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DATE	20 August 2021
REFERENCE	CGM/210820-01
SUBJECT	Advice following the European consultation on the authorisation process of GMOs in medical applications

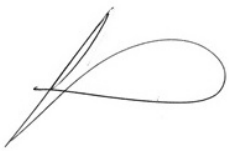
Dear Ms Van Nieuwenhuizen,

In response to a request for advice from the Ministry of Infrastructure and Water Management (IENW/BSK-2021/204176), regarding a consultation from the European Commission (EC) to the member states concerning the environmental risk assessment of clinical studies with GMOs, COGEM would like to inform you of the following.

Summary:
The Ministry of Infrastructure and Water Management has asked COGEM whether an environmental risk assessment is necessary for all clinical gene therapy applications, and whether generic criteria can be drawn up for medical GMOs that require a more or less extensive environmental risk assessment.
The term gene therapy covers a wide range of applications. For some applications of gene therapy, the nature of the GMO and the acquired experience with risk assessments suggest that there is room to simplify and facilitate the authorisation process. COGEM has implemented this by drawing up a number of generic environmental risk assessments. These advices have been converted or are being converted into a set of standard licence conditions (so-called Vergunning onder Vaste Voorwaarden, or VoV) in the Netherlands. This will make it possible to authorise most current gene therapy applications at an accelerated rate without requiring an additional environmental risk assessment.
COGEM notes that it would be advisable for such a system or a comparable one to be introduced throughout the EU, also in the context of harmonising regulations and the authorisation process between member states.
Because of the wide range of potential applications of gene therapy with GMOs, COGEM is of the opinion that it is not possible to draw up generic criteria beforehand, on the basis of which the safety of human health and the environment for all gene therapy applications is ensured. The process by which authorisation is granted should be a learning system, that allows for generic environmental risk assessments to be drawn up for other GMOs in the future, based on the knowledge and experience gained. These could then be incorporated into similar VoVs to speed up and simplify the authorisation process.

The attached report contains COGEM's advice on this topic and a discussion of the underlying reasoning.

Yours sincerely,



Prof. dr. ing. Sybe Schaap
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- Drs. K.E. Kok, Ministry of Health, Welfare and Sport
- Y. de Keulenaar, Head of the GMO Office

Advice following the European consultation on the authorisation process of GMOs in medical applications

COGEM advice CGM/210820-01

1. Introduction

COGEM was asked for advice by the Ministry of Infrastructure and Water Management (IENW/BSK-2021/204176), following a consultation from the European Commission (EC) to the member states concerning the environmental risk assessment of clinical studies with GMOs. This consultation was prompted by a study into new genomic techniques by the EC, which concluded that the legislation for genetically modified organisms (GMOs) is no longer sufficiently in line with current practices. The EC has indicated that it is planning to review the GMO legislation for plant breeding for various new genomic techniques. For adjusting the regulatory requirements for the use of GMO's in medical applications, the EC refers to the Pharmaceutical Strategy.[1,2] The aim of the consultation is to identify and gather experiences with environmental risk assessments during the authorisation process of medical GMOs in the different member states.

The Ministry of Infrastructure and Water Management (I&W) has requested advice from COGEM in response to this consultation, specifically asking answers to the following two questions:

- Currently, generic environmental risk assessments exist for certain medical applications, which means that these applications no longer need to be assessed on a case-by-case basis. Stakeholders have suggested that environmental risk assessments may not be necessary in all cases, or could even be abolished altogether for clinical applications involving GMOs.[3] What is COGEM's opinion on these developments?
- Is it possible to draw up criteria for medical GMO applications that require a more or less extensive environmental risk analysis or for which no environmental risk analysis is necessary?

