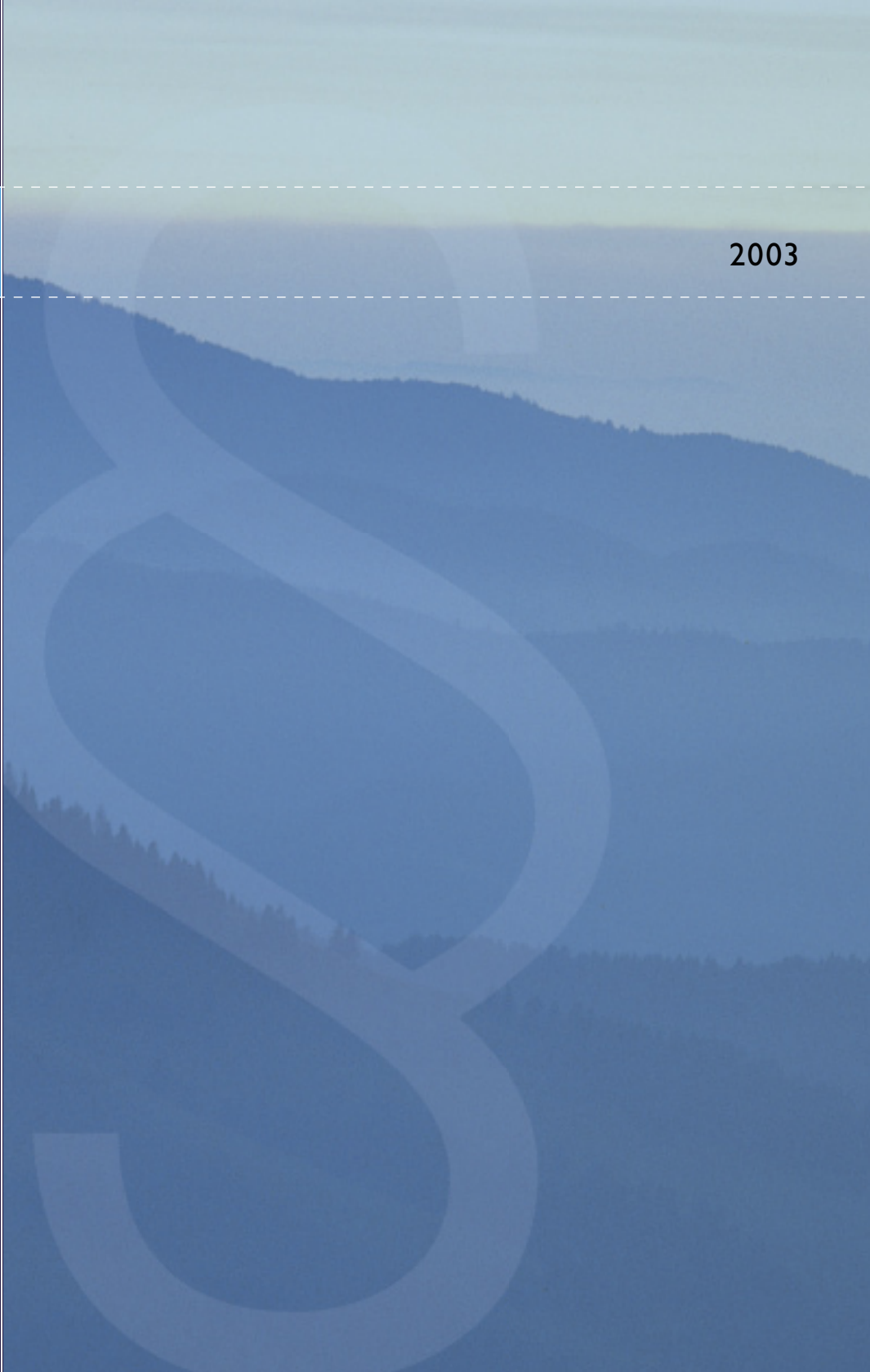


Discussion paper

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Regulation of DNA vaccines and gene therapy on animals

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The Norwegian Biotechnology Advisory Board is an independent body appointed by the Norwegian government and was established in 1991. The Board is founded in the Act relating to the application of biotechnology in medicine and the Act relating to the production and use of genetically modified organisms.

