

## WHY ARE MANUFACTURERS LAUNCHING CLINICAL TRIALS FOR GENE THERAPY OUTSIDE THE NETHERLANDS?

*Sharon van Norden & Renate Bik*

### Introduction

Why are manufacturers launching clinical trials for gene therapy outside the Netherlands? Strenuous efforts are being made around the world to develop a vaccine for the coronavirus as quickly as possible – including in the Netherlands. Recently, it was announced that Janssen Biologics, a Dutch biotechnology company, has developed a possible vaccine and it will test this vaccine no later than September of this year. Partly due to strict Dutch regulations, these tests will likely not take place in the Netherlands. What exactly is going on here? Why is this detrimental to the Netherlands?

### Genetically modified organisms (GMOs)

The reason behind the strict regulations is that the potential vaccine qualifies as a genetically modified organism ("GMO"). Genetic modification is the artificial alteration of certain parts of an organism's genes in a manner that is not possible through reproduction or natural recombination. The technique is, amongst others, used in the production of food and in the development of vaccines or other medicines. A common GMO is, for example, a typical vaccine: here a virus that causes the common cold was made harmless, but still triggers an immune response.

### Clinical research involving GMOs

Clinical trials that test a medicine or a vaccine on humans are a required element in the development of vaccines and other medicines. After completing the clinical trials and obtaining the required permit(s), a manufacturer can launch its developed medicine or vaccine on the Dutch market. The clinical trial is subject to strict rules designed to ensure the participants' safety. In case of GMOs the manufacturer must comply with additional rules. These rules are set out in the laws and regulations governing GMOs ("GMO rules").

### The laws and regulations on GMOs

The GMO rules aim to protect human health and the environment from genetically modified organisms. At the European level, Directive 2001/18/EC on the deliberate release into the environment of genetically modified organisms, and Directive 2009/41/EC on the contained use of genetically modified microorganisms are particularly relevant. Directive 2009/41/EC concerns the situation of 'contained use', which means that specific containment measures are used to limit the contact of GMOs with, and to provide a high level of safety for, the general population and the

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*Sharon van Norden is a senior associate of Baker McKenzie's Dispute Resolution Practice Group in Amsterdam and is a member of the Global Health Care Industry Group. Sharon advises and represents multinational corporate clients on cross-border commercial disputes and regulatory and compliance matters with a special focus on healthcare.*

*Renate Bik is an associate of the Baker McKenzie's Litigation & Arbitration practice group in Amsterdam and a member of the Global Healthcare Industry Group. Renate focuses her practice on advising and representing clients in general commercial and corporate litigation. Furthermore, she advises and represents both domestic and international companies in the healthcare industry on regulatory and compliance matters.*

environment. In the Netherlands, the European rules have been implemented in the Decree on GMOs and the Regulations on GMOs.

The EU does not take a position on whether gene therapy falls under the scope and procedures of either Directive 2001/18/EC or Directive 2009/41/EC. As a result, EU Member States have implemented the two directives in different ways, causing deviations in the daily execution of, among other things, the licensing practices to gene therapy. The Netherlands takes the view that Directive 2001/18/EC covers gene therapy because the GMO could infect the environment after the patient leaves the facility and therefore 'contained use' cannot be guaranteed. For this reason, the gene therapy activities involving GMOs, like GMO related clinical trials, are covered by higher standards and an RE permit (*IM vergunning*) is required.

### **The Dutch authorization procedure**

Under Directive 2001/18/EC, an environmental risk assessment must be carried out prior to the potential contact of GMOs with the environment. In the Netherlands, this environmental risk assessment must be carried out before the application for the RE permit. The environmental risk assessment differs from the risk assessment that must be completed for clinical trials that are qualified as "contained use." Although both assessments aim to protect human health and the environment, their focus and implementation differ. The risk assessment focuses on the safety of the workplaces in which the activities involving GMOs are carried out. By contrast, the environmental risk assessment focuses on whether the risks associated with the intended release into the environment are acceptable. Furthermore, the environmental risk assessment requires more information than the risk assessment. Consequently, it generally takes longer to complete the procedure for obtaining the RE permit compared to the duration of the licensing application procedure or the notification requirement for contained use.

In comparison to other Member States that also apply Directive 2001/18/EC to gene therapy, the authorization procedure takes significantly longer in the Netherlands. In the Netherlands, securing an RE permit takes an average of 12 months. Spain and Sweden also follow Directive 2001/18/EC, but procedures there take an average of three to four months. The length of the Dutch procedure is caused by many different local factors, including workload and the fact that three different authorities are involved (Ministry of Health, Welfare and Sport ("VWS"), Ministry of Infrastructure and the Environment ("IenW") and Central Committee on Research Involving Human Subjects ("CCMO")).

### **Consequences**

Due to the lengthy authorization procedure for gene therapy, numerous manufacturers choose to conduct their clinical trials outside of the Netherlands. According to the report of the Alliance for Regenerative Medicine ("ARM") of October 2019, manufacturers consider the speed of approval by regulatory authorities for launching clinical trials as the second most important reason for choosing a particular country, after the expertise and the skills of the clinical centers and healthcare professionals.<sup>1</sup> Other relevant factors are the health authorities' quality of review and expertise, the place of establishment or country of origin, the costs and the market potential, etc.