1.1 Gene therapy

Gene therapy is a catch-all term, and many different definitions are used. The legal definition of a clinical gene therapy study is:[4,a]

> "*Clinical research in humans either involving activities with genetically modified organisms (GMO), or whereby genetically modified cells can be created in the human body, or whereby changes are made to the genetic material of human cells.*"

The legal definition differs from the scientific terminology. Scientifically, the term gene therapy refers to a modification of the hereditary material of (somatic) cells of a patient or test subject. Currently, a wide range of different genetically modified (GM) viruses, so-called viral vectors, are used to modify

[a] This definition is in line and concordance with the descriptions and definitions of cell and gene therapy contained in the various European Directives and Regulations.

hereditary material. The introduction of a GMO into the human body (GM viruses, GM bacteria or GM parasites) for other purposes in which no changes are made to the hereditary material, such as in vaccine research, also falls under the legal definition of gene therapy. This advice follows the legal definition of gene therapy.

Gene therapy seems to be on the rise, and the potential of gene therapy for the treatment of various types of cancer, (auto-)immune diseases, hereditary diseases and for the prevention of viral infections is being researched. By far the most clinical applications of gene therapy have been treatments with GM cells, which involve genetically modifying cells from the patient (or a donor) outside the body using a viral vector before reintroducing these cells into the patient (ex vivo gene therapy),[b] and the use of adeno-associated virus (AAV) vectors, which are administered directly to the patient or test subject (in vivo gene therapy). Some of these treatments with GMOs have received a European market authorisation.[5,6,7,8,9,10,11] In addition, several so-called vector vaccines have been approved in Europe, including vaccines against Ebola,[12,13,14] dengue,[15] and recently the Janssen[16] and AstraZeneca[17] adenoviral vector vaccines against COVID-19. European marketing authorisation has also been granted to a vaccine against cholera, based on an attenuated bacterium,[18] and for a therapy with an oncolytic GM virus to treat metastatic melanoma.[19]

2. Generic environmental risk assessments

COGEM is in favour of shortening and facilitating the authorisation process for the application of GMOs where possible, as long as the safety of human health and the environment is ensured. For frequently used GMOs, COGEM has issued generic environmental risk assessments in recent years, allowing for a faster authorisation process. This concerns studies with AAV vectors[20], GM cells transduced ex vivo with retroviral or lentiviral vectors[21,22], replication-deficient adenoviral (AdV) vectors[23] or Modified Vaccinia virus Ankara (MVA) vectors.[24] In the Netherlands, the generic environmental risk assessments for the use of transduced cells and AAV vectors have been converted into so-called sets of standard licence conditions (‘Vergunning onder Vaste Voorwaarden’, or VoV), which significantly shortens the authorisation process.[25] New VoVs will also be drawn up shortly in response to published advices from COGEM. These include clinical studies with AAV transduced cells, and studies with GM cells transduced with a lentiviral vector in which residual infectious vector particles may still be present. The generic environmental risk assessments for replication-deficient AdV vectors and MVA vectors will also be converted into VoVs in the near future. These generic environmental risk assessments and VoVs cover the majority of clinical gene therapy applications.

The generic environmental risk assessments and VoVs issued so far concern certain replication-deficient and replication-incompetent[c] GMOs. There is ample experience with the use of these GMOs in clinical studies and the potential environmental risks of these treatments have been identified, as have the

[b] These studies often involve GM T-cells (immune cells), in which new genetic information for a T-cell receptor (TCR) or a chimeric antigen receptor (CAR) has been inserted into the cell's genome using lentiviral or retroviral vectors. This allows the GM T-cells to carry out a specific immune response to the intended target, the malignant cells.

[c] For a more detailed explanation of the concepts of replication-deficient and replication-incompetent, see section 3.2.

measures that should be taken to mitigate these environmental risks. Based on the available knowledge about these GMOs, certain preconditions have been set in the generic environmental risk assessments and the VoVs derived from them. If these preconditions are met, the likelihood of specific replication-competent GMOs arising and the likelihood of their spreading to third parties is negligible.

