The Challenge of GMO Medicinal Products in Clinical Trials
Contents

Abbreviations .......................................................................................................................................................... 4-5

1 Introduction .......................................................................................................................................................... 6

2 Regulatory Requirements ...................................................................................................................................... 10
   2.1 EU clinical trial application with GMOs ...................................................................................................... 10
   2.1.1 EU environmental legislative framework of a GMO .............................................................................. 10
   2.1.2 EU country requirements ........................................................................................................................ 11
   2.1.3 Harmonization efforts within the EU ...................................................................................................... 14
   2.1.4 GMOs under the new EU clinical trial regulation .................................................................................... 15
   2.2 GMO in clinical trials in US ........................................................................................................................ 16
   2.3 GMO in clinical trials in Australia ............................................................................................................... 16
   2.4 GMO in clinical trials in Japan ...................................................................................................................... 17
   2.5 GMO in clinical trials in China ...................................................................................................................... 18
   2.6 GMO in clinical trials in South Africa ........................................................................................................... 19

3 Study on the Implementation of a Global Trial with a GMO: Country and Site Selection ......................... 20
   3.1 Region/country selection ............................................................................................................................ 20
   3.2 Site Selection ............................................................................................................................................. 21
   3.3 GMO Clinical trial application ...................................................................................................................... 22
   3.4 Lessons learned ........................................................................................................................................... 22

4 Summary and Conclusion .................................................................................................................................. 23

5 References .......................................................................................................................................................... 26
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAV</td>
<td>Adeno-Associated Viral vector</td>
</tr>
<tr>
<td>AC</td>
<td>Advisory Committee at DAFF (South Africa)</td>
</tr>
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<td>ANSM</td>
<td>Agence Nationale de Sécurité du Médicament et des Produits de Santé/Agency for the Safety of Health Products in France</td>
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<td>BVL</td>
<td>Bundesamt für Verbraucherschutz und Lebensmittelsicherheit/Federal Office for Consumer Protection and Food Safety in Germany</td>
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<tr>
<td>CAR-T</td>
<td>Chimeric Antigen Receptor T-cells</td>
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<tr>
<td>CDE</td>
<td>Center for Drug Evaluation in China</td>
</tr>
<tr>
<td>CIOMP</td>
<td>Consejo Interministerial Organismos Modificados Genéticamente/Interministerial Council for Genetically Modified Organisms at Ministry of Agriculture, Food and Environment in Spain</td>
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<tr>
<td>CTA</td>
<td>Clinical Trial Application</td>
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<td>CTC</td>
<td>Clinical Trial Expert Committee under SAHPRA in South Africa</td>
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<td>CTN</td>
<td>Clinical Trial Notification</td>
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<td>CTX</td>
<td>Clinical Trial Exemption scheme in Australia</td>
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<tr>
<td>DAFF</td>
<td>Department of Agriculture, Forestry and Fisheries in South Africa</td>
</tr>
<tr>
<td>DIR</td>
<td>Dealing Involving Intentional Release Licence in Australia</td>
</tr>
<tr>
<td>DNA</td>
<td>Deoxyribonucleic Acid</td>
</tr>
<tr>
<td>DNIR</td>
<td>Dealing Not Involving Intentional Release Licence in Australia</td>
</tr>
<tr>
<td>EC</td>
<td>Executive Council Under DAFF in South Africa</td>
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<td>EMA</td>
<td>European Medicines Agency</td>
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<td>ERA</td>
<td>Environmental Risk Assessment</td>
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<td>EU</td>
<td>European Union</td>
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<td>FDA</td>
<td>US Food and Drug Administration</td>
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<td>FD&amp;C Act</td>
<td>Federal Food, Drug, and Cosmetic Act</td>
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<td>GCP</td>
<td>Good Clinical Practice</td>
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<tr>
<td>GCP-V</td>
<td>GCP-Ordinance in Germany</td>
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<td>GenTG</td>
<td>Genetic Engineering Act in Germany</td>
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<tr>
<td>GMO</td>
<td>Genetically Modified Organism</td>
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<tr>
<td>GT Act</td>
<td>Gene Technology Act in Australia</td>
</tr>
<tr>
<td>HCB</td>
<td>Haut Conseil des Biotechnologies/High Council for Biotechnology-France</td>
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<tr>
<td>HREC</td>
<td>Human Research Ethics Committee</td>
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<tr>
<td>IBC</td>
<td>Institutional Biosafety Committee</td>
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<tr>
<td>IMP</td>
<td>Investigational Medicinal Product</td>
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<tr>
<td>IND</td>
<td>Investigational New Drug (program)</td>
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<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>IP</td>
<td>Investigational Product</td>
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<td>LMO</td>
<td>Living Modified Organism</td>
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<tr>
<td>MTES</td>
<td>Ministry of Environment (Ministère de la Transition Écologique et Solidaire) in France</td>
</tr>
<tr>
<td>MESR</td>
<td>Ministry of Research (Ministère de l'Enseignement Supérieur, de la Recherche et de l'Innovation) in France</td>
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<tr>
<td>MHLW</td>
<td>Minister of Health, Labour and Welfare in Japan</td>
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<tr>
<td>MoE</td>
<td>Ministry of Environment</td>
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<tr>
<td>NExTRAC</td>
<td>Novel and Exceptional Technology and Research Advisory Committee under NIH</td>
</tr>
<tr>
<td>NIH</td>
<td>National Institutes of Health (US)</td>
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<tr>
<td>NMPA</td>
<td>National Medical Products Administration in China, formerly CFDA</td>
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<tr>
<td>OGTR</td>
<td>Office of the Gene Technology Regulator in Australia</td>
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<tr>
<td>OSP</td>
<td>Office of Science Policy (office under NIH in US)</td>
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<tr>
<td>PEI</td>
<td>Paul Ehrlich Institute (German national competent authority for CTA)</td>
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<tr>
<td>PDUFA</td>
<td>Prescription Drug User Fee Act</td>
</tr>
<tr>
<td>PI</td>
<td>Principal Investigator</td>
</tr>
<tr>
<td>PMDA</td>
<td>Pharmaceuticals and Medical Devices Agency in Japan</td>
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<tr>
<td>PPE</td>
<td>Personal Protective Equipment</td>
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<tr>
<td>PRIME</td>
<td>PRiority MEdicines Scheme at EMA</td>
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<tr>
<td>QIDP</td>
<td>Qualified Infectious Disease Product (designation by FDA)</td>
</tr>
<tr>
<td>R&amp;D</td>
<td>Research and Development</td>
</tr>
<tr>
<td>RAC</td>
<td>Recombinant DNA Advisory Committee, under NIH, now renamed to NExTRAC</td>
</tr>
<tr>
<td>RMAT</td>
<td>Regenerative Advanced Medicine Therapies (designation by FDA)</td>
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<tr>
<td>RMP</td>
<td>Regenerative Medical Products</td>
</tr>
<tr>
<td>RS</td>
<td>Regulatory Science</td>
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<tr>
<td>SAHPRA</td>
<td>South African Health Products Regulatory Authority, formerly known as MCC (Medicines Control Council)</td>
</tr>
<tr>
<td>SNIF (Part B)</td>
<td>Summary Notification Information Format for the release of gene-modified organism other than plants, applicable for deliberate release of GMOs for any other purposes than placing on the market in accordance with Part B of DIRECTIVE 2001/18/EC</td>
</tr>
<tr>
<td>SOP</td>
<td>Standard Operating Procedure</td>
</tr>
<tr>
<td>TGA</td>
<td>Therapeutic Goods Administration, competent authority for clinical trials in Australia</td>
</tr>
<tr>
<td>URPL</td>
<td>Urzad Rejestracji Produktow Leczniczych/Department of Registration of Medicinal Products in Poland</td>
</tr>
<tr>
<td>US</td>
<td>United States of America</td>
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Introduction

