CATAPULT
Cell and Gene Therapy

GMO Contained Use Authorisation Procedures for Clinical Trial Products in the UK

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We work with
Innovate UK

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1. Glossary of Terms

ACRE	*Advisory Committee on Releases to the Environment*
CA	*Competent Authority*
CTA	*Clinical Trial Authorisation*
CU	*Contained use*
DR	*Deliberate Release*
EU	*European Union*
EC	*Ethics Committee*
EMA	*European Medicines Agency*
GMO/M	*Genetically Modified Organism/Microorganism*
GMSC	*Genetic Modification Safety Committee*
HSE	*Health and Safety Executive*
HSENI	*Health and Safety Executive Northern Ireland*
MHRA	*Medicines and Healthcare products Regulatory Agency*
NI	*Northern Ireland*
RA	*Risk Assessment*
SACGM	*Scientific Advisory Committee on Genetic Modification*
UK	*United Kingdom*

2. Introduction

This guidance summarises the authorisation process for Genetically Modified Organisms (GMO) as Investigational Medicinal Products (IMP) for contained use (CU) within the United Kingdom (UK). These submissions are unique to GMOs, in addition to Clinical Trial Authorisation (CTA) and Ethics Committee (EC) review. The specific operational steps outlined herein are based on country-specific requirements and submission experience with gene modified cells and gene therapy viral vectors. The information contained is correct as of June 2019.

3. GMO Regulatory Framework in the UK

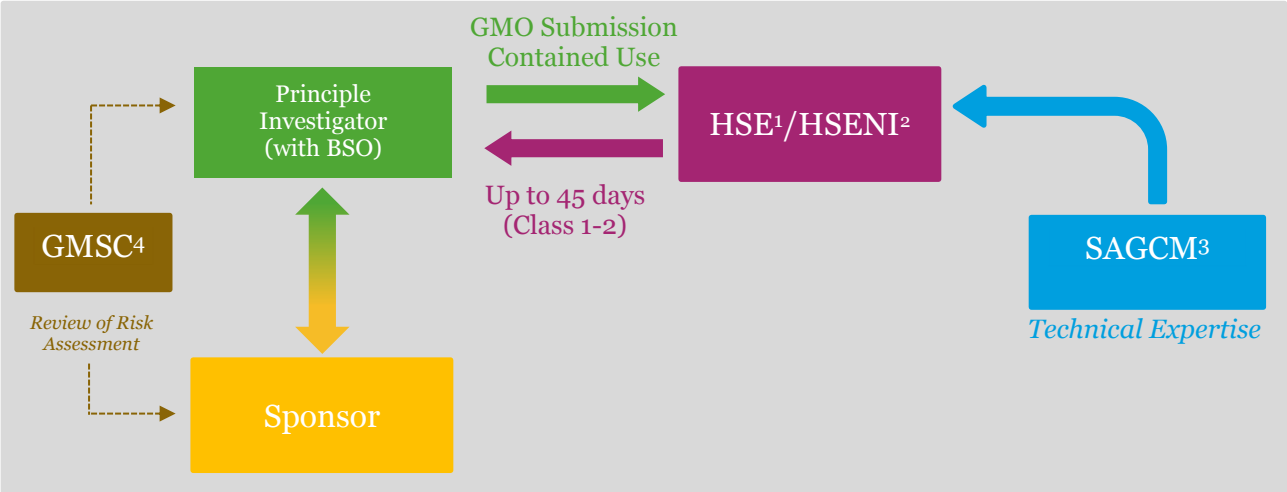
The UK regulatory framework for GMO-IMP authorisation is based primarily on Regulation 2014 for CU. In principle, based on the characteristics of the genetically modified (GM) product (i.e. replication ability, possibility of shedding, survival in the environment), GMOs could be approved according to deliberate release (DR) procedures as defined in Regulation 2002. However this is rare; according to the UK Health and Safety Executive (HSE), most clinical research studies involving GMOs have been for CU and classified in the lowest hazard categories (Class 1 and 2).

Detailed guidance on the use of genetically modified microorganisms in a clinical setting, produced in association with all relevant agencies, is available online. However, this legislation applies only to Great Britain (England, Scotland and Wales). Northern Ireland has distinct parallel legislation with analogous procedures.

UK Agencies for GMO Approval

For CU submission in England, Scotland and Wales, the relevant Competent Authority (CA) is the HSE. CU submission in Northern Ireland is made to the Health and Safety Executive Northern Ireland (HSENI).

Figure 3-1 Overview of the Contained Use Authorisation Procedure in the UK



1	HSE = Health and Safety Executive
2	HSENI = Health and Safety Executive Northern Ireland
3	SAGCM = Scientific Advisory Committee on Genetic Modification
4	GMSC = Genetic Modification Safety Committee Where hospitals are carrying out clinical research studies on behalf of a pharmaceutical company (as part of a connected programme of work), the risk assessment may be provided by company and the hospital would not need to establish its own 'local' GMSC.

For Class 1 containment, activities can commence once the risk assessment (RA) has been agreed by the Genetic Modification Safety Committee (GMSC), if the premises has already been notified to the HSE/HSENI.

For Class 2 containment, activities can commence either immediately after application receipt or up to 45 days later, depending on whether the premises notification is in place.

A formal approval is not needed for Class 1 and 2 containment if the premises notification has been made (if CU activities have already been notified elsewhere on the premises, then the project may be covered under the existing premises notification).

Class 3 and 4 containment requires a formal approval before an activity can begin and takes up to 90 days.