3. Categories of GMOs used in gene therapy studies

The possibilities for developing gene therapy applications are extensive and much research is being done on new GMOs with potential clinical use. These concern applications with replication-deficient or replication-incompetent GMOs, but also with replicating GMOs. In the advisory report *Beoordeling van risico's voor derden bij gentherapiestudies* ('Assessment of third-party risks in gene therapy studies', published in January 2020)[26], COGEM briefly addressed the environmental risks of gene therapy with GM somatic cells, with replication-deficient GMOs or with replication-competent GMOs. These GMO categories will be discussed further in the following paragraphs.

3.*1 Ex vivo genetically modified cells*

Treatment with GM cells which are modified outside the body using viral vectors, is widely studied in clinical trials. As human GM cells cannot survive outside the body, and blood contact or exchange of cell material is necessary for transmission, the chance of unintended spread of GM cells to third parties is very small. Risks to third parties cannot be ruled out entirely, for example in the case of tissue or blood donation, tissue or organ transplantation, or a future pregnancy and subsequent breastfeeding. The assessment of these risks is covered by other authorities that can take measures to control these risks (see also the earlier COGEM advisory report *Beoordeling van risico's voor derden bij gentherapie-studies*).[26,d]

The viral vectors used to modify (or transduce) the cells can also pose risks to third parties.[22,e] These vectors are replication-deficient and are removed from the final medical product through washing and inactivation steps, after which the GM cells are administered to the patient.

As previously described, the authorisation process for these studies has now been greatly simplified. The preconditions for the use of these applications in clinical studies have been defined in a number of generic advisory reports by COGEM[21,22,27] and converted into VoVs. If applications with GM cells fall within the framework defined by the preconditions of the generic environmental risk assessments and the VoVs, the risks for human health and the environment are negligible. COGEM notes that these applications qualify for accelerated authorisation, which has already been achieved in the Netherlands.

[d] A potential risk of treatment with GM cells (immune cells) at a young age is the possible transfer of these GM cells to the foetus during a future pregnancy. However, whether transmission occurs, and how transmission would affect the foetus is still unknown, as this has not been studied. In this case, the risk cannot be mitigated, but the patient and parents/carers must be informed by their attending physician.

[e] In most cases, these are retroviral vectors derived from Moloney murine leukemia virus (MoMLV), or lentiviral vectors derived from Human immunodeficiency virus 1 (HIV-1), although AAV is also occasionally used for cell transduction.

3.2 Replication-deficient and replication-incompetent GMOs

In clinical gene therapy studies other than those described above, replication-deficient or replication-incompetent GMOs are administered directly to the patient. Replication-deficient or replication-incompetent GMOs are unable to replicate and spread due to the absence (or disruption) of one or more critical genes. A GMO is said to be replication-deficient when it lacks the (essential) genes that are involved in the replication of the genome. A GMO is replication-incompetent when the genome can still be replicated, but there are other obstacles that block the formation of new GMOs. In replication-incompetent viruses, for example, the structural genes may have been deleted. In both cases, the vectors cannot multiply after the initial infection. Most replication-deficient or replication-incompetent GMOs are derived from viruses, but clinical studies have also been conducted with replication-incompetent GM malaria parasites, for example. These GM parasites have been modified in such a way, by one or more mutations, that they can no longer complete their life cycle.[28,29,30,31]

There are no clear-cut criteria for defining a GMO as either replication-deficient or replication-incompetent. Therefore, a separate assessment must be carried out for each type of GMO. In addition, it is possible for GMOs to regain their ability to spread, for example, by acquiring compensatory or reversion mutations in the genome. Deleted functions can also be restored by recombination with a wildtype parent organism or related organism that is present in the patient, or they may be compensated or mobilised by complementation. Through recombination, a new replication-competent variant of the GMO could be created with different properties than the parent organism. In the environmental risk assessment of these GMOs the risks associated with these scenarios are considered, which depend on the pathogenicity, the biological properties of the parent organism in combination with the mutations that are introduced, the way the GMO is produced and the possibility of exchanging genetic information with related organisms.

Because these factors can vary widely, COGEM does not consider it possible to determine, beforehand, a generic set of preconditions for all clinical studies with replication-deficient and replication-incompetent GMOs, in order to conclude that the environmental risks are negligible.