Novel therapeutic strategies, such as immunotherapy and gene therapies, have revolutionized the medicinal product market. The FDA and European Commission have issued two approvals for CAR T-cell therapies in blood cancer within the last years (Kymriah, Novartis, US August 2017, EU August 2018; and Yescarta, Kite, US October 2017; EU August 2018). Both are advanced therapy products including genetically modified white blood cells (genetically modified organism, GMO).

Innovations in drug development for therapeutic areas with unmet medical needs are facilitated by EMA with accelerated approval pathways via the PRIority MEdicines scheme (PRIME). Indeed Kymriah and Yescarta were two of the first candidates to have received PRIME status; 15 from 54 approved requests for PRIME were granted for oncology and nine for hemophilia until present day. The remaining 20 were GMO products (June 2019; PRIME). While EU marketing authorization applications of products containing GMOs via the mandatory centralized procedure are streamlined and the environmental and biosafety aspects of the GMO are evaluated under the lead of one competent authority responsible for the environmental assessment, the clinical trial applications (CTA) is handled on a national level.

Kymriah and Yescarta were also candidates from expedited programs in the United States. For more than three decades, FDA has strived to address unmet medical needs in the treatment of serious conditions. By 1992, and under the Prescription Drug User Fee Act, FDA had agreed to specific goals for improving the drug review time and expediting drug approval of drugs and biologics by 1) creating a two-tiered system of review times—standard review and priority review aiming to complete and act upon reviews of priority drugs within six months instead of the standard ten-month review period; and 2) implementing an accelerated approval program when a surrogate or an intermediate clinical endpoint is reasonably likely to predict clinical benefit. In subsequent years, the Federal Food, Drug, and Cosmetic Act (FD&C Act) has been amended several times to include new programs for expedited product development and review such as fast-track designation (1997), and breakthrough therapy designation (2012) to facilitate the development and expedite the review of drugs and biologics targeting serious and life-threatening conditions or that may represent substantial improvement over available therapies for the treatment of a serious condition, so that an approved product can reach the market expeditiously. In 2012, FDA introduced the Breakthrough Therapy Designation pathway preliminary clinical evidence of a treatment effect that may represent substantial improvement over available therapies for the treatment of a serious condition. Most recently, US Congress has amended section 506 of the FD&C Act to specifically address the expedited development and review of certain Regenerative Advanced Medicine Therapies designated as RMATs to keep up with the rapidly expanding field of regenerative medicine. This new regulatory pathway is intended for cell therapies, therapeutic tissue engineering products, human cell and tissue products, and combination products using any such therapies or products specifically. Since its implementation in 2016, FDA received 108 RMAT designation requests and granted 40 designations.
In addition to the more familiar orphan drug designation, other programs have been implemented by the FDA to provide incentives such as priority review vouchers for rare pediatric diseases and neglected tropical diseases, and Qualified Infectious Disease Product (QIDP) designation for the development of antibacterial and antifungal drugs for human use intended to treat serious and life-threatening infections. All these expedited programs are distinct designation programs with different programmatic requirements, and sponsors may apply for and receive more than one designation for a given product, but sponsors should apply for each designation separately.

The increased research in medicinal products consisting of GMOs can also be observed by the total number of clinical trials on gene therapy clinical trials from 1989 to 2018 (Figure 1). During the past 20 years, CTA on gene transfer medicinal products/GMOs have increased by about 300%.9

**Figure 1:** Global clinical trials of gene transfer medicinal products/GMO during the years 1989 to 2018

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The FDA also sees a rapid increase in investigational new drug applications (IND) for gene therapies and currently has more than 700 active INDs\textsuperscript{10} awaiting 250 new INDs per year.\textsuperscript{11}

As of June 2019, a search in Citeline with the terms “gene therapy” renders more than 1,200 clinical trial results, most of them (81.5%) in the oncology field (Figure 2).\textsuperscript{12} Of note, 25% of the total studies cited are in planning phase.

