Understanding the European GMO legislation for gene therapy products in clinical trials

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Summary

- Cell & Gene Therapy Catapult
- Complex regulatory pathway
- GMO legislation
- Contained use vs deliberate release
- Some examples
Cell and Gene Therapy Catapult
Cell and Gene Therapy Catapult

- Established by **Innovate UK** (formerly the Technology Strategy Board)
- **Bridge the gap** between businesses, academia, research and government
- Long-term investment to **transform** the UK’s ability to create new products and services
- Open up global opportunities for the UK and **generate sustained economic growth** for the future
Cell and Gene Therapy Catapult

Facilities

- £70m development laboratories
  - London clinical research cluster
  - 1,200m² on 12th floor Guy’s Tower
  - 110 people

- £55m large-scale advanced therapies manufacturing centre
  - Stevenage Biocatalyst
  - Opening 2017
  - 7,200m²
  - 150 people
# Teams

<table>
<thead>
<tr>
<th>Business</th>
<th>Manufacturing and supply</th>
<th>Clinical and regulatory</th>
</tr>
</thead>
</table>
| • Business development | • Process development  
                        | • Analytical development  
                        | • Regulatory                                                  |
| • Business models   | • GMP process proving   
                        | • Clinical trial sponsor                                         |
| • Health economics | • Supply chain   
                        | • Clinical operations                                           |
|                   | • Late clinical phase manufacturing  
                        | • Pre-clinical safety                                          |
|                   | • Initial in market supply                                                  |                                       |
Complex regulatory pathway
Clinical trial of product

EU Tissues and Cells Directive or Blood Directive

- Non-substantial manipulation / homologous use
  - Substantial manipulation or non-homologous use
  - Transplantation/Transfusion
    - Clinical trial of ATMP (medicinal product)
    - Non GMO
    - GMO
Clinical trial of product

EU Tissues and Cells Directive or Blood Directive

- Non-substantial manipulation / homologous use
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- GMO
GMO legislation
The definition of gene therapy medicinal product according to Annex I, part IV, section 2.1 of Directive 2001/83/EC, as amended, is articulated into two conditions that have both to be fulfilled simultaneously:

1) the product has to be of biological origin and contains recombinant nucleic acid(s) and

2) the recombinant nucleic acid(s) should be directly involved in the mechanism of action and hence therapeutic action of the product.
GMO definitions
- (Directive 2001/18/EC, Art. 2 (1) (2))

Genetically modified organisms (GMOs, also referred to as genetically-modified micro-organisms, or GMMs) are defined as:

“...organism(s), with the exception of human beings, in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination...”

Organisms are defined as:

“...any biological entity capable of replication or of transferring genetic material”

Thus, GTMPs will be classified as GMOs in most cases (whether delivered by in-vivo or ex-vivo methods)
Medicinal products as GMO

- Clinical gene therapy trials often involve genetically modified organisms (GMOs) like recombinant viral vectors.
- Some EU member states consider clinical trials with gene medicines as *deliberate release* according to Directive 2001/18/EC.
- Others consider them as *contained use* according to Directive 2009/41/EC.
- Although the approach of Directive 2009/41/EC is different from Directive 2001/18/EC, both directives aim at protecting the environment and human health.
- Both require a risk assessment preceding the activity.
Assessing risk for a GMO

EU legislation defines a classification system based upon the use of the GMO:

- **Contained use (Directive 2009/41/EC)**
  
  “...any activity for which specific containment measures are used to limit their contact with, and to provide a high level of safety for, the general population and the environment...”

- **Deliberate release (Directive 2001/18/EC)**
  
  “...any intentional introduction into the environment...for which no specific containment measures are used...”

If there is a choice of contained use / deliberate release procedures in the MS, the sponsor must decide which category the GMO falls under and make the justification for that decision.
GMO – Contained use

- Contained use is defined as any activity with GMOs for which specific containment measures are used to limit their contact with the environment.

- The focus of Directive 2009/41/EC is on the assessment of the biosafety level classification of the GMO and the implementation of physical, chemical and biological barriers. The risk classification has consequences for the procedure and review period of the application.
**Contained use – risk classification**

- All contained use procedures are based on classification of risk – as decided by appropriate agency / authority
  - Class 1: No or negligible risk, level 1 containment
  - Class 2: Low risk, level 2 containment
  - Class 3: Moderate risk, level 3 containment
  - Class 4: High risk, level 4 containment
- Classification is dependent upon strength of argument / data contained in a risk assessment / biosafety dossier
- Class 3 / 4 GMOs require prior consent from the competent authority but most ATMPs should be Class 1 / 2
- Contained use often requires clinical site-specific notifications and / or submissions to authorities
GMO - Deliberate release

Deliberate release is defined as any activity with GMOs that is not contained use.

Directive 2001/18/EC is based on a environmental risk assessment (ERA) covering effects on human health or the environment.