3.3 Environmental risks posed by replication-competent GMOs

Clinical gene therapy may also involve the use of GMOs that are capable of multiplying or spreading in the environment. Such replication-competent GMOs often contain mutations, deletions or insertions that reduce the pathogenicity of the GMO compared to the organism from which it is derived. In most cases, these concern GM viruses, but clinical studies are being conducted with GM bacteria or GM parasites as well. Research is also being done with so-called 'conditionally replicating' GMOs, which are only able to replicate under certain conditions. One example is the use of oncolytic GM viruses, which are modified to multiply specifically in cancer cells with the aim of destroying these cells.

In gene therapy with replication-competent GMOs, the conditions under which and the extent to which the GMOs can replicate depend on the parent organism and the genetic modifications made. Depending on the method of administration and the type of GMO, the GMO may be excreted by the patient or test subject and spread to, for example, hospital staff, visiting relatives or other persons with whom this person comes into contact. Because the GMO is able to multiply, it can, in principle, spread further among the population or in the environment. COGEM regularly recommends that additional

measures be taken in clinical studies to prevent or limit the spread of a replication-competent GMO.[e.g,32,33,34]

In some clinical studies genetically modified animal viruses are used. These involve animal viruses that are capable of infecting humans, but are not transmitted from human to human ('dead-end host'). Also, animal viruses can be modified in such a way that the host range is altered or broadened, in order to also infect human cells.[35] When using GMOs derived from animal viruses, the possibility of spreading to and within animal populations, with possible adverse effects on the animal populations concerned, cannot be excluded altogether beforehand. For these types of clinical applications, it is therefore necessary to also assess the risks of spread of the GMO to animal populations.

In the environmental risk assessment of replication-competent GMOs it is essential to consider, for each GMO, the likelihood of spread in the environment and the possible effects thereof, and whether containment measures are necessary and possible. In addition, the degree of attenuation of the GMO may change due to complementation, recombination or spontaneous reversion during production or after administration to the patient.[36] The extent to which this will constitute an environmental risk depends, amongst other things, on the characteristics of the parent organism, the mutations introduced and the possibility of exchanging genetic information with related organisms. When using GM bacteria or GM parasites, genetic information may be exchanged with other micro-organisms of the same or other species, a process that is called ‘horizontal gene transfer’. This could result in the incorporation of transgenes or other 'new' properties that may have been introduced into the GMO (such as antibiotic resistance genes) in wild-type populations.

4. Conclusion

The Ministry has asked COGEM whether an environmental risk assessment is necessary for all gene therapy applications, or whether such assessments could be abolished altogether. COGEM notes that the term gene therapy covers a wide range of applications. Acquired knowledge and experience have taught us that some applications of gene therapy pose minimal environmental risks, leaving room for the simplification and facilitation of the authorisation process. In the Netherlands, this has been implemented by drawing up generic environmental risk assessments for several replication-deficient and replication-incompetent GMOs, and the corresponding VoVs. If gene therapy studies using these GMOs meet the defined preconditions, they may be authorised at an accelerated rate without requiring an additional environmental risk assessment. In recent practice, the introduction of the VoVs has greatly simplified and accelerated the authorisation process of the majority of gene therapy studies in the Netherlands. COGEM notes that it would be advisable for such a system or a comparable one to be introduced throughout the EU, also in the context of harmonising regulations and the authorisation process between member states.

COGEM was also asked whether generic criteria could be drawn up beforehand for medical GMOs that require a more or less extensive environmental risk analysis. However, due to the wide variety of possibilities for gene therapy applications with GMOs, COGEM is of the opinion that it is not possible

to draw up a fixed set of generic criteria that applications of gene therapy must meet, on the basis of which the safety of human health and the environment can be ensured. COGEM notes that the authorisation process should be a learning system that allows for other generic environmental risk assessments to be drawn up for other GMOs, if the nature of the GMO and the experience with its risk assessment permit such a development. These new environmental risk assessments could then also be incorporated into VoVs to facilitate and accelerate authorisation processes.

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