\textbf{Figure 2: Clinical trial with gene therapy}\textsuperscript{13}
One of the major challenges is that GMO medicinal products have to comply with different laws: the GMO law that mainly focuses on the biosafety aspect and covers all GMOs (mainly genetically modified food and agriculture products); the drug law; and if genetically modified cells are concerned, tissue/cell and blood regulations. GMO authorities have other questions than drug regulators. The definitions are often not aligned and requested information is not tailored for medicinal products, which can lead to misunderstanding when filling out application forms. The biosafety aspects are described in Figure 3. All potential risks by the GMO on human health and the environment, through direct or indirect exposure, with immediate or delayed effects, must be identified and appropriate mitigation strategies developed, so that the overall environmental impact of the GMO in the medicinal product can be concluded and a GMO approval can be obtained.

**Figure 3: Biosafety aspects of gene therapy products**

**GMO as Component of a Medicinal Product Environmental Risk Assessment**

- **RISKS**
  - Unintended contact with human beings
  - Dispersal of portions of product
  - Accidental dissemination
  - Disposal of unused or waste medicinal product
  - Dispersal of GMO containing patient excreta

- **CONSEQUENCES**
  - Transfer genetic material
    - Spread
    - Infect tissue
    - Degrade
  - Genetic or phenotypic change
    - Remain latent
    - Reproduce
  - Complete with existing species
2 Regulatory Requirements

2.1 EU clinical trial application with GMOs

Investigational medicinal products (IMP) containing GMO require additional approval steps for the use and release of the GMO, which are different in each country, and can be time consuming and may delay the start of the clinical trial by as many as 12 months. CTAs are evaluated by different bodies. Besides the standard review of a CTA (in accordance with harmonized rules and timelines implemented from Directive 2001/20/EC into national law or the new Clinical Trial regulation No 536/2014 (once it becomes applicable)), a biosafety review for the GMO has to be performed. The relevant environmental authority evaluates the clinical trial in accordance with Directive 2009/41/EC and Directive 2001/18/EC, which cover the contained use of GMOs and deliberate release of GMOs into the environment for an experimental setting, including the export and import, respectively.

Some EU member states (MS) consider clinical trials with GMO medicines as deliberate release according to Directive 2001/18/EC (e.g., Germany, Hungary, Ireland, Romania, Slovakia, Slovenia, Spain, Sweden and the Netherlands). Other MSs consider them as contained use according to Directive 2009/41/EC (e.g., Denmark, Poland, and Bulgaria), or case by case (e.g., France, Belgium, UK). Both directives aim to protect environment and human health. If the GMO is classified under the contained use, biosafety approvals are required for the clinical sites as well, which are an additional hurdle to start a clinical trial.

The requirements on the documentation are not harmonized, so that the level of information for each country might be different. In some countries even regional differences exist, and application to several institutions might be necessary. Finally, manufacturers, distributors, clinical sites and laboratories dealing with the drug or samples from the patients, require additional approvals. The biosafety boards also often require the application in their country language, all factors that increase the burden and restrict patients to participate in a clinical trial.

2.1.1 EU environmental legislative framework of a GMO

Clinical trials with medicinal products consisting of GMOs are regulated under contained use, deliberate release or both legislations.

Contained use is defined in accordance with Directive 2009/41/EC as any activity with GMOs* for which specific containment and control measures are used to minimize the risk to human health and the environment. The risk assessment will determine the class into which the contained use activity will fall, and strong arguments are needed to justify the classification and its containment levels. While class 1 and 2 are appropriate for products with negligible or low risk, which the most gene-modified medicinal products should belong to, class 3 and 4 are for products of moderate to high risk and require further approvals from competent authorities and/or clinical site specific notifications. The risk classification has consequences for the procedure and review period of the application. After provisional assignment of the classification, the risk assessment in accordance to Annex III is performed and protective measures identified to control the risk. The final classification of the contained use is then confirmed by reviewing the completed assessment.

* Classification is only pertinent for genetically modified microorganism, as used as medicinal products, and is not applicable for other GMOs such as genetically modified plants and animals.
Where premises are being used for the first time for any contained use activity, a notification to the competent authority is required to obtain a permit for carrying out the activity in a manner that it does not present a hazard to human health and the environment. Information on the premises on the responsible person for supervision and safety, the work to be performed, classification and risk assessment has to be provided for class 1. For class 2 and higher, technical information on the GMO, volumes to be used, accident prevention and emergency plans have to be added in addition as described in Annex V of Directive 2009/41/EC Information required for the notification referred to in Articles 6 (class 1), 8 (class 2) and 9 (class 3).

Notifications are not required for subsequent class 1 contained use activities at premises that are in compliance with Article 6 of the Directive. Higher classes may require further approval for subsequent contained use activities. A public notice of the proposed contained use may be required in accordance to country regulation (Article 12 of Directive 2009/41/EC).

People employed in contained uses should be consulted in accordance with the requirements of Directive 2000/54/EC on the protection of workers from risks related to exposure to biologic agents at work. Deliberate release is defined as any activity with GMOs that are not classed as contained use. Directive 2001/18/EC is based on an 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:

- The GMO characteristics, which may cause adverse effects, should be identified; potential consequences of each adverse effect and its likeliness of occurrence need to be evaluated.
- A detailed risk analysis on each identified characteristic of the GMO should be provided and how the risk will be managed if the GMO is released into the environment. The overall risk of the GMO ought to be evaluated.
- The ERA following the EMA guidance for marketed GMO medicinal products fully complies with the requirements of Annex II of Directive 2001/18/EC.