It appears that manufactures do not just prefer to launch their clinical trials outside of the Netherlands, they often prefer to avoid Europe altogether. On a global scale, the report shows that Europe is less attractive than North America and Asia when it comes to conducting clinical trials involving GMOs. Over the past five years, 323 new interventional clinical trials of cell and gene therapy have been conducted in Europe. By contrast, 845 new clinical trials took place in North

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<sup>1</sup> Alliance for Regenerative Medicine, "Clinical Trials in Europe: Recent Trends in ATMP Development," October 2019, via <https://alliancerm.org/publications-presentations/>.

America and 736 in Asia. The number of new clinical trials with advanced therapy medical products increased globally by 32% between 2014 and 2018. Whereas in Europe, the number of new clinical trials decreased by 2% during the same period. According to the ARM report, the lower number of gene therapy clinical trials in Europe may be due to the fragmentation of regulatory bodies, the lack of harmonization on various aspects (e.g., donor testing requirements) and the level of investment and risk capital available in Europe. Improving and accelerating the consistent approach for review of GMOs among the Member States is, therefore, critical in order to dissolve any barriers to initiating clinical trials in Europe.<sup>2</sup>

### Chances for the Netherlands

According to a paper published by the Dutch Association for Innovative Medicines, there are a number of reasons why it is important that clinical trials be carried out in the Netherlands. First, clinical trials would give Dutch patients access to new treatments at an early stage. Second, such trials could boost the expertise and improve the quality of the available healthcare providers. After all, healthcare providers gain experience working with innovative vaccines and other medicines, and thus become pioneers in their field. Third, manufacturers will be quicker to set up shop in the Netherlands if the conditions are right in the country for the development of vaccines and other medicines. This will, among other things, mean generating more employment and greater investment in the Dutch economy. Of course, it goes without saying that protecting people and the environment remains a primary interest that must be safeguarded in this regard.<sup>3</sup>

### Plan for improvement

Dutch politicians are aware of the problem concerning the lengthy authorization procedures and introduced regulatory plans for improvement. The past year, the Dutch government has taken several measures to shorten the procedure. Some factors contributing to the duration of the application procedure in the Netherlands have now been adjusted. For instance, the statutory maximum decision period for granting the permits for gene therapy of 120 days, was often exceeded by the National Institute for Public Health and the Environment ("RIVM"). The RIVM has assured the minister that it has adjusted its work processes to such an extent that the statutory procedural deadlines are no longer exceeded. Furthermore, the waiting period of six weeks after the permit is granted has been abolished. The Dutch GMO Office is currently comparing directive-implementation practices in the Netherlands with those in other Member States, in order to gain greater insights into useful practices that the Netherlands could adopt.

On 3 July 2019, the Lower House of the Dutch Parliament passed a motion to improve the regulation of clinical research regarding gene therapy. Arne Weverling, who introduced the motion, noted that Dutch regulations impose more restrictions than other European countries, and that this is harmful for the Dutch innovation climate. Furthermore, Weverling asked the Dutch Government to speed up all potential policy improvements and, where necessary, to create more capacity within the RIVM as a matter of urgency.

On 14 October 2019, the Dutch IenW Minister, who is responsible for the GMO regulations, informed the Dutch Lower House that the problem is urgent and introduced a package of measures. The package aims to improve the permit granting process, shorten procedural timelines, reduce the information requirements, and reduce the differences between the Netherlands and other EU Member States. Moreover, the minister sought the full harmonization of European legislation in order to create a more level playing field among the Member States when it comes to environmental

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<sup>2</sup> ARM report October 2019, p. 1, 2 and 8.

<sup>3</sup> VIG, *Hoe wordt Nederland koploper op het gebied van klinisch onderzoek?*, <https://www.vereniginginnovatievegeneesmiddelen.nl/stream/folder-hoe-wordt-nederland-koploper-op-het-gebied-van-klinisch-onderzoek.pdf>.

legislation in general. The minister confirmed that the Netherlands aims to be internationally competitive when it comes to granting permits for gene therapy.

On 26 March 2020, the Dutch Lower House passed a motion calling on the government to accelerate procedures for clinical trials in order to more rapidly develop and test new medical treatments and technologies in the Netherlands. On 31 March 2020, the temporary regulations on the alternative handling of permit applications for gene therapy relating to the fight against COVID-19 entered into force. Under this emergency regulation, permit applications relating to GMOs that aim to fight COVID-19 will be handled through the regular preparatory procedure, instead of the uniform preparatory procedure. The maximum decision period for granting permits for gene therapy is thereby lowered from 120 days to 28 days. Furthermore, on 15 April 2020, the minister published a draft decree that includes a regular shortening of the decision period for granting permits for most gene therapy applications (from 120 days to a maximum of 56 days). Until the regulations are amended, a maximum decision period of 70 days is envisaged.

### **Conclusion**

The minister's aim is to reduce the length of the permit procedure from 120 to 56 days. Until the regulations are amended, a period of 70 days is envisaged. If a given clinical trial concerns a possible vaccine or other medicine for the coronavirus, authorization may be granted within no more than 28 days. In view of the exceptional situation and in the public interest, it took just a few days to make this reduction a reality. We hope that these are just the first steps toward a faster procedure for clinical trials of vaccines and other drugs. After all, this is entirely in keeping with the ambition of the Netherlands to become a leading European player in clinical research.