SOPs and worksheets in place and approval by appropriate pharmacy staff in line with the Figures 5 and 6.

GTMPs should be issued immediately prior to preparation/administration to avoid prolonged storage in the clinical area.

The product and label should be checked as per normal nursing procedures.

Protective clothing should be used as appropriate for the class of gene therapy being handled.

Staff with appropriate training and competency levels should be assigned to the handling and preparation of GTMP. All staff handling GTMPs should have documented evidence of competency.

Roles and responsibilities assigned across multi-disciplines should be clearly documented.

## 9.0 Glossary

Genetic Modification (GM)	Genetic modification (GM) occurs when the genetic material of an organism (either DNA or RNA) is altered by use of a method that does not occur in nature and achieved by one of the techniques set out in Part 1 of Schedule 2 of the Genetically Modified Organisms (Contained Use) Regulations 2014. The requirements of the regulations e.g. risk assessment and application of control measures apply to the activity in which GMOs are created, used or disposed of rather than the techniques themselves.
Genetically Modified Organism (GMO)	The organism that has been altered is referred to as a Genetically Modified Organism (GMO)
GMSC	Genetic Modification Safety Committee
Contained Use	The term “contained use” covers any activity involving GMOs in which measures are taken to limit contact between them and people and the environment thus providing a high level of safety. It relates to the process of genetic modification and also to the use, storage, transport and destruction of GMOs.
Gene Therapy	Treatment of certain disease states by the deliberate introduction of genetic material into the cells of patients or the deliberate introduction of nucleic acids into human somatic cells for therapeutic, prophylactic or diagnostic purposes.
Gene Therapy Medicinal Product (GTMP)	Any therapeutic agent which meets the WHO or HSE definitions of gene therapy / GMO as described above
HSE	Health and Safety Executive



**10. References**

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5. <http://www.hse.gov.uk/pubns/misc208.pdf>
6. The Role of Pharmacy in the Successful Delivery of Advanced Therapy Medicinal Products Information for Chief Pharmacists – log into the SPS website to access document
7. <http://www.hse.gov.uk/pubns/books/l29.htm>
8. <http://www.hse.gov.uk/biosafety/gmo/acgm/acgmcomp/part6.pdf>

## **Regulations**

### **Genetically Modified Organisms (Contained Use) Regulations 2014**

The regulations are made under the powers of the Health and Safety at Work Act 1974 and European Communities Act 1972 and are concerned with the harm to human health or the environment that arises from contained use involving genetically modified organisms (GMOs). The regulations state that contact with GMOs must be limited through the use of biological, chemical and physical barriers and the risk to human health and the environment must be considered through a risk assessment process.

Most contained use activities involve organisms which do not cause disease and are very unlikely to survive in the environment outside the contained facility.

However, it is important to assess the risks of all activities relevant to the preparation and handling of gene therapy medicines to ensure that all necessary controls are in place to protect patients, staff and the environment.

Main duties under the Regulations are to:

- Carry out an assessment of the risks to human health and the environment of every contained use activity before carried out. The assessment should be reviewed and revised as necessary and approved prior to commencing contained use.
- Establish a genetic modification safety committee to advise on risk assessments.
- Classify all activities according to the Regulations.
- Make a notification to the competent authority before starting a contained use of with GMOs, in respect of first use of a premises as well as ongoing.
- Notify the HSE and other relevant authorities of the intention to use premises for contained use activities and to prepare gene therapy products on an ongoing basis.
- Adhere to the safety principles and apply the necessary containment risk control measures as defined in classification level to protect human health and the environment.
- Design any necessary contingency plans in event of containment failure.
- Notify the competent authority of any accidents.

EHP guidance on handling of gene medicines provides specific requirements for each step in the process from storage, dispensing and administration to the disposal of materials involved in handling such therapeutic agents.

### **Clinical Trials Directive 2001/20/EC**

#### **Medicines for Human Use (Clinical Trials) legislation 2004 as amended.**

Similar arrangements regarding trial set up, management and data evaluation can be applied to gene therapy and local processes and SOPs should be used.



**Example of a GMSC Risk Assessment**
**RISK ASSESSMENT FOR HANDLING OF GENETICALLY MODIFIED  
MICRO-ORGANISMS FOR GENETIC MODIFICATION SAFETY COMMITTEE (GMSC)**
**SECTION 1**
**Basic Information**

<b>Project Title</b>	
<b>Trial Organisers/Sponsor</b>	
<b>Principle Investigator (PI)</b>	
<b>PI Address</b>	
<b>PI Telephone</b>	
<b>PI e-mail</b>	
<b>Date submitted to Trust GMSC</b>	

<b>Does the project have GTAC approval?</b>	
<b>State any provisional containment level that has been assigned for the GM product /activities.</b> (see SACGM for guidance)	

## SECTION 2

### Information on the proposed Investigation/trial and GMTP product

This information should be available in the risk assessment from the trial sponsor or GMTP manufacturer.

