Specialist Pharmacy Service

Pan UK Pharmacy Working Group for ATMPs

Gene Therapy Medicinal Products Governance and Preparation Requirements

Version 3
February 2024

Specialist Pharmacy Service

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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, being used as unlicensed medicines 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 Medicinal Products wishing to understand governance and preparation requirements for these innovative medicines.

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1.0 Executive Summary

As GTMPs are ATMPs it is important that organisations that wish to introduce a gene therapy medicinal product for use either in a trial, as an unlicensed medicine 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)[6]

This document has been produced to facilitate the introduction of GTMPs into healthcare organisations. It outlines the governance requirements and operational 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.

The following process flow chart outlines the governance requirements which should be in place and require Pharmacy input when an organisation wishes to use a GTMP.

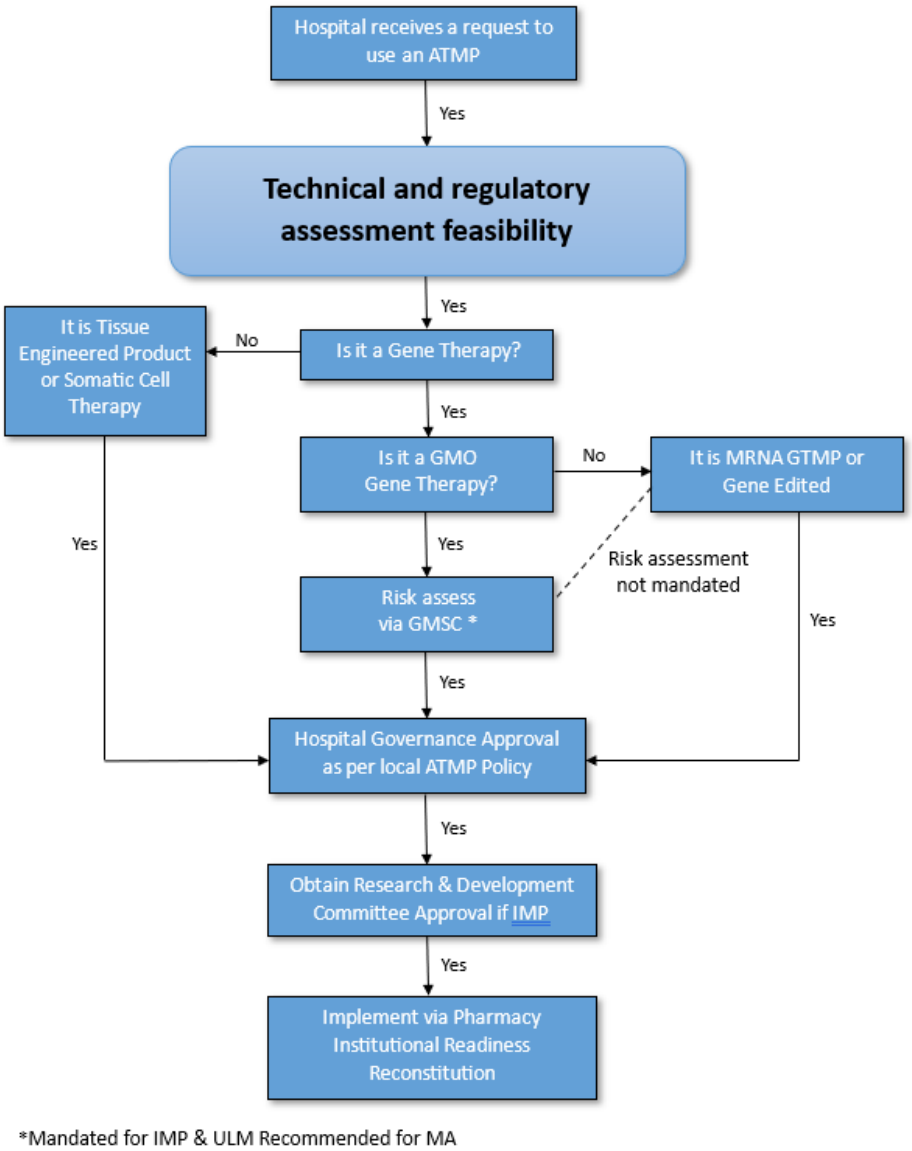

Figure 1: Organisational Governance Requirements for initiating a GTMP

Part 1 Governance

2.0 What is a Gene Therapy Medicinal Product?

Gene therapy medicinal products (GTMPs) are advanced therapy medicinal products (ATMPs)[1].

GTMPs are defined as a biological medicinal product which has the following characteristics: 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; and

a) Its 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.

A vaccine against infectious diseases is not to be treated as a gene therapy medicinal product.

Most GTMPs are classified as a genetically modified organism (GMO) and are therefore subject to Contained use or Deliberate Release Regulations (see Section 3). However, there are some GTMPs which are not classed as GMO including mRNA immunotherapies e.g. used in cancer and a gene edited GTMP e.g. CRISPR technology. (See section 2.2.1)

This document covers both GMO and non-GMO GTMPs and aims to provide governance and operational guidance for all GTMP scenarios.

Currently, most GTMPs are used in clinical trials[2] although there are GTMPs with marketing authorisations (e.g. CAR-T therapy and adeno-associated viral vectors containing genes) and horizon scanning would predict that this trend is increasing.

On occasion a GTMP 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.

2.1 Genetically Modified (GMO) GTMPs

Genetically Modified Organism (GMO) GTMP modes of action are well documented[3]. 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 GMO 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.

2.1.1 *"In vivo" (Non-Cellular) vs "Ex vivo" (Cellular) GMO GTMP*

A GMO GTMP is classified as 'in vivo' where the GTMP consists of injection of the viral vector directly into a specific tissue in the body where it is then taken up by individual cells, or where the GTMP is administered intravenously (IV). An example of 'in vivo' GTMP is Onasemnogene Abeparvovec.