Detailed technical information in accordance to Annex IIIa of Directive 2001/18/EC is also part of the GMO application.

Clinical trials with IMPs containing GMOs in the deliberate setting are to be published according the Directive 2001/18/EC in the GMO-register of the Joint Research Centre of the EU commission with the so-called Part B SNIF (summary notification information format) application form.

### 2.1.2 EU country requirements

Information about the basic national requirements regarding GMO aspects for IMPs containing GMOs has been published on the European Commission website. In the following table, typical scenarios are presented: application following deliberate release of GMOs, contained use or both scenarios.
<table>
<thead>
<tr>
<th>Scenario of regulation</th>
<th>Country (example)</th>
<th>Submission</th>
<th>National legislation</th>
<th>Review timelines</th>
<th>Specific considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contained use¹ Directive 2009/41/EC</td>
<td>Denmark</td>
<td>Application to Danish Working Environment Authority and CTA in parallel; GMO authorization is not required for CTA application</td>
<td>Danish Environment and Gene Technology Act; Danish Ministry of Labour’s Executive Order (No. 910 of 11 September 2008) on “gene technology and working environment”¹⁸</td>
<td>90-180 days for the CTA and 45 days for MoE approval</td>
<td>Application for GMO authorization is for the investigational project itself as well as the investigational sites. The notification will be sent to the Danish Working Environment Authority, but evaluation will be made under a joint agreement between Danish Working Environment Authority and Danish Environmental Protection Agency to safeguard both the working environment and the external environment. The Danish Working Environment Authority will then issue a joint approval for the GMO trial and the sites.²⁰</td>
</tr>
<tr>
<td>Contained use and/or deliberate use²</td>
<td>Poland</td>
<td>Prior CTA to URPL application to MoE (Minister Środowiska) for permit of use. Approval needed for CTA</td>
<td>Act of 3 Oct 2008 on providing information on the environment and its protection, public participation in environmental protection and on environmental impact assessments (Ustawa z dnia 3 października 2008 r. o¹¹</td>
<td>MoE 30 days for the permit of use in the clinical trial after public consultation (silent approval if no concerns) 90-180 days for the CTA</td>
<td>The site also requires a permit for a GMO facility (first time permit).</td>
</tr>
<tr>
<td>Contained use and/or deliberate use²</td>
<td>France</td>
<td>1. Request of classification and the conditions of contained use to MESR and request for approval of hospital sites at MESR (22), (23) 2. CTA application to ANSM can be performed in parallel.</td>
<td>Law 2008-595 from 25 June2008 article 13 Décret 2011-1177 du 23 septembre 2011 Décret 2012-384, Arrêté du 16 juillet 2007 du ministère du Travail, Arrêté du 28 mars 2012 du ministère de l’Environnement et du ministère de la Recherche¹⁴</td>
<td>1. Review timeline 45 days. In case of containment levels 3 or 4 90 days for the first application. The review timeline includes a public consultation of about 15-30 days on GMO aspects. Approvals are valid for five years. 2. 90 to 180 days. GMO classification must be provided in the second phase of the ANSM evaluation</td>
<td>1. MESR evaluates the type of contained use regarding manufacturing and administration If risk for deliberated release is also confirmed by the MESR the MTEs (MoE) will assess the deliberate use.¹⁶ The GMO approval itself is managed by Haut Conseil des biotechnologies (HCB, an independent body that delivers opinions on all biotechnology-related issues.¹⁶ HCB will inform MESR about its opinion for the hospital sites.</td>
</tr>
<tr>
<td>Scenario of regulation</td>
<td>Country (example)</td>
<td>Submission</td>
<td>National legislation</td>
<td>Review timelines</td>
<td>Specific considerations</td>
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<tr>
<td>Deliberate use</td>
<td>Germany</td>
<td>Single submission of CTA to PEI including the relevant information for the competent authority for the deliberate release of GMOs in Germany to BVL.²⁵,²⁶</td>
<td>Ordinance on the implementation of Good Clinical Practice in the conduct of clinical trials on medicinal products for use in humans (GCP Verordnung - GCP-V vom 9. August 2004 as amended.²⁷</td>
<td>90 days, extension to 180 days possible, if special expert opinion for the decision has to be sought.²⁷</td>
<td>Storage &gt; 3 days at the site,²⁸ external transport, manufacture of the IMP, and activities with subject samples that may allow replication of the GMO (e.g., biodistribution and shedding analyses) are not covered by the CTA approval. Notifications in accordance to Genetic Engineering Act (§ 8 (1) or (2) GenTG (Gesetz zur Regelung der Gentechnik))²⁹ to local GMO authorities are then required.</td>
</tr>
<tr>
<td>Part B of Directive 2001/18/EC³</td>
<td>Spain</td>
<td>GMO application to CIOMG at Ministry of Agriculture, Food and Environment is not linked to CTA: The submission can be done independently. Parallel or prior submission is recommended</td>
<td>Law 9/2003, of April 25, which establishes the legal regime of confined use, voluntary release and commercialization of genetically modified organisms, Royal DECREE178/2004 as amended.³⁰</td>
<td>CIOMG: 2 months for the approval of the GMO after evaluation of the biosafety committee and 30-day public consultation on the website of Ministry for Ecological Transition in accordance to article 25.4 of Royal Decree 178/2004. 90-180 days for the CTA.</td>
<td>CIOMG works in coordination with the National Biosafety Commission, and is responsible for the coordination and exchange of information with the Autonomous Communities and with the European Commission. The National Biosafety Commission is of advisory nature and belongs to the Ministry for Ecological Transition, it consists of representatives of the different Ministries involved and representatives of the Autonomous Communities, as well as persons and institutions that are experts in the field.</td>
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</tbody>
</table>

¹ Bulgaria also evaluates the GMO as contained use. ² Belgium and UK also evaluate the GMO case by case, either as deliberate use or contained use; ³ Hungary, Ireland, Romania, Slovakia, Slovenia, Spain, Sweden and the Netherlands evaluate the GMO as deliberate use. ⁴ A single submission procedure has been put in place also in other countries such as Sweden, Estonia, Lithuania and Greece²⁵,³¹
2.1.3 Harmonization efforts within the EU

Harmonization efforts have been initiated to streamline the assessment of GMO-related aspects in the context of clinical trials with gene therapy medicinal products that can cover some of today’s unmet medical needs. An EU working group has been established and recently reached consensus on common application requirements for human cells genetically modified and in vivo gene therapy.