<b>Overview of the proposed investigation/trial.</b>	
<b>Full description of the vector. Include information on the extent to which it is attenuated/disabled.</b>	
<b>Full description of the insert including function.</b>	
<b>How will the product be administered?</b>	
<b>Where will the product be administered?</b>	

## SECTION 3

### Assessment of risk to humans

This information should be available in the risk assessment from the trial sponsor or GMTP manufacturer.

**Vector:** Factors to consider include whether the recipient microorganism is listed in ACDP hazard groups 2, 3 or 4. Other relevant factors may be the micro-organism's mode of transmission, disease symptoms, host range, and tissue tropism as well as an indication as to whether vaccines or chemotherapeutic agents are available. Information should also be provided on any disabling mutations and whether there is any possibility of any disabling mutations being complemented or reverting.

**Insert:** Consideration should be given to whether the inserted DNA encodes a toxin, an oncogenic protein, an allergen, a modulator of growth or differentiation (hormone or cytokine) or any other protein, which may result in potentially harmful biological activity. Please note that even a normal human gene may be harmful if over expressed, especially if the over expression is in tissues that do not normally express the protein.

<b>Risks associated with the vector</b>	
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<b>Risks associated with the insert</b>	
<b>Is there the potential for genetic material to be transferred to a related micro-organism (e.g. gene transfer/recombination)</b>	

**SECTION 4**

**Assessment of risk to the environment**

This information should be available in the risk assessment from the trial sponsor or GMTP manufacturer.

**Vector:** Factors to consider include whether the recipient microorganism is capable of infecting any plants, animals or insects in the environment and whether there is any possibility of any disabling mutations being complemented or reverting. In particular it should be ascertained whether the recipient microorganism is a pathogen that is controlled by DEFRA.

**Insert:** Factors to consider include whether the sequence encodes an insect or animal toxin or a product which can cause silencing of a gene encoding a crucial metabolic enzyme in susceptible hosts.

<p><b>Environmental risks associated with the vector</b></p>	
<p><b>Environmental risks associated with the insert</b></p>	

**SECTION 5**

**Nature of the work and control measures**

This information should be contained in information/SOPs/risk assessment provided by the trial sponsor or lead investigator for multicenter studies. HOWEVER, it is important to take into account and detail local arrangements.

**a) Handling of the GMTP product prior to administration.**

It is strongly recommended that the Trust pharmacy is consulted when completing this section.

<b>Specify arrangements for safe receipt of the GMTP</b>	
<b>Specify arrangements for safe storage of the GMTP</b>	
<b>Specify arrangements for the safe preparation of the GMTP</b>	
<b>Specify arrangements for the safe transport of the GMTP to the site of administration.</b>	

**b) Administration of the GMTP.**

Investigators may wish to discuss this section with the GMSC chair or Infection Control and Pharmacy

<p><b>Identify any procedures which will involve sharps, and specify arrangements for their safe use</b></p>	
<p><b>Identify any work procedures likely to generate aerosols, and the control measures to be applied.</b></p>	
<p><b>Specify the protective clothing and any other personal protective equipment to be used at each stage.</b></p>	
<p><b>Specify the disinfectants to be used at each stage.</b></p>	
<p><b>Specify specific actions in the event of an accidental spill.</b></p>	
<p><b>Does the nature of this work preclude it being undertaken by any workers who have a serious skin condition (e.g. eczema) or other health problems that might make them more susceptible to infection?</b></p>	
<p><b>Specify any health surveillance requirements for staff involved in the work.</b></p>	
<p><b>Will potentially contaminated clinical samples (e.g. fluids, tissues) be collected from the patient for routine analysis by hospital laboratories? Specify arrangements for their safe handling.</b></p>	
<p><b>Is there potential for shedding of the GMTP after administration? If yes answer the following questions:</b></p>	
<p><b>Will the patient be isolated following the procedure?</b></p>	

	Provide details.	
	Specify precautions for HCWs in contact with the patient or patient's body fluids. .	
	Identify any specific precautions or restrictions required for visitors to the patient.	
	Other than standard arrangements, are any additional safety measures or procedures required for cleaning the patient's bed linen or laundry?	
	Other than standard hospital cleaning procedures, specify any additional arrangements required when cleaning the patient's room during and at the end of the treatment period.	
	Will the patient need to be transported within the hospital following administration of the GM product? Identify any specific safety procedures required for such transportation of the patient.	

**c) Management of Waste.**

It is strongly recommended that the Trust Waste Officer is consulted when completing this section.

Detail how residual/unused GMTP will be safely disposed of.	
Detail what contaminated waste is expected during administration and how this will be safely disposed of.	
Is there potential for shedding of the GMTP after administration? If so, how will subsequent contaminated waste be disposed of.	