Alternatively, a donation of cells can used as the starting material for an ex-vivo gene therapy. In this case a viral vector is used to introduce the gene to the starting material cells in the pharmaceutical manufacturing unit. 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. Where the cells are harvested from the patient, this is called an autologous 'ex vivo' GTMP e.g. CAR-T cell therapy, Yescarta®, Kymriah®, Tecartus®. Allogeneic (starting material from a donor) ex vivo gene therapies are currently in clinical trials.

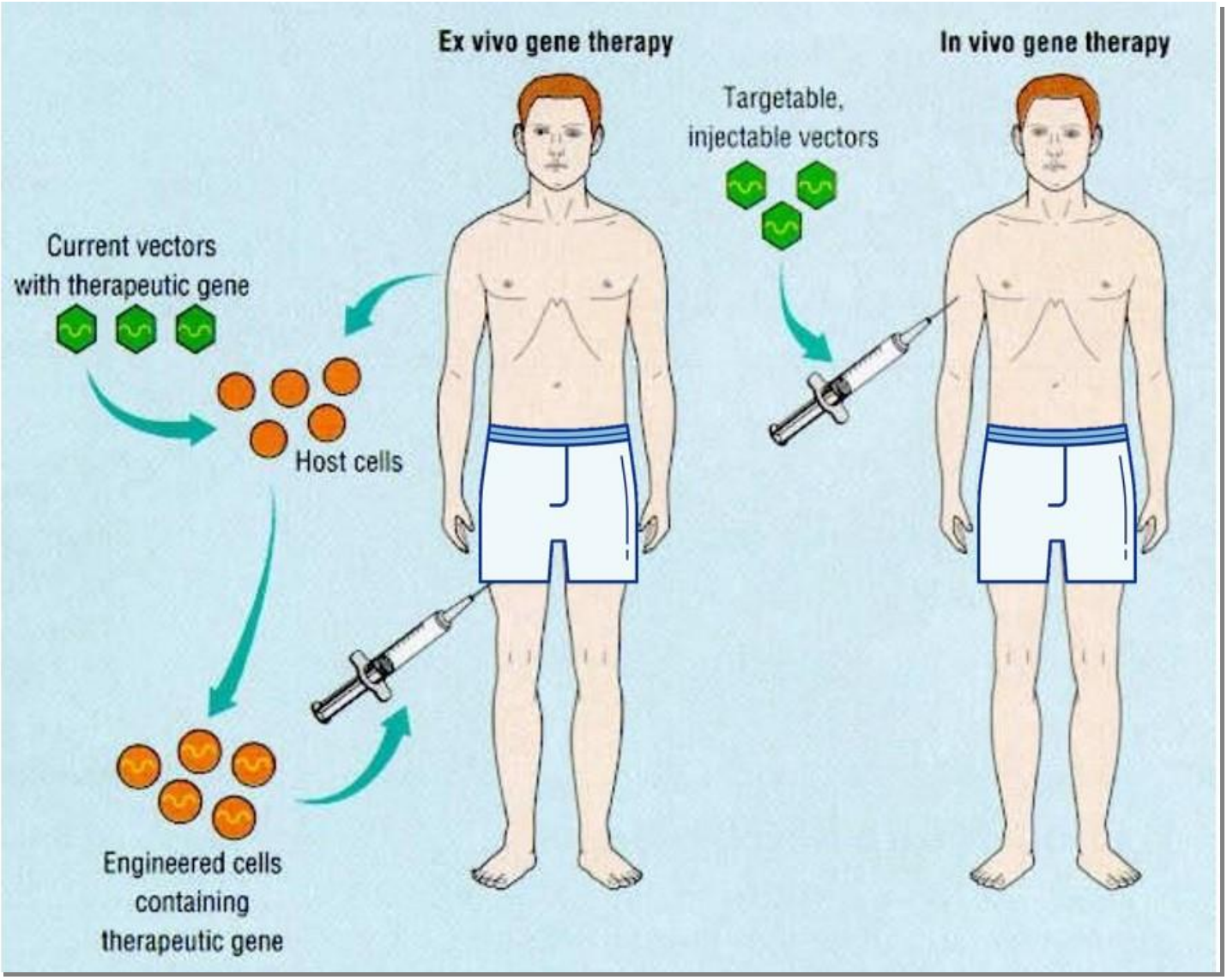

Figure 2: In Vivo vs Ex Vivo GTMP[4]

2.2 non-GMO GTMP

Some innovative therapies are classed GTMPs but not as GMOs. For example, mRNA immunotherapies and gene edited medicines are considered as GTMPs.

2.2.1 *mRNA Immunotherapies*

There are many clinical trials using mRNA technology to treat cancers – so-called "cancer vaccine" trials. As vaccines against infectious diseases are excluded from the legal / regulatory definition of a gene therapy the term "cancer vaccine" is frequently used incorrectly. mRNA products to treat cancer are immunotherapies, but they are not vaccines because they are not substances to prophylactically treat an infectious disease (definition of a vaccine).

Additionally, in order for an mRNA immunotherapy to be classed as a GTMP, it must be a biological medicine. Hence if the mRNA is chemically synthesised – it is not a GTMP.

So, where mRNA is purely made from chemical synthesis then it is a chemical (and a molecule made in this way could not be classified as a gene therapy medicinal product). However if mRNA is made involving chemical synthesis from a DNA-template (called in vitro transcription), where the DNA template is a linearised plasmid produced in E.Coli. then it is considered to be a biological, and therefore provided the product fulfils the rest of the definition of a gene therapy, and the mRNA would be considered a gene therapy medicinal product.

2.2.2 *Gene Editing Technology*

Another type of GTMP which is not classed as GMO is gene (or genome) edited GTMP. In these products the DNA is altered during the manufacturing process as the DNA is cut at a specific spot. Manufacturers then remove, add, or replace the DNA where it was cut.
A genome editing tool called CRISPR, has revolutionised this process.

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/DEFRA. Licensed GTMPs are governed by the medicine's regulators only. Unlicensed medicines require HSE/DEFRA considerations, but their quality and clinical assessment is governed by local Unlicensed Medicines Policies.