In July 2018 GMO application for clinical trials with **human cells genetically modified by means of retro/lentiviral vectors** were facilitated by a Good Practice document and a common application form. ERA requirements are simplified, since “human cells cannot proliferate in the environment as they can only survive inside the human.” The “potential for formation of a replication competent virus” and/or the “presence of residual infectious viral vector particles” as the remaining risks of genetically modified human cells by retro/lentiviral vectors have to be demonstrated to be absent. The data requirements from Annex II of Directive 2001/18/EC are then replaced by the Annex of the Good Practice document and the common application form asks for less scientific and technical information as normally required per Annex III of Directive 2001/18/EC. Many member states such as Austria, Belgium, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Luxembourg, Malta, the Netherlands, Norway, Portugal, Romania, Spain and Sweden already accepted this procedure.

In October 2019 a Good Practice document and a common application form have been published for **investigational medicinal products that contain or consist of adeno-associated viral vectors (AAV)**. AAV clinical vectors are regarded as negligible risk for biosafety aspects: AAVs have not been associated with any pathogenic disease in humans or animals, are unable to replicate unless the cell is co-infected with a helper virus. Any unintended contact of the vector molecule to nontarget individuals is expected to be eliminated by the immune system. Also transmission to animals will not cause significant infections in animals. Overall transmission by shedding into the environment will unlikely be a hazard due to low amount (less than clinical dose) of exposure. The good practice document provides a template for a specific ERA, which is only applicable to AAV vector products not capable of formation of replication competent virus and demonstrating that the transgene is not harmful. Austria, Belgium, Croatia, Czech Republic, Denmark, Finland, France, Germany, Hungary, Ireland, Italy, Latvia, Luxembourg, the Netherlands, Portugal, Romania and Spain endorsed the common application form; however, country requirements are still to be respected and several applications are required, especially if different sites are concerned or the trial is assessed under the contained use framework.
Harmonized and simplified GMO application:
Under the following conditions the common application forms and specific environment risk assessments (ERA) can be used:

- The IMP consists of human cells genetically modified by means of retro/lentiviral vectors, and
  - There is no risk of formation of replication competent virus, and
  - The IMP is free of infectious viral vector particles that can be released in the environment.
- The IMP contains or consists of adeno-associated viral vectors (AAV)
  - There is absence of formation of replication competent virus and
  - The transgene is not harmful.

2.1.4 GMOs under the new EU Clinical trial regulation

The EU Clinical Trial Regulation No 536/2014 becoming applicable once the EU portal is functional (presumably not before 2021) is without prejudice to Directive 2009/41/EC (contained use of GMOs) and Directive 2001/18/EC (deliberate release of GMO). The Clinical Trial Regulation does not address GMOs, and the EU portal will not have the possibility to submit ERA or other GMO documents. Stakeholder associations drafted a catalog of proposals on how to ensure competitiveness of future research activities within EU to overcome this un-harmonized hurdle in the new streamlined process of clinical trial applications.36 A working group at EU commission has been established to ensure effective application of CT Regulation and GMO legislation. A Questions and Answers document has been published on the European Commission website31 and describes the interplay of clinical trial application and GMO application in the current situation, but also with view on the new Clinical Trial regulation No 536/2014. A prior authorization under the GMO framework can no longer be a prerequisite for the clinical trial approval, and a CTA following Regulation (EU) No 536/2014 cannot be rejected due to lack of GMO approval. Currently prior authorization of the GMO is required when submitting CTAs in Poland, Slovenia, Slovakia, Romania and Bulgaria.16,31 However under the new procedure the Competent Authorities and the Ethics Committees will jointly review the CTA. Though CTA approval has been obtained, the GMO legislation has still to be respected, so that a clinical trial cannot start until GMO approval has been issued on a country level.

CAR T-cell therapies engineered for cancer therapies by using lentiviral vectors such as the aforementioned Kymriah, a retroviral vector such as Yescarta, or in vivo gene therapies such as Luxturna, using AAV viral vectors will profit from the harmonized procedure and bring products to market earlier.
2.2 GMO in clinical trials in US

The National Institutes of Health (NIH) Office of Science Policy (OSP), responsible for the safety of biomedical research, and the FDA streamlined their review process “to eliminate duplicative review and reporting requirements for human gene transfer protocols.”

Initially the review of gene therapy protocols by the “Recombinant DNA Advisory Committee” (RAC), an institution founded in 1974 by NIH for evaluation and advice, was mandatory for all clinical trials with gene therapy; however, from April 2019 onward the registration and reporting requirements were removed from RAC and such protocols will only be reviewed by FDA. RAC also renamed to Novel and Exceptional Technology and Research Advisory Committee (NExTRAC) providing advice on emerging biotechnologies in recombinant or synthetic nucleic acid research field.

In addition, as with all NIH-supported research gene therapy research remains subject to the NIH oversight. Biosafety incidents occurring during the conduct of GMO studies are to be reported to NIH/OSP in accordance with NIH guidelines.