The main tasks of the Norwegian Biotechnology Advisory Board are to identify and examine the ethical questions raised by applications of modern biotechnology on humans, animals, plants and microorganisms, provide advice that can assist policy-making and stimulate public debates on the issues.

The Board consists of 24 members and has observers from six ministries. The Board's secretariat has five to eight employees. For 2003 the budget of the Biotechnology Advisory Board is 6.3 million NOK (appr. 750.000 €).

Preface

At present the Norwegian Gene Technology Act provides no clear answer as to how animals receiving DNA vaccines and gene therapy are to be regulated and whether or not they are to be termed as genetically modified.

The Norwegian Biotechnology Advisory Board raised this problem for the first time at an internal seminar in Namsos on 5 September 2001. In the light of the seminar, the Ministry of the Environment asked the Biotechnology Advisory Board to discuss how DNA vaccines and gene therapy on animals should be regulated and what status should be given to DNA-treated animals.

Since the problem is highly complex, the Biotechnology Advisory Board's secretariat has drafted this discussion paper setting out the various aspects of the issue.

The Biotechnology Advisory Board has discussed regulatory alternatives for DNA vaccines and gene therapy on animals in the light of the internal seminar and the discussion paper. The Biotechnology Advisory Board's recommendations are set out in its reply letter to the Ministry of the Environment dated 26 February 2003, which is an enclosure to this discussion paper.

Dr Grethe S. Foss from the Biotechnology Advisory Board's secretariat has been responsible for preparing the discussion paper, and members of the Biotechnology Advisory Board and the secretariat, specialists and others have provided valuable contributions and comments.

The discussion paper has been translated with the assistance of Ms Anne Bryn and Dr Graham Harrod.

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1. Background for the discussion paper

New and promising methods for preventing and combating disease are now being developed for humans and animals in the form of DNA vaccines and gene therapy. Both methods are based on the transfer of genetic material to cells in the body.

Besides good nutrition and clean water, vaccines have revolutionized public health. Traditionally, weakened or dead disease organisms have been used as vaccines. Most vaccines provide such good protection that the benefits more than outweigh the rare cases of disease that may occur as a result of the vaccine. However, for many disease organisms, especially viruses, it has proven difficult to develop vaccines. DNA vaccines are, moreover, cheap to produce and stable under transportation. Trials are currently in progress to develop DNA vaccines against malaria and AIDS.

In order to gain public acceptance for the use of genes for medical and veterinary purposes, there is a need for information and an appropriate regulatory framework, of which risk assessment must be an integral part.

The methods used in DNA vaccines and gene therapy are similar to those applied in the genetic modification of organisms. This raises the question of whether an animal is to be considered a genetically modified organism (GMO) when it has received a DNA vaccine or gene therapy. If this is the case, the Act relating to the production and use of GMOs (the Gene Technology Act) becomes relevant and regulates the animal's movements in nature as a deliberate release of a GMO. Human beings are not covered by the Gene Technology Act. Hence, under no circumstances, will humans receiving gene therapy be classified as GMOs under today's legislation.

At present, the Gene Technology Act provides no clear-cut answer as to how animals receiving DNA vaccines and gene

therapy are to be regulated. The ambiguity lies in the Act's definition of GMOs as "microorganisms, plants and animals in which the genetic material has been altered by means of gene or cell technology" and more particularly what an alteration of "genetic material" implies. Would there have to be a heritable alteration, or would it suffice if one of the animal's cells had received a foreign DNA fragment? No biological answer to this question is evident and, in this respect, it remains up to the public authorities to define an appropriate regulatory system for human-created technologies.

The problem has become of current interest following specific enquiries made to the Ministry of the Environment and the Norwegian Directorate for Nature Management by two different firms – one wishing to develop DNA vaccines for fish, the other to enhance fish growth through gene therapy by introducing a growth hormone gene into somatic cells in the fish. These firms asked whether vaccinated fish or fish treated by means of gene therapy would be subject to the provisions of the Gene Technology Act. In view of the methods applied, interpretations of the Gene Technology Act and the preparatory work of the Act, the Directorate held that DNA vaccines and gene therapy would be regulated by the Gene Technology Act, which would mean that animals receiving such treatment would be classified as genetically modified.