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 (see Appendix 1)
Medicines for Human Use (Clinical Trials) 2004 SI: 2004- No.1031 as amended
Clinical trials - Regulation EU No 536/2014
The Genetically Modified Organisms (Deliberate Release) (Amendment) (England) Regulations 2022

Table 1 GTMP legislation and guidance documentation

The use of gene therapy containing GMO in nearly all clinical use falls under the Contained Use Regulations. (See 3.1 and 3.2). The first time that an organisation undertakes activity with any class of GMO they must notify the HSE and have an entry of the premises made in the public register. After the first notification, further notification is required for activity which is class 2 and above only. There are fees associated with these notifications. (See 5.7)

Deliberate release of GMO is rarely applied in a clinical setting (see 3.3).

3.1 Classification and Containment Levels for GTMP

Containment Level assessment is the legal responsibility for the Trust/Site

If the GTMP has been genetically modified, the Genetically Modified Organisms (Contained Use) Regulations 2014 will usually apply (see 3.3 for deliberate release). There are four classes of activities according to the regulations[5]. The classification is based on the level of risk to humans and the environment and will vary if the GMO is replication competent and if it is shedding (i.e. appears in the patients’ excretions after administration).

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 for clinical use 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 for example the use of some 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 as detailed above 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

3.2 Biosafety levels

Biosafety levels are defined as a set of biocontainment precautions used to contain and identify the protective measures needed to protect staff, patients, and the environment for biological products. GTMPs are classified by HSE class as detailed in 3.1, but there are some occasions when GTMPs are classified by biosafety levels e.g. when the GTMP does not contain a GMO and /or where the GTMP is manufactured outside of the UK. Other biological products, including somatic cell therapy, may also have a biosafety level, but as they are not a GTMP, they do not fall under this guidance or the HSE legislation e.g. cytotoxic T lymphocytes.

3.3 Deliberate Release

Where a GMO GTMP is assessed by the local GMSC and the conclusion is that the GMO cannot be contained, every effort should be made to ensure that all containment options have been exhausted (PPE, pharmacy preparation, waste management etc). It is envisaged that preparation and administration locations should not be insurmountable barriers; even in cases where home preparation is required, and open systems are in use – there will usually be a way to mitigate and contain the risk.

If the Healthcare Organisation is unable to do so, however, then they may wish to proceed with the complex process of obtaining Deliberate Release approval.

In the first instance – the Healthcare Organisation will need to liaise with DEFRA via gm-regulation@defra.gov.uk.
It is also important to note that when progressing down the deliberate release approval route, in principle it is a requirement to list the sites of administration publicly – where this will breach patient confidentiality sites are advised to liaise with DEFRA to understand the potential for an exception being made for patient addresses. All clinical sites would need to be listed.

3.4 non-GMO GTMP (e.g. mRNA and gene edited technologies) do not require consideration under either the contained use or deliberate release regulations, since they do not contain a GMO.

4.0 What Governance Is Required?

The Pan UK Pharmacy Working Group for ATMPs recommends that for introduction of *any GTMP*, organisational governance is required and that a clear process should be documented in a local ATMP Policy.

The mandatory requirements for assessment by a GMSC, in practice, apply only to clinical trials and unlicensed medicines. These are laid out in Genetically Modified Organisms (Contained Use) Regulations 2014 Schedule 8. Full GMO Risk assessment is only mandated 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. The Pan UK Pharmacy Working Group for ATMPs recommends, however, that any clinical trial or unlicensed GMO GTMP is assessed by a GMSC and that organisations consider the use of their GMSC for the introduction of marketed GMO GTMP in the absence of any other suitable local governance committee.

For non-GMO GTMP a suitable organisational governance process is required. The use of the GMSC is not mandated but the Pan UK Pharmacy Working Group for ATMPs recommend that its use is considered as part of a robust local governance strategy unless another distinct organisational committee exists for this purpose (e.g. dedicated ATMP committee).

The expertise of the GMSC may be 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. Many organisations choose to combine their GMSC with their ATMP committee to optimise robust governance arrangements.

4.1 Genetic Modification Safety Committee (GMSC)

Requirements and Recommendations for GMSC involvement with Clinical Trial Investigational GMO GTMP

- For GMO GTMPs 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 appointedto 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 Schedule 18 (principles of occupational and environmental safety).

4.1.1 *GMSC Membership*

The suggested GMSC membership includes the following groups:

- Representatives of various technical disciplines and professions, representing management and employees, and health and safety. Individual representatives can cover multiple membership roles.
- Suggested membership roles:
    - Trust biological safety officer/Adviser (if appointed)
    - Local biological safety officers (if appointed)
    - Health and Safety
    - Governance
    - Staff representatives (can be local biological safety officers)
    - Consultant Microbiologist/ Virologist/Infectious diseases (suggested Chair)
    - Occupational Health
    - Senior Pharmacist (e.g. ATMP, Aseptic, clinical trial)
    - Senior Nurse
    - Infection Control representative (can be covered by Consultant Microbiologist/ Virologist/Infectious diseases)
    - Management representative
    - Technical expert
    - Estates representative (waste)

4.1.2 *Establishing a GMSC*

Organisations should set up a GMSC in line with the HSE GMO guidance to fulfil the HSE[7] and pharmacy governance requirements[6] 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.

4.1.3 *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.

4.1.4 *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

4.1.5 *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.

4.1.5.1 The Pan UK Pharmacy Working Group is developing a collaborative process to facilitate consistent pharmacy information in GMSC risk assessments. A link will be added to this document when it is available.

4.1.6 *General Information*

Schedule 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[8]:

- 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 (see also 8.3.4)
  - 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 requiremodification 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.

4.1.7 *Notifications*

It is recommended that the Chair of the GMSC prepares the notification to the HSE for any applicable unlicensed or investigational GTMP.

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,* must 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 contained use does not require HSE notification via the premises notification form (this could be because it is non-notifiable[7] 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 advicereceived.