Rigorous local oversight will continue to be provided by Institutional Review Boards and Institutional Biosafety Committees (IBC).

IBCs are the institutional bodies responsible for oversight of activities involving biohazardous materials as required by the NIH Guidelines. IBCs evaluate the sites’ capability for safe storage, handling, administration, and disposal and shedding of gene-modified, biohazardous materials. The IBCs are responsible for establishing guidelines and implementing practices that ensure safe usage of all infectious agents, recombinant or synthetic nucleic acids, biological toxins and human samples within the research laboratories in accordance with federal, state and local regulations.

Approval timelines of clinical trials with IBCs vary by committee and may run prior to, in parallel, or sequential to traditional IRB/EC approvals, typically adding 60 to 90 days to the approval process. The Principal Investigator (PI) is notified of the result following any IBC meeting in which the application is discussed. A patient cannot be enrolled at the site until the IBC approval is obtained.

2.3 GMO in clinical trials in Australia

Prior to starting a GMO trial in Australia, consultation with the Office of the Gene Technology Regulator (OGTR) is required to determine any obligations under the Gene Technology Act 2000 (GT Act) and the Gene Technology Regulations 2001. The type of GMO trial approvals are as follows:

- Genetically modified products that do not contain live GMOs, and which cannot give rise to infectious agents when introduced into host cells, are not regulated under the act.
- GMO that is a modified human somatic cell, including autologous cells might be classified as an exempt dealing under Schedule 2 of Regulations. “For exemption, the somatic cell must not be capable of producing in infectious agents as a result of the genetic modification. Additional, if a viral vector was used, the vector must no longer be present in the cell and must not contain viruses likely to recombine with introduced general material.” TGA may require confirmation before the CTX application. In this case, intentional release of GMOs into the environment is not allowed.
• All other GMOs require approval depending on the type of product:
  - Dealing Not Involving Intentional Release (DNIR) license is required, if the GMO is not likely to be shed or exposed into environment,
  - Dealing Involving Intentional Release (DIR) license is required, if the viable GMO has the potential to be shed, excreted or transmitted into environment

• Some DNA vaccines are excluded from regulation if incapable of giving rise to infectious agents and not encapsulated. If DNA vaccines are encapsulated (coated in a protein, lipid or other nanoparticle):
  - DNIR license is required, if no infectious agents will be produced,
  - DIR license is required, if potential GMO infectious agents will be produced, when administered

Licenses are considered based on suitability. Because license holders assume certain responsibilities and legal obligations imposed by the GT Act, organizations operating in Australia such as universities, hospitals and companies are usually considered. License holders require accreditation. Both applications can be submitted at the same time. License applications must be endorsed by an Institutional Biosafety Committee (IBC) prior to being submitted to OGTR, and IBCs are usually associated with accredited organizations. An application can be endorsed by the IBC of another organization when the submitting organization does not have its own IBC. The IBC must have appropriate collective technical and scientific expertise to review the application.

An application for a GMO license for a clinical trial can be submitted to the OGTR at the same time as seeking approval from an HREC and the TGA (if required). All clinical trials must be conducted in accordance with requirements of the Therapeutic Goods Act 1989, regardless of its GMO status. If the experimental development is conducted under a CTN scheme, the HREC is responsible for initial ethical review and scientific review. The clinical trial application usually needs to follow the CTX scheme; however, if the product has been approved by another country’s regulatory agency accepted by TGA and assurance of acceptable quality and safety is available, the CTN scheme might be accepted.

2.4 GMO in clinical trials in Japan

In Japan, pharmaceutical products containing GMOs are regulated as Regenerative Medical Products (RMPs). RMPs in Japan are defined as processed live human/animal cells that are intended to be used for 1) the reconstruction, repair, or formation of structures or functions of the human body or 2) the treatment or prevention of human diseases, or for gene therapy. RMPs were introduced as a new product category in the revised Pharmaceuticals Affairs Law (the Pharmaceuticals and Medical Devices Law), enacted in 2014.

Investigational medicinal products and their ingredients/materials containing GMOs are regulated under the Cartagena Act, the law to regulate the use of Living Modified Organisms (LMOs) in Japan, which was implemented from the internationally agreed Cartagena Protocol on Biosafety in 2007. Therefore, when the Cartagena Act is applied, pharmaceutical products containing GMOs require an approval and/or a confirmation of the Minister of Health, Labour and Welfare (MHLW) prior to submission of clinical trial notification (CTN) to the Pharmaceuticals and Medical Devices Agency (PMDA). In the Cartagena Act, uses of products are separated into two types as described below. Application according to classification is required depending on how the product is used in Japan.
To facilitate these Cartagena related application process related to the clinical trials, the PMDA newly introduced the consultation category of the Cartagena Act in April 2019, which consists of three categories as shown below.

<table>
<thead>
<tr>
<th>Consultation Categories</th>
<th>Contents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-application consultation for Type I use</td>
<td>To consult the sufficiency and appropriateness of the application documents for Type I use</td>
</tr>
<tr>
<td>Pre-application consultation for Type II use</td>
<td>To consult the sufficiency and appropriateness of the application documents for Type II use</td>
</tr>
<tr>
<td>Consultation on matters relating to the Cartagena Act</td>
<td>To consult the applicability to the Cartagena Act and advise on the technical requirements for the Cartagena Act</td>
</tr>
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In addition, as clinical trial related consultations, Regulatory Science (RS) General Consultation and RS Strategy Consultations (R&D) are also available for RMPs. In order to confirm whether product quality and safety could suffice to initiate a clinical trial in Japan, RS Strategy Consultations on the Quality and Safety of RMPs are recommended to be held prior to submission of CTN in addition to the Clinical Trial Consultation.