The ERA should be carried out in accordance with the principles set out in Annex II of this Directive. 5 steps:

i) identification of potential adverse effects,
ii) estimation of the likelihood,
iii) risk estimation,
iv) risk management
v) assessment of the overall environmental impact.
GMO - Deliberate release

- All submissions for deliberate release must contain the following:
  (a) information relating to the GMO(s)
  (b) information relating to the conditions of release and the potential receiving environment
  (c) information on the interactions between the GMO(s) and the environment
  (d) an environmental risk assessment

- It is also required that a dossier in the summary notification information format (SNIF) is submitted, which is added to a publically available EU register (no confidential information)
Clinical trials using GMOs classified as contained use or deliberate release for selected EU member states

<table>
<thead>
<tr>
<th>Member State</th>
<th>Contained use or Deliberate release</th>
</tr>
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<tbody>
<tr>
<td>Germany</td>
<td>Deliberate release</td>
</tr>
<tr>
<td>UK</td>
<td>Either (most studies are considered contained use)</td>
</tr>
<tr>
<td>France</td>
<td>Either (until recently all studies considered contained use but deliberate release also applicable)</td>
</tr>
<tr>
<td>Sweden</td>
<td>Clinical studies are now normally considered as deliberate release</td>
</tr>
<tr>
<td>Spain</td>
<td>Either</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>Deliberate release</td>
</tr>
<tr>
<td>Belgium</td>
<td>Either</td>
</tr>
</tbody>
</table>
Contained use vs deliberate release

- Generally, GMOs regulated under deliberate release come under greater scrutiny from competent authorities.
- Contained use has a greater administrative burden (requiring both clinical site submissions and sponsor submissions) which may slow approvals.
- However, lower classification equates to lighter regulatory touch and once approved, there are less likely to be conditions applied.
- Deliberate release or high risk contained use may require significant safety data / risk mitigations prior to or during the trial.
GTMPs as GMOs in clinical trials
GTMPs as GMOs in clinical trials

Core documents for EU Clinical Trial Authorisation (CTA) applications are common to all EU Member States (MS):
- Clinical Protocol
- Investigator’s Brochure (IB)
- Investigational Medicinal Product Dossier (IMPD)
- In addition to administrative forms, proposed labelling, etc.

CTAs for GTMPs classified as GMOs can be more complex and involve procedures outside of regulatory / ethical review.

Differences in specific GMO requirements in each MS can be significant.

Approval for GMO specific aspects MUST be gained before a clinical trial can start – requires submission of dossiers to appropriate authorities.
Some examples
Germany

Submission of CTA including GMO required documentation

PEI

Ethics Review of Trial

SPONSOR

CI (Multi) / PI (Single)

GMO Risk assessment
(always viewed as Deliberate Release)

National Level

Federal

APPROVAL
UK

INVESTIGATOR SITE
- GMO assessment
- Contained Use (*HSE*)
- Site specific registration

SPONSOR
- Submission of CTA
  - MHRA
- Ethics Review of Trial
  - IRAS Portal

National Level
- National
  - HRA – GTAC
    - London – West London & GTAC
    - North East – York
    - South Central – Oxford A
    - Scotland A REC

LOCAL NHS R&D approval

APPROVAL

Procurement under EU Tissues and Cells Directive
EudraCT Number (*EMA*)
IRAS Portal
LOCAL NHS R&D approval
Belgium

GMO assessment

Submission of CTA to FAMHP

Ethics Review of Trial

Regional

Federal

National Level

Local (all sites)

GMO assessment

Contained Use Risk assessment to SBB & BAC

Deliberate Release SBB & BAC

SBB – Biosafety and Biotechnology Unit, BAC – Biosafety Advisory Council

FAMHP – Competent Authority
France

As of June 2015, deliberate release legislation can now be applied in France if contained use requirements not considered sufficient.

MESR – Ministry for Environment and Scientific Research
Conclusions

- GMO requirements are implemented very differently across Europe and can require regional interactions with numerous bodies / authorities.

- Admin burden can be great for small companies and lack of clarity with procedures can be frustrating.

- Benefits of using contained use procedures depends upon MS but generally seen to be less burdensome in terms of negating risk to humans and environment.

- Deliberate release or higher risk contained use (Class 3/4) may require significant safety data / risk mitigations prior to, or during the trial.

- It's not about contained use vs deliberate release – just need the approval!
Directive 2009/41/EC Contained use of genetically modified micro-organisms
Directive 2001/18/EC deliberate release into the environment of genetically modified organisms

Regulation (EC) No 726/2004 procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a EMA
Regulation (EC) No 1394/2007 advanced therapy medicinal products regulation

General Principles to Address Virus and Vector Shedding EMEA/CHMP/ICH/449035/2009
Guideline on Follow-up of patients administered with gene therapy medicinal products (CHMP/GTWP/60436/07).

Guideline on the non-clinical studies required before first clinical use of gene therapy medicinal products (EMEA/CHMP/GTWP/125459/06).

General Principles to Address the Risk of Inadvertent Germline Integration of Gene Therapy Vectors (CHMP/ICH/469991/2006).

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