Subsequent notifications:

Class 1 activities – do not require notification.

Class 2 activities – Schedule 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 - Schedule 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 subsequentwork 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.

On occasion if patients take the GMO home, their addresses may also be required to be notified to the HSE – the organisation/sponsor must have discussions with the HSE to ensure patient confidentiality and that these details do not appear on the public register.

https://www.hse.gov.uk/biosafety/gmo/notifications/what.htm

4.2 Considerations for non-GMO GTMP Governance

Where an organisation prefers not to convene a GMSC for non-GMO GTMPs, an alternative local governance process is required to ensure that all aspects of medicines management (clinical, operational and financial) governance are knowledgeably considered.

In practice, the regulatory knowledge in this area is evolving and often the classification of non-GMO GTMPs may not be clear in clinical trial protocols and investigator brochures. Pharmacists must find out from the Sponsor whether the medicine is considered to be a biological and therefore classed as a gene therapy medicinal product. If it is, then this guidance applies.

Part 2 Operational

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

5.0 Receipt and storage

5.1 In vivo (non-cellular) GTMP

Operators must 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 must be defined locally for each product in line with the appropriate waste management risk assessment.

The Pan UK pharmacy working group for ATMPs recommends that GTMPs should be stored correctly and securely at an appropriate temperature. This temperature should be monitored with calibrated equipment continuously with suitable arrangements in place for dealing with excursions at all times.

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 it is necessary to store the product outside of pharmacy, it is recommended that a risk assessment is carried out to ensure that the same standard of storage and temperature monitoring is carried out as for storage within the pharmacy department. Storage locations must beinaccessible to unauthorised personnel and must not pose a risk of undue exposure or environmental hazard.

5.2 Ex vivo (cellular) GTMP

Where cellular GTMPs are provided ready to administer or simply requiring a thaw and are delivered in a shipper that is validated for storing at the correct temperature for the time required prior to administration, 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 any complex preparation/assembly or manipulation steps are required, then a decision re' the most appropriate local aseptic facilities, which may be found in a local or third party stem cell laboratory, is required (See Figure 8).

If it is necessary to store the product outside of pharmacy (e.g. vapour phase nitrogen storage tanks), it is recommended that a risk assessment is carried out to ensure that the same standard of storage and temperature monitoring is carried out as there would be within a pharmacy department. Storage locations must be inaccessible to unauthorised personnel and must not pose a risk of undue exposure or environmental hazard. A technical agreement should be considered and the principals for consideration are detailed in this document which is limited to licensed ATMPs, however, the principals can be applied to unlicensed and investigational products: TA-for-Outsourced-Storage-for-Marketed-ATMPs-v2.pdf (sps.nhs.uk)

6.0 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.

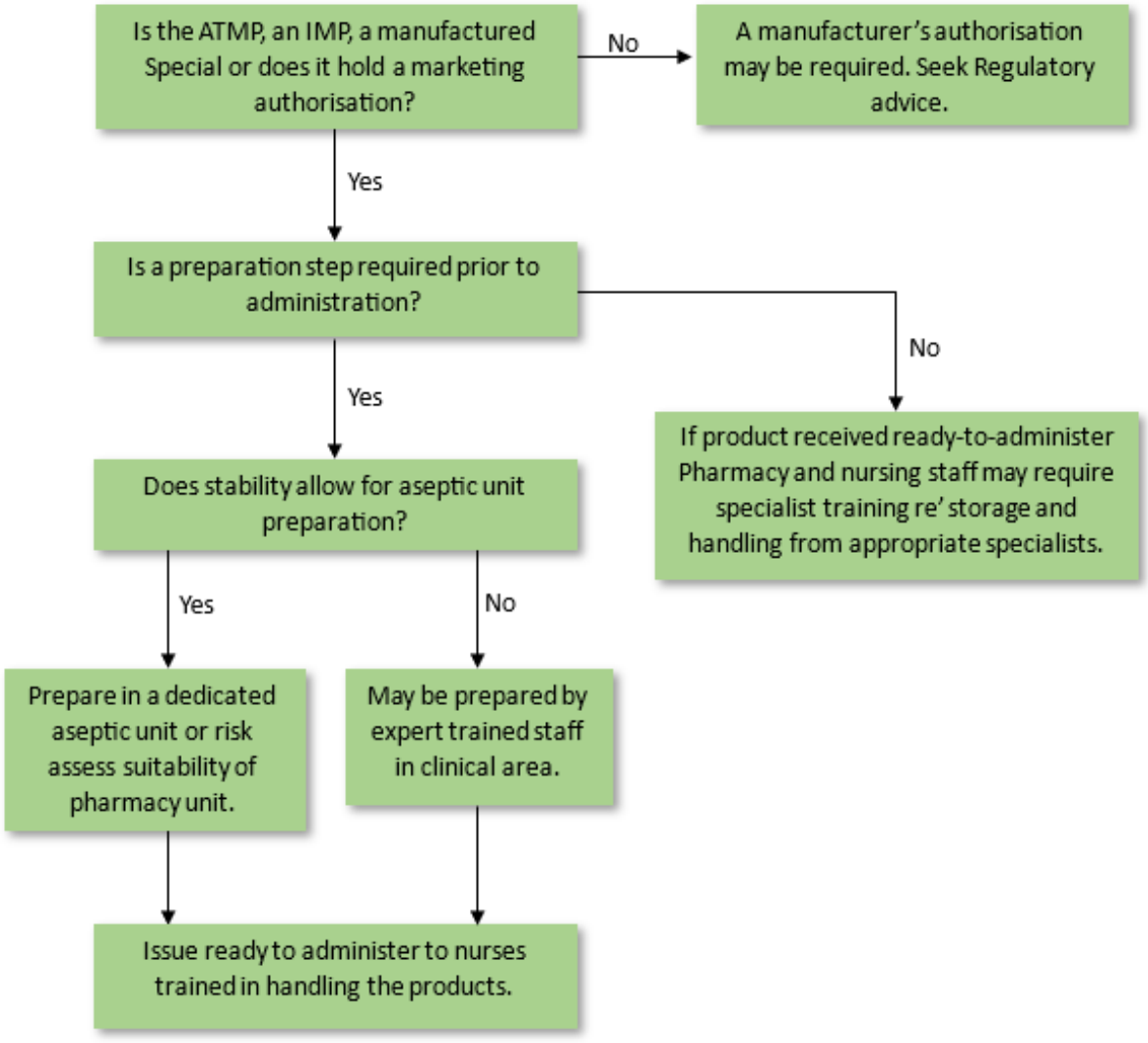

Figure 3 Technical Feasibility Process[6]

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 as 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 6.1

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 in Section 6.2.