2.5 GMO in clinical trials in China

NMPA has incorporated GMO into drug management systems. GMO production needs to be strictly in accordance with GMP standards; safety and efficacy should be assessed through scientifically designed clinical trials. In China’s current Drug Registration Regulation, GMO is listed as category 3 of therapeutic biological products.
Since 2017, pre-IND meeting with Center for Drug Evaluation (CDE) has been encouraged by the NMPA, to discuss the protocol design or other critical development questions. It is highly recommended to have a pre-IND meeting prior to starting a GMO trial in China. The pre-IND meeting allows researchers to gather important advice and understanding of requirements. Currently, it takes approximately two to four months to get a response from CDE. CDE will make the final decision on whether a face-to-face meeting or written response is appropriate.

After getting alignment with CDE of the application, IND can be submitted. It takes 60 working days to get the approval notification from CDE.

For the data obtained from past non-registration purpose GMO trials initiated by clinical site, CDE is open for discussion.

2.6 GMO in clinical trials in South Africa

In South Africa the GMO must be submitted to South African Health Products Regulatory Authority (SAHPRA) and Department of Agriculture, Forestry and Fisheries (DAFF) for GMO approval. The GMO application is a separate submission and can be performed in parallel to the SAHPRA application. DAFF approval is a condition listed for full approval from SAHPRA. As timelines are sometimes longer than the SAHPRA review, it is recommended to start the GMO application shortly before the SAHPRA submission, which usually has timelines about five to six months (120 working days).

First, three advertisements in two local newspapers and one national newspaper need to make the GMO trial public. Within 30 days from date of publication of the articles, the public can raise objections. Within seven days of the publication of the advertisement, the submission must be sent to DAFF along with a copy of the publication in each of the newspapers. The application consists of two documents – import application and trial release application. The Advisory Committee (AC) is a panel of independent scientists that evaluates all applications.

The Executive Council (EC) then issues the GMO approval.43

The timing of the application is crucial. DAFF has six meeting dates that have to be considered for the application. The decision to approve the trial will be made at the meeting.

The GMO license will cover any activity with GMO, such as importation, exportation, transit, development, production, release, distribution, storage and use.44 For GMO under contained use, according to GMO regulation (§2),45 a permit is not required, as long it is a GMO of containment level 1 or 2 and the site, where contained use of a GMO takes place, is a registered facility.46

Clinical trial applications to SAHPRA must be submitted by the due date according to a schedule published annually on the SAHPRA website. The CTA will then be reviewed at the next Clinical Trial Expert Committee (CTC) meeting, which takes place six times a year. The overall timelines for the approval are determined by the responses to CTC questions, the availability of the DAFF approval and the final ratification by SAHPRA.
3 Study on the Implementation of a Global Trial with a GMO: Country and Site Selection

The case study presented in this document is based on Syneos Health global experience in clinical trials with GMOs.

3.1 Region/country selection

As discussed above, due to the variety and complexity of applicable legislations, feasibility for global clinical trials with GMOs should be as extensive as possible.

In our case, Syneos Health conducted the GMO study feasibility in eight different world regions and 30 countries, in order to identify 100 eligible sites (Figure 4). Search was conducted in North America (Canada and US), Central America (Mexico), South America (Argentina, Brazil, Chile, Colombia, Peru), Africa (South Africa), Europe (Czech Republic, Denmark, Hungary, Netherlands, Poland, Romania, Russia, Serbia, Spain, Sweden, Ukraine, United Kingdom), Middle East (Turkey), Asia (China, Malaysia, Pakistan, India, South Korea, Taiwan, Vietnam), and Australia.

The result of the feasibility yielded the following lessons:

- Applicable legislation on clinical trials with GMOs was absent in many of these countries; therefore, any potential constraints on the conduct of the study needed to be checked at individual site level, even during feasibility.

- Initial country/site selection was based on individual investigator’s interest. However, as site selection proceeded, sites initially selected were dropped out, because of the lack of adequate site facilities and/or reluctance of pharmacy staff to manage GMO products.
3.2 Site selection

During the site selection process, Syneos Health assessed the availability and willingness of all potential stakeholders to participate in the GMO clinical trial.

These stakeholders included the principal investigator and team; the head of the pharmacy and pharmacy staff; the nurses and personnel in charge of administering the study drug to the patients; and, in some instances, the Local Safety Committees and/or Working Councils at each institution.

Failing of one of the stakeholders to agree/approve the participation in the GMO clinical trial would lead a site to drop out of the study. In order to avoid this risk, and to facilitate the sites’ compliance with GMO guidance on conduct of clinical trials, Syneos Health developed a Site Standard Operation Procedure (SOP). Syneos Health provided extensive SOP training in local language for site staff and pharmacists, both prior to and during the study.
The SOP template included the following sections/topics, which were adapted individually, at site level:

- GMO Investigational Product (IP) Package, reception and storage conditions at site
- GMO Biosafety Level, description of personal protective equipment (PPE) needed, laboratory personnel training in handling pathogenic agents, contamination prevention/sharp items, use of physical containment equipment such as biosafety cabinets/hoods, limited access to the laboratory, use of biohazard signs
- GMO risk information: routes of exposure, anticipated effect of exposure, first aid measures, notification obligations in case of accidental spills
- In-house GMO transportation and traceability
- Procedure for GMO administration to the patients
- In house biohazard waste disposal

3.3 GMO clinical trial application

To streamline the clinical trial application and the required GMO approval in many countries, a core GMO documentation was prepared as required for EU countries, following the regulation for deliberate release in EU. The technical file in accordance to Annex IIIA and ERA in accordance to Annex II of Directive 2001/18/EC following the EMA guidance for ERA on GMO medicinal products as described in Section 2.1.1 were prepared. Using these documents, the country-specific forms were filed, if required by country regulation. Countries such as Poland regarded the GMO as contained use Class 1, the risk assessment was adapted as described in Annex III of Directive 2009/41/EC for contained use. Non-EU countries also used the same core documentation either in the same format or adapted to country requirements.

