Regulatory Factsheet

Clinical Trials with Genetically Modified Organisms (EU)

EU Regulatory Framework

Investigational medicinal products (IMPs) that contain or consist of genetically modified organisms (GMOs) constitute a special regulatory case. In addition to the standard review of the clinical trial application by the competent authority and ethics committee, GMO IMPs are subject to an assessment and approval process under the GMO legislation.
Relevant GMO legislation:

- **Directive 2001/18/EC** on the **deliberate release (DR)** into the environment of genetically modified organisms
- **Directive 2009/41/EC** on the **contained use (CU)** of genetically modified micro-organisms.

Please note: This GMO regulatory framework is not affected by the Regulation (EU) No 536/2014 on clinical trials (CTR) coming into effect as the CTR excludes GMOs from its scope.

Challenges for GMO Clinical Trials

EU Directives are legislated at country level, leaving room for national interpretation. Consequently, application requirements and administrative procedures differ significantly between member states (MSs).

GMO Classification: MSs can decide if clinical studies are to be conducted under CU, DR or both frameworks. Some MSs only allow DR or CU, while others base classification on the GMO characteristics and implementation of containment measures. If CU applies, often the sites play a key role in the application process.

Application Process and Review Timelines: Regulatory approval process, responsible agencies, submission requirements, and review timelines vary between countries and for CU and DR as they are not embedded in EU legislation and depend on local processes and potential publication obligations. As GMO and CTA application processes are not harmonized, overlapping questions from different authorities in different countries can be received.

GMO Application Dossiers

Content of the application dossiers and assessment methodologies differ between CU and DR and additional country-specific requirements apply. The Annexes to the GMO Directives provide information on the assessment methodologies and content of the application.

- DR (Directive 2001/18/EC):
  - Annex II: Principles for the environmental risk assessment [ERA]
  - Annex III: DR technical dossier
  - Summary notification information format (SNIF) (Article 11)
- CU (Directive 2009/41/EC):
  - Annex III: CU risk assessment, basis for assignment of containment level
- For several common product types (AAVs, viral vectors, genetically modified [GM] human cells), a European Common Application Form (CAF) can be used for both CU and DR if the GMO IMP falls within the pre-specified parameters. For AAVs and GM human cells, specific ERAs are also available.
- While these CAFs are endorsed in many MSs, not all MSs accept them for all product types. If the CAF is accepted, several MSs still expect country-specific information or additional documents to be provided.

Definitions at a Glance

Genetically Modified Organism (GMO)

'an organism, 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'
(Directive 2001/18/EC, Article 2)

A similar definition exists for genetically modified micro-organisms (GMM) (Directive 2009/41/EC, Article 2).

Deliberate Release (DR)

'any intentional introduction into the environment of a GMO or a combination of GMOs for which no 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'
(Directive 2001/18/EC, Article 2)

Contained Use (CU)

'any activity in which microorganisms are genetically modified or in which such GMMs are cultured, stored, transported, destroyed, disposed of or used in any other way, and 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'
(Directive 2009/41/EC, Article 2)

Strategic Considerations to Mitigate Risks for Clinical Trials with GMO IMPs

- Understanding of the local transposition of GMO Directives and interplay with other applicable legislation, application processes and timelines to build a targeted submission strategy
- Considering the potential target countries and product characteristics/risks to develop a smartly written GMO application dossier that can serve for multiple applications and be easily adapted
- GMO feasibility assessment for clinical trial sites, early communication and support for inexperienced sites without established GMO procedures
- Early interaction with GMO competent authorities for complex or novel products

If you would like to speak to a member of the Boyds team, contact **info@boydconsultants.com** or visit **www.boydconsultants.com** and we will be happy to help.

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