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. It should be noted however that the flow charts below should only be applied in the absence of any specific preparation location instruction in either the SmPC, clinical trial protocol, clinical trial pharmacy manual, stem cell lab manual or commissioning guidance.

6.1 Preparation and handling of in vivo (non-cellular) GMO GTMPs

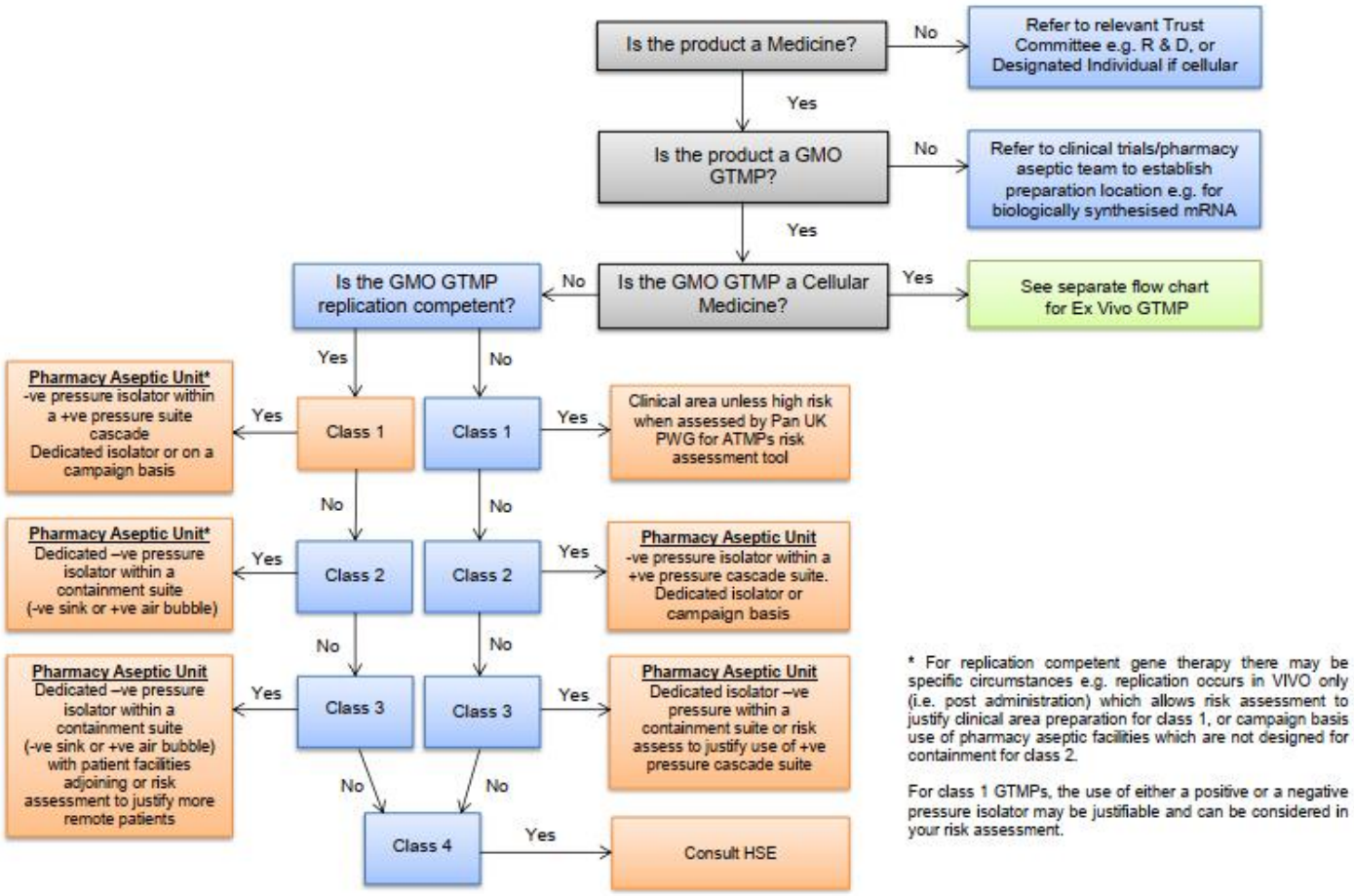

Figure 4 GMO GTMP Preparation Location – non-cellular

It is recommended that where possible an in vivo GTMPs (both GMO and non-GMO) is handled and prepared in pharmacy departments to minimise the risk of environmental contamination, product microbial contamination and medication errors.