An overview of the UK CU authorisation procedure is given in Figure 3-1. Applicants are encouraged to contact the CA responsible for CU in the event of any uncertainty related to the regulatory strategy.

Note: *The approval process for GMOs is independent to CTA application to the Medicines and Healthcare products Regulatory Agency (MHRA) and relevant EC, however both authorisations must be in place prior to initiating a clinical trial with a GMO-IMP.*

4. Preparing for GMO Submission

Biological Safety Officer

The Biological Safety Officer (BSO) plays a central role coordinating GMO activities between clinicians/researchers and internal/external GMSCs. The BSO on-site will be familiar with infection control procedures and ensures that any measures required by a RA are properly applied.

It is recommended that the local BSO establishes contact with the sponsor's Regulatory Affairs Manager from the outset, to discuss the relevant submission requirements and responsibilities. The BSO will act as the sponsor's partner for submission, providing local information and follow-up.

Establishing a 'Connected Programme of Work' (only applicable to class 2, 3 and 4 containment)

UK CU notification requirements are sufficiently flexible to allow for the most practical implementation of GMO legislation during clinical research. A 'connected programme of work' can be established for multi-centre studies where the containment is classified as Class 2, 3 or 4; allowing an organisation to notify the HSE for a single activity across multiple premises with the sponsor having overall management and responsibility. The advantages of a connected programme of work are that there is only a single notification fee for a notification covering several CUs, information does not need to be duplicated and notification does not need to be limited to a specific clinical study or GMO.

For further information on connected programme notifications, refer to Regulation 13 and Article 40-42 in the SACGM Compendium of guidance.

Establishing a Genetic Modification Safety Committee

CU legislation requires that any organisation carrying out a RA on Class 2-4 GMOs should seek GMSC advice prior to submission. The purpose of the GMSC is to advise on the adequacy of the RA undertaken relating to GM activities.

Hospitals with active research departments will often already have a GMSC and teaching hospitals usually have access to a committee operating in one of the university departments. The GMSC is

typically formed of a group of relevant stakeholders such as management, trial nurses, pharmacists, infection control staff, health and safety advisors (such as a BSO) and clinicians. Centres should avoid having unnecessarily large committees and limit participation to representatives with relevant expertise. The GMSC members can be tailored per GMO and outside expertise can be drafted in where necessary. For further information on GMSCs, refer to Regulation 8 and Article 24-31 in the SACGM Compendium of guidance.

Where hospitals carry out clinical trials on behalf of a pharmaceutical company under a 'connected programme of work', the RA may be provided by the company. In these situations, the company would establish a central GMSC and the participating hospitals would not need to establish their own. The RA would remain the same for each hospital, although SOPs may require adaptation to meet local needs.

At a local level, hospitals need to ensure that the local management is aware of the trial, as would be the case for any clinical trial, and it may be prudent for the relevant PI's/BSO's to form part of the GMSC. The person responsible for the trial on site must ensure that management and other staff are aware of the RA, and are involved in drawing up the necessary SOPs, including those covering emergency procedures.

5. Procedure for Contained Use Authorisation

Overview

The overall CU procedure is identical for all regions in the UK, with some minor differences in the forms submitted. The document preparation is usually carried out by the clinical site with support from the sponsor and when applicable is submitted to the relevant agency (i.e. when a premises notification is required – see below).

The essential requirements include:

- Risk assessment of activities involving GMOs;
- All activities must be assessed for risk to humans and risk to the environment;
- A classification based on the risk of the activity;
- Notification of all premises to HSE/HSENI before they are used for genetic modification activities **for the first time** and the proof of payment (HSE fees are listed in Revised GMO notification fees with effect from 6 April 2016 , HSENI fees are found in Schedule 6 of the NI regulations).

Submission Information

HSE/HSENI prefers documentation to be submitted electronically by email to bioagents@hse.gsi.gov.uk (HSE) or mail@hseni.gov.uk (HSENI). HSE Forms can also be completed via the Online forms page. Note that it's not possible to save the form as you go and therefore the relevant information should be available upfront. Alternatively, a hard copy can be posted, but this option is only generally used for information that is of a sensitive nature and can delay approval.

Post-Approval Maintenance

Following approval, any changes made to an ongoing CU. Significant changes affecting the RA should be notified to the HSE/HSENI (changes considered to be 'significant' are listed in Regulation 15 (Table 2)).

Administrative changes that do not affect the RA should also be notified according to Regulation 14. Additional sites/locations can be added to the existing notification and should be notified as administrative changes. There is no fee for the addition of further sites.

6. Relevant Legislation and Guidance

GMO Contained Use

The Genetically Modified Organisms (Contained Use) Regulations 2014

Directive 2009/41/EC of the European Parliament and of the council of 6 May 2009 on the contained use of genetically modified micro-organisms

SACGM Compendium of guidance - Part 6: Guidance on the use of genetically modified microorganisms in a clinical setting

The Genetically Modified Organisms (Contained Use) Regulations (Northern Ireland) 2015

GMO Deliberate Release (for information)

Genetically Modified Organisms (Deliberate Release) Regulations 2002

Directive 2001/18/EC of the European Parliament and of the Council of 21 March 2001 on the deliberate release into the environment of genetically modified organisms

Useful Websites

Health and Safety Executive (HSE)

Health and Safety Executive Northern Ireland (HSENI)

Advisory Committee on Releases to the Environment (ACRE)

Medicines and Healthcare products Regulatory Agency (MHRA)

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