**d) Identify any stages of the work or manipulations of the GMTP not already covered, which may pose increased risk, and the measures which will be applied to control those risks.**


**SECTION 6****Final assignment of containment measures and risk class**

**The following aspects of this project are assigned to class 1.**

**The following aspects of this project are assigned to class 2.**

Each Trust will have capability approved by HSE. Where the classification is out with the approval the HSE must be notified.



## **Genetic Modification [GM] Safety Committee Terms of Reference**

<b>Title</b>	<b>Genetic Modification Safety Committee: Terms of Reference</b>
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<b>History</b>	<p>Terms of Reference were developed in xxx for the Genetic Modification Safety Committee</p> <p>Revised version approved by Trust Management Executive Meeting: xxxx</p>
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Hospital Board Approval	
Date	

### **1. Authority**

- 1.1 The Genetic Modification [GM] Safety Committee is constituted as a sub-group of the Hospital Infection Prevention and Control Committee (HIPCC), a sub-committee of the Clinical Governance Committee, which is in turn accountable to the Trust Management Executive. The constitution and terms of reference of the GM Safety Committee shall be as follows, subject to amendment at future meetings of the HIPCC.
- 1.2 The Committee is authorised by the HIPCC to undertake duties and investigate any activity within its terms of reference. It is authorised to seek any information from any member of staff and all members of staff are directed to co-operate with any request made by the Committee.
- 1.3 The Committee has no executive powers other than those specified in its Terms of Reference.

## 2. Purpose

- 2.1 The purpose of the Committee is to provide advice to the Trust on the contained use of Genetically Modified Organisms [GMOs] within the clinical and research facilities provided under the auspices of the Trust.
- 2.2 Although not a statutory requirement, the GMSC may also be convened to provide advice regarding the implementation of gene therapy medicinal products holding marketing authorisations, or which do not contain a GMO.

## 3. Membership

- 3.1 The Chair of the Committee has the overall responsibility for the performance of the Committee and also has the final decision on actions required in order to comply with the Terms of Reference.

## 4. Attendance and Quorum

- 4.1. The quorum for any meeting of the Committee shall be attendance by the Chair or Vice-Chair (or a nominated deputy) and a minimum of two other people, subject to the Chair or Vice-Chair (or nominated deputy) determining that those attending can provide sufficient expertise, relevant to the issues which are due to be considered, for the meeting to proceed.
- 4.2 All members of the Committee are expected to attend at least half of all meetings. An annual register of attendance of members will be maintained by the Committee.
- 4.3 If a member is unable to attend, a nominated deputy may attend with the agreement of the Chair. Deputies will be counted for the purpose of the quorum.
- 4.4 The Chair may request attendance by relevant staff at any meeting.

## 5. Frequency of meetings

- 5.1. Meetings of the GM Safety Committee shall be held at least annually. Other meetings may be held at the discretion of the Chair.

## 6. Specific Duties

- 6.1 To consider risk assessments for new activities for the contained use of GMOs on Trust premises and/or involving Trust employees, ensuring full compliance with the requirements of the *Genetically Modified Organisms (contained use) Regulations 2014*, Requirements include that:
  - Proper and valid assessments have been made of the risks to human health and an Occupational Health Risk Assessment has been carried out



- Proper and valid assessments have been made for safety of the environment
- The criteria for classification of GMOs have been properly applied
- The premises where the activity is to be carried out have been notified to the HSE.

6.2 To consider the feasibility of conducting the activity in the premises, ensuring that:

- The GMOs can be stored and transported safely and appropriately.
- Appropriate measures are in place to deal with accidental spillage, waste disposal and that accident /incident reporting and review procedures are in place.
- Standard Operating Procedures and local rules are in place.
- Staff training needs for those involved in using GMOs have been adequately considered.

6.3 To check that the premises have access to expertise e.g. from a local Biological Safety Officer.

6.4 To check that other approvals have been sought and received as appropriate:

- Gene Therapy Advisory Committee (GTAC)
- NHS ethics committee
- University or other GMSCs if appropriate
- Medicines Regulator

6.5 To liaise as appropriate with the Trust's Health and Safety Committee, and the Joint Research and Development Committee.

## **7. Sub-committees**

7.1 The GM Safety Committee has no established sub-committees.

## **8. Administrative Support**

8.1 Describe administration arrangements.

## **9. Accountability and Reporting arrangements**

9.1 Describe reporting arrangements

9.2 Describe escalation arrangements.

## **10. Monitoring Effectiveness and Compliance with Terms of Reference**

- 10.1 The Committee will carry out an annual review of its effectiveness and provide an annual report to the relevant local governance group detailing work in discharging its responsibilities, delivering its objectives and complying with its terms of reference, specifically commenting on relevant aspects of the Board Assurance Framework and relevant regulatory frameworks.

## **11. Review**

- 11.1 The Terms of Reference of the Committee shall be reviewed at least annually by the Committee and approved by the HIPCC.

**Date approved:**

**Approved by:**

**Next review date:**

**Upon review, for approval by:**