6.2 Preparation and handling of ex vivo (cellular) GMO GTMPs

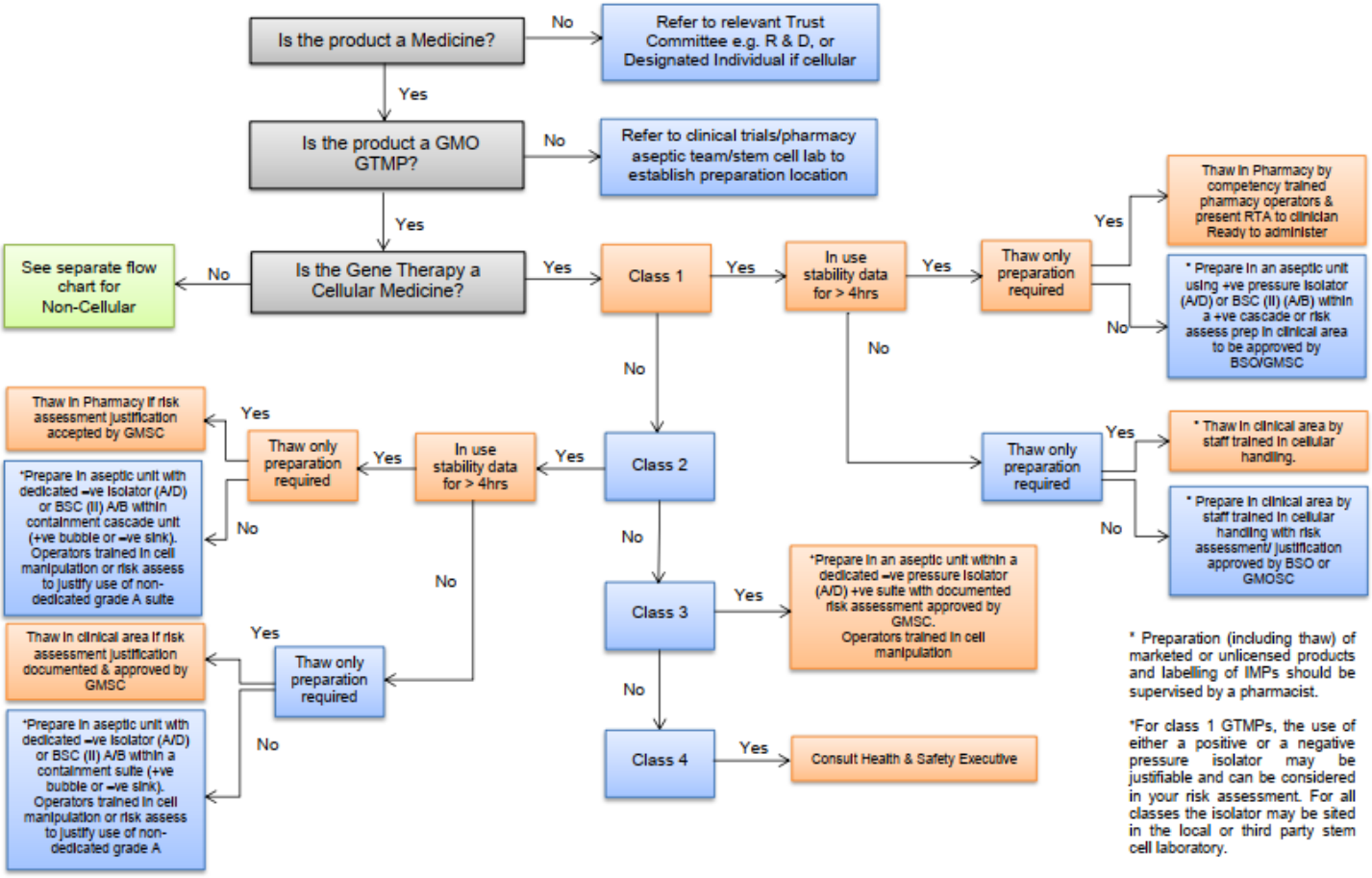

Figure 5 GMO GTMP Preparation Location – Cellular

The manipulation of cellular/tissue-based 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 aseptics operators. As advised in the Advice for Chief Pharmacists on Advanced Therapy Medicinal Products (February 2017)[6], 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.

6.3 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.

6.3.1 Operator Protection

- Personal protective clothing selected must 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.

6.3.2 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 & disposal of components used in the preparation/ reconstitution of the genetherapy 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 appropriate local governance committee.

6.3.3 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.

6.3.4 Waste Management

6.3.4.1 *GMO GTMP waste management*

The management of GTMP waste within a hospital requires multi-departmental working.

With GTMP waste, like any waste, there is a statutory duty of care which applies to everyone in the waste management chain (9). It requires all involved in producing or managing waste (i.e. every single person in the hospital) to *take all reasonable measures to ensure that the waste is dealt with appropriately from the point of production to the point of final disposal* (9). This is important for safety of staff and patients but also for environmental and sustainability reasons.

As the GTMP has been genetically modified, the Genetically Modified Organisms (contained use) Regulations 2014 (7) will apply and there is further information and best practice guidance in the SACGM compendium of guidance (Part 6 is dedicated to the use of GMOs in a clinical setting) (8). However, it must be remembered that hospitals are experienced in preventing the transmission of infections and disposal of hazardous waste and we are encouraged to be pragmatic in their approach (8).
Waste handling is dependent on class of GTMP.

Part of the GTMP risk assessment will detail the waste pathway and *considers all GMM-contaminated waste, including:*

- *stages at which contaminated waste is generated;*
- *transport and containment of waste;*
- *inactivation and disposal* (8).

Depending on local facilities and type/volume of GMO waste generated, there are several acceptable methods of GMO waste management, but each must be subject to local approval by the local Genetic Modification Safety Committee (with input from the Biological Safety Officer) and the local Trust waste management team/ waste management outsourced contract. All GTMPs in clinical trials must be risk assessed by a GMSC. This is also recommended for licenced GTMP (8), as waste management needs to comply with GMO regulations.

The HSE regulations document (7) and the SACGM compendium part 3 (8) recommend the following for waste disposal:

	Containment Level	
Containment Measure	1	2
Inactivation of GMMs in contaminated material and waste (7)	required by validated means where and to extent the risk (7)	required by validated means (7)
Autoclave (8)	Required on site (8)	Required in building (8)
Inactivation of GMMs in contaminated material and waste (8)	Required by validated means (8)	Required by validated means (8)

Table 2: GTMP waste containment (7, 8):

As detailed in the above table class 2 waste must be inactivated by a validated means however inactivation of class 1 waste is not required if all of the following criteria are met (7):

a) *do not have the potential to cause harm to human health or the environment;*
b) *must be biologically contained (e.g. possess multiple disabling mutations or restrictive nutrient requirements that cannot be met outside the laboratory);*
c) *do not have the capacity to establish and multiply in the environment; and*
d) *do not have capacity to transfer genetic material to other micro-organisms (e.g. non-mobilisable plasmid)* [B].