3.4 Lessons learned

Some of Syneos Health lessons learned during the conduct of this global study with a GMO:

- Classification of the GMO and evaluation of the risks for human health and the environment, through direct or indirect exposure, with immediate or delayed effects, is challenging, as national GMO legislation is different. Drafting of core documents for the technical information and the risk assessment facilitates the preparation of the country submissions.
- Systematic reconfirmation of regulatory pathways with sites and all authority stakeholders for the different levels of approvals (country, region, site) ensures full compliance with GMO and clinical trials requirements. Well-coordinated submission timelines also avoid lengthy delays of the start of the clinical trial.
- Early site staff training, in local language, is critical to overcome any potential cultural/personal prejudices on working with GMOs.
- Storage of GMOs at the site pharmacy will usually require an individual storage space (cabinet, fridge, freezer), even if risk of cross-contamination with other drugs is minimal. This contingency has to be planned in advance, to minimize cost.
- Time slots for the use of biosafety cabinets need to be discussed/negotiated well in advance, as GMO IP preparation can interfere with the daily workflow at the institution.
Site staff training includes how to address patient education topics, to address GMO related questions and overcome potential fears.

In summary, the conduct of clinical trials with GMOs requires additional regulatory and operational considerations, including GMO core documentation for the GMO approval procedure, and the creation of a specific SOP. The SOP guarantees that the study is conducted in compliance with the optimal GMO management guidelines. The further adaptation of this SOP to the site-specific requirements, including all stakeholders, and its extensive training, performed in local languages, guarantee the safety of site personnel and patients. Extensive training, performed in local languages, guarantees the safety of site personnel and patients. For an interplay of GMO with all activities in Good Clinical Practice (GCP) area, see Figure 5.

Figure 5: Good clinical practice with GMO as a medicinal product

4 Summary and Conclusion
Genetically modified organisms need special consideration for clinical trial applications; additional GMO authorities’ approvals according to the regulation of the country have to be obtained.

Either the GMO requires specific containment measures to limit the contact with the environment (contained use) with focus on biosafety classification of the risk and its minimization by implementing appropriate control measures, or it is not contained use (deliberate release) with focus on the impact on human health and the environment to be provided in an ERA.
In Europe clinical trials with GMO medicines viewed as deliberate release have to follow Directive 2001/18/EC; the contained use GMO follow Directive 2009/41/EC. Although the approaches of the two directives are different, both require a risk assessment that will be evaluated by GMO boards. While in some countries a single application to the Competent Authority is sufficient and the CTA approval includes the GMO approval, other countries require interaction with different national and/or regional GMO boards, some with lengthy review timelines that can delay the start of the clinical trial by up to 12 months.

To overcome these hurdles some processes have been initiated, and agreement has been made among the member states to harmonize the application, as recently with IMPs of human cells genetically modified by means of retro/lentiviral vectors or in vivo gene therapy products that contain or consist of AAV.

Other initiatives and harmonization of GMO applications of IMP of other categories are urgently awaited.

A streamlined and harmonized process would be desirable in Europe to be competitive concerning biomedical innovation and development of gene therapies. Furthermore, the GMO application should be aligned with the new Clinical Trial regulation No 536/2014. The advantages from the new Clinical Trial Application will not become visible if separate GMO applications on country level still apply in Europe. Sponsors might avoid running clinical trials in Europe, and patient access to innovative treatments could be delayed or impeded.

In the US, the NIH office for the safety of biomedical research and the FDA recently streamlined their review process to eliminate duplicative reviews and reporting requirements for GMO protocols. The FDA will review such protocols. NIH-funded research projects with recombinant or synthetic nucleic acids remain under NIH oversight, follow the NIH guidelines and require approval of an IBC to ensure safe usage of GMO or infectious material.

In Japan PDMA recently introduced a consultation process to facilitate the GMO application to Minister of Health, Labour and Welfare. GMOs are regulated as RMP, and under the Cartagena Act Consultations on the Quality and Safety of RMPs are basically required prior to submission of CTN.

In China consultation with CDE in a pre-IND meeting is highly recommended for GMOs. GMOs are regulated as therapeutic biological products of category 3 and have to comply with GMP safety standards. There are no special biosafety approvals required prior to CTA approval by NMPA.

In Australia, GMO products require approval from GMO-regulating agency OGTR independent from the CTX approval process (or the CTN, if applicable). License holders require accreditation, and the application has to be endorsed by an IBC.

In South Africa DAFF is responsible for the GMO approval. Prior application publication in three newspapers is required. The applications need to cover the import and export, as well as release and the handling in the hospital. SAHPRA CTA approval procedure is the same as for other products, but full CTA approval will only be received after DAFF has issued the GMO approval.
Each country follows its own process for GMO trials, with additional approval timelines, which prolong the start-up of the clinical trial. Sometimes interpretation is different among the countries, regions, and regulatory bodies, as GMO review processes are often created for GMOs in agricultural products and are not aligned to IMP release.

A globally harmonized framework for the assessment of GMO IMPs is urgently needed. However, the challenges faced in the above-mentioned case study could be overcome with well-prepared core documents that were used for all countries with the appropriate country adaptations.

In order to perform smooth approval processes for the clinical trial, as well as for future marketing applications, early involvement of regulators that offer expedited programs are strongly recommended, as PRIME in Europe or diverse programs offered by FDA in US such as RMAT. The success of Kymriah and Yescarta was due to a well-planned development program agreed upon with regulators.

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THE CHALLENGE OF GMO MEDICINAL PRODUCTS IN CLINICAL TRIALS

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