The risk assessment should conclude whether inactivation of waste at class 1 is required and the methods for achieving this. For the purposes of the Regulations, any of the following methods, i.e. disinfection, off-site treatment (e.g. rotaclave, incinerator), or on-site autoclave may be considered to be validated means and comply with the Regulations. This is provided appropriate steps are taken to confirm the efficacy of the method, the appropriate control measures are put in place for the safe transport and storage of the waste material and the process is completed in a safe manner (7).

Recommended best practice for Class 2 waste is to be autoclaved in the building prior to offsite treatment/disposal (9).

The usual waste management system should be used where appropriate for class 1 GTMPs. Sharps and other contaminated disposable equipment must be placed in appropriate containers (sharps bins) or yellow bags (swabs etc) for disposal. If class 2 GTMPs are autoclaved or chemically inactivated prior to disposal, it is not considered necessary in such circumstances for the incinerator or waste contractor to be registered under the Contained Use Regulations.

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 (8). If no autoclave is available derogation may be sought from the HSE as long as a validated means of inactivation is in place (8).

Alternative methods, including waste removal by waste management contractors, may also be acceptable provided that the contractor has a license to dispose of GMO waste and a contract with the Trust to dispose of GMO waste. The waste will have to be stored and transported in a way that does not increase risk and aligns with HSE guidance. It is advised to discuss this with the Trust waste manager to ensure the appropriate contracts and licenses are in place.

See Appendix 4 for an example of a waste disposal SOP for class 1 and class 2.

CAR-T cells are autologous T-cells which have been genetically modified, there are several products licenced and NICE approved. The SmPCs for current licensed products must be followed with local guidelines on handling class GTMP biological waste.

CAR-T cells are class 1 GMO and autoclaving of waste is not required. Class 1 GTMP waste disposal can therefore be followed.

6.3.4.2 *non-GMO GTMP*

Non-GMO GTMP waste should be dealt with in line with local organisation medicines waste policy, clinical trial protocols and the manufacturer's guidelines.

6.3.5 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. Aspill kit to be available at all times.

Transport of GTMPs should be carried out directly to point of administration where possible. The outer container must be labelled as "biohazard".

Where preparation is undertaken on a different site to administration, this must be considered in the risk assessment. An appropriate good distribution practice compliant arrangement should be in place with assurance of chain of custody e.g. pharmaceutical courier.

6.4 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 in the risk assessment to handling them in the clinical setting. Appropriate SOPs and worksheets should be in place and approved by appropriate pharmacy staff in line with Figures 4 and 5. It should be noted however that Figures 4 and 5 should only be applied in the absence of any specific preparation location instruction in either the SmPC, clinical trial protocol, clinical trial pharmacy manual, stem cell lab manual or commissioning guidance. The organisational governance has to have approved non pharmacy handling in the clinical setting.

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

The product and label must be checked as per normal nursing medicine preparation/administration procedures.

Protective clothing must be used as appropriate for the GTMP 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.

6.4.1 Spillage

A spill is a potentially serious incident, even if there is no obvious accidental exposure. Examples may include: breakage of a sample container and/ or spillage of whole vials.

Where the risk assessment has recommended that a spillage kit is required during manipulation, transportation and administration, a spillage kit must be made available. Suggested spillage kit contents are listed below:

1. 2x plastic aprons
2. 2x disposable gowns
3. 2 pairs of disposable gloves
4. 2x masks
5. 1x safety goggles
6. Absorbent wipes (e.g. paper towels)
7. Yellow clinical waste bag
8. Disinfectant (e.g. Virkon and water container to make 2% virkon solution, 1,000 ppm chlorine, or 6% hydrogen peroxide).

6.4.1.1 Decontamination of Spillage

1. All non-essential personnel will leave the contaminated area.
2. Collect the spillage kit.
3. Staff attending the incident will wear personal protective clothing appropriate to the class of spilled agent (disposable gown, apron, gloves - available in the spillage kit) and goggles for eye protection.
4. Pour sufficient disinfectant onto the spill.
5. Leave for 5 minutes. Longer exposure does not increase hygiene whilst risking damaging surfaces.
6. Use absorbent cloth/pad to absorb all the liquid.
7. Thoroughly wash the area using water. Do not use other disinfectants or alcohol, as it is likely to cause frothing or smearing which may be difficult to remove.
8. Dry area using absorbent cloth, e.g. paper towels.
9. All waste from the spillage must be treated as appropriate for that Class in line with the waste disposal procedure.
10. Treat affected clothes, uniform or bed linen as for infectious linen.

7.0 Glossary

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.
DEFRA	Department for Environment, Food and Rural Affairs.
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
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. GTMPs can be classified as GMO and non-GMO GTMPs as detailed in section 2.0. The full regulatory definition of a gene therapy medicinal product (HMR 2012 Regulation 2A) is: A gene therapy medicinal product means 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) its 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. Gene therapy medicinal products shall not include vaccines against infectious diseases.
Genome editing technology	See description provided in 2.2.2.
HSE	Health and Safety Executive
mRNA	Messenger ribonucleic acid. See description provided in 2.2.1.

8.0 References

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9. NHS England (2022) Health Technical Memorandum 07-01: Safe and sustainable management of healthcare waste
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Appendix 1

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.

EAHP 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 - Regulation EU No 536/2014
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.

Appendix 2

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

Project Title	
Trial Organisers/Sponsor	
Principle Investigator(PI)	
PI Address	
PI Telephone	
PI e-mail	
Date submitted toTrust GMSC	

Does the project have GTAC approval?	
State any provisional containment level thathas been assigned for the GM product/activities. (see SACGM forguidance)	

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.

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

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 anydisabling 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 inpotentially 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.

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

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 micro-organism 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.

Environmental risksassociated with the vector	
Environmental risksassociated with the insert	

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 multicentre 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.

Specify arrangements for safe receipt of the GMTP	
Specify arrangements for safe storage of the GMTP	
Specify arrangements for the safe preparation of theGMTP	
Specify arrangements forthe safe transportof the GMTP to the site of administration.	

b) Administration of the GMTP.
Investigators may wish to discuss this section with the GMSC chair and/or Infection Control and/or Pharmacy

Identify any procedures which will involve sharps, and specify arrangements for their safe use	
Identify any work procedures likely to generate aerosols, andthe control measures to be applied.	
Specify the protective clothing and any other personal protective equipment to be usedat each stage.	
Specify the disinfectants to beused at each stage.	
Specify specific actions in theevent of an accidental spill.	
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 mightmake them more susceptible to infection?	
Specify any health surveillance requirements for staff involvedin the work.	
Will potentially contaminatedclinical samples (e.g. fluids, tissues) be collected from the patient for routine analysis byhospital laboratories? Specifyarrangements for their safe handling.	
Is there potential for shedding ofthe GMTP after administration? If yes answer the followingquestions:	
Will the patient be isolated following the procedure?	

Provide details.	
Specify precautions for HCWsin contact with the patient or patient's body fluids.	
Identify any specific precautions or restrictionsrequired for visitors to the patient.	
Other than standard arrangements, are any additional safety measures or procedures required for cleaning the patient's bed linenor laundry?	
Other than standard hospitalcleaning procedures, specifyany additional arrangementsrequired 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 theGM 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 andhow this will be safely disposed of.	
Is there potential for shedding of the GMTP after administration? Ifso, how will subsequent contaminated waste be disposed of.	

d) Identify any stages of the work or manipulations of the GMTP not already covered, which maypose 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.

Specialist Pharmacy Service

Appendix 3

Genetic Modification [GM] Safety Committee Terms of Reference

Title	**Genetic Modification Safety Committee: Terms of Reference**

History	Terms of Reference were developed in xxx for the Genetic Modification Safety Committee Revised version approved by Trust Management Executive Meeting: xxxx

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 theenvironment.
- 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 theJoint 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.

Appendix 4

Example of waste disposal section of SOP

Disposal of Waste

1. **Class 1 GMO waste**

1.1. Class 1 waste only requires single packaging and can be collected with the usual clinical waste collections.

1.2. Seal all soft waste (e.g. personal protective clothing) in an United Nations (UN) approved yellow bag OR place all waste in a yellow sealed rigid container for hard or more complex waste. Use department traceability zip tie to identify the origin of the waste on the yellow bag or yellow sealed rigid container. Dispose of waste immediately after use. Yellow sealed rigid containers to be used are limb bins.

1.3. Place all sharps and used containers (e.g. empty IV fluid bags and administration sets) in a yellow lidded sharps bin.

1.4. Seal the limb bin (solid rigid container) or yellow bag and the sharps bin as soon as the procedure is complete.

1.5. Use the Trust traceability ties for the yellow bags, sharps bin, and limb bins, and take it to the designated waste collection point without delay.

2. **Class 2 GMO waste**

2.1. Inactivation via validated means via autoclave within the building. If the autoclave is on the same site but in a different building, then a risk assessment is required to move the product between buildings on the same site for autoclaving.

2.1.1. See separate autoclave SOP for local area to ensure waste will be appropriately autoclaved.

2.1.2. Place all sharps and used containers (e.g. empty IV fluid bags and administration sets) in a yellow lidded sharps bin and seal as soon as the procedure is complete.

2.1.3. Seal all personal protective clothing, equipment and materials and in a yellow bag (a tied single yellow HTI sack) immediately after use.

2.1.4. Autoclave waste in sharps and yellow bag within the building.

2.1.5. Place autoclaved yellow bag and sharps bin in a yellow limb bin.

2.1.6. Tag the limb bin with a yellow HTI tag to identify the origin of the waste with the department zip tie.

2.1.7. Take waste to waste collection point.

2.1.8. The limb bin will be taken directly to the main waste compound and placed it inside a separate 770l, UN approved, all yellow wheeled bin for collection by waste contractor.

2.2. Chemical inactivation is permitted as a validated means in non-clinical areas, e.g. pharmacy. Chemical deactivation can be undertaken with 2% Virkon, 1,000 ppm chlorine, or 6% hydrogen peroxide.

2.2.1. Place all chemically deactivated sharps and used containers (e.g. empty IV fluid bags and administration sets) in a yellow lidded sharps bin and seal as soon as the chemical deactivation procedure is complete.

2.2.2. Tag the sharps bin with a yellow HTI tag to identify the origin of the waste with the department zip tie.

2.2.3. Take waste to waste collection point.

3. GMO waste will be collected from the designated waste collection point by the Trust waste contractor in line with Trust waste policy.

4. Clean all non-disposable items used when handling a gene therapy medicine with a viricidal agent as detailed in product specific risk assessment or with e.g. 2% Virkon, 1,000 ppm chlorine, or 6% hydrogen peroxide.

5. Non disposable bedlinen/patient gown should be laundered following Trust Infectious Waste procedures.

6. All other waste will be disposed of securely as per Trust waste policy.

7. <u>Procedure for autoclaving</u>

- Microbiology departments may require advance notice of generation of GMO waste for autoclaving. Trust documentation to accompany the waste must be completed as appropriate.
- Place sharps into a small sharps bin, closing the bin slightly to prevent spillage, but not locking or taping.
- Place the sharps bin in the yellow clinical waste bag along with all PPE and consumables/ infusion bag/ vial/ infusion lines.
- Seal the yellow clinical waste bag and place into a large sharps bin, ensuring the lid is not locked.
- Wipe the outside of the sharps bin with disinfectant as specified in the agent specific SOP.
- Place the sharps bin in a yellow bag and tag/label as ‘GMO infectious waste’.
- The waste must be transported by suitably trained staff to Microbiology where the autoclave is situated, following a route with minimal footfall.