The Biotechnology Advisory Board raised this issue at a seminar held in Namsos on 5 September 2001, where invited lecturers from industry and public administration discussed DNA vaccines, recombinant living viral vaccines, various risk elements involved and the environmental administration's assessment of the situation to date. On the basis of the different views expressed, the Ministry of the Environment wanted the regulation of DNA vaccines and gene therapy of animals to be assessed on grounds of general principles, pinpointing the various

consequences and considerations that are involved.

The Gene Technology Act is currently due for revision as a result of the new EU Directive (2001/18/EC) on the release of GMOs. In conjunction with such a revision, the authorities wish to define precisely how DNA vaccines and gene therapy on animals are to be regulated.

The Ministry of the Environment asked for the assistance of the Biotechnology Advisory Board in these endeavours. The present paper has been drawn up as an underlying document for discussions on how DNA vaccines and gene therapy on animals

should be regulated. The fundamental and practical aspects of the issue have been set out and possible alternative regulatory methods have been outlined. The various considerations that have been stressed in the GMO debate have been assessed in relation to DNA vaccines and gene therapy on animals, and the major consequences and challenges entailed by the various regulatory alternatives have been set out. Through the work on this discussion paper, members of the Biotechnology Advisory Board and the secretariat, specialists and others have made valuable contributions and comments. The Biotechnology Advisory Board's recommendations for a regulatory system have been set out in a separate document (see enclosure).



Photo: Tom A. Kolstad, Aftenposten / Scanpix

2. Introduction

Throughout the ages, humans have influenced the species and ecosystems of their surroundings. Modern agriculture is the result of millennia of selection and deliberate breeding. The last decade has seen the development of mutants and new varieties by means of radiation and chemical treatment. However, with the advent of gene technology, the power of humans over nature has significantly increased. We are now capable of deliberately changing the heritable material of animals and plants, combining genes from entirely different species and thereby influencing evolution and development to a greater degree and at a swifter pace than ever before. The consequences may be unpredictable and unmanageable. Hence, as far back as 1975, the researchers who developed gene technology also drew up guidelines for the use of this technology. Legislation subsequently developed is based on these guidelines.

The Norwegian Gene Technology Act of 1993 covers living organisms whose genetic composition has been altered by means of gene or cell technology. The deliberate release of GMOs requires an authorisation that is based on an impact study taking into account the environment, health, benefit to society, ethics and sustainable development. Humans are exempted from the Gene Technology Act and are never classified as “genetically modified”. The use of gene technology on humans is instead regulated by the Act relating to the application of biotechnology in medicine (the Biotechnology Act). This Act prohibits any heritable alteration of humans, and the use of gene therapy is restricted to the treatment of somatic cells in persons who are seriously ill and then only subject to special approval, after the Biotechnology Advisory Board and other bodies have had the opportunity of considering the case at hand.

At present, the deliberate release of GMOs is a topic of intense debate and subject to extensive regulation. The genetic modification

of animals raises a question of values that engages many people. Staking out the borderline between what might constitute the medical treatment of an animal and what might entail the genetic modification of that animal will have serious consequences for researchers and manufacturers. Few people would like to see genetically modified salmon in our shops today. If DNA-vaccinated animals are defined as genetically modified, this would, in practice, prevent the use of DNA vaccines on animals, even if such vaccines might be better than today’s vaccines for consumers, the animals, the environment and the manufacturer. On the other hand, if we opt for a liberal regulation of DNA vaccines and gene therapy, the intentions of the Gene Technology Act might conceivably be circumvented, for example, by means of gene therapy with genes that might give the animal new traits and that might also become heritable.

New gene technology applications give rise to new grey areas that the 1993 definition of GMOs has failed to take into account. DNA vaccination and gene therapy may be able to prevent and treat diseases in animals and humans for which there is no treatment today. But the concepts of vaccine and therapy can be stretched. Vaccine trials have been conducted producing immune responses aimed at eliminating the boar taint in pigs and giving ewes more lambs (1). In trials with gene therapy on fish, the addition of a growth hormone gene results in significantly faster growth than in untreated fish. The same effect could be imagined without the use of DNA, as with the direct administration of hormones. But the picture for DNA vaccines and gene therapy is further complicated by the fact that there is the possibility that the genetic material added may move around inside the animal as well as outside in the surrounding environment. Furthermore, there is also the slight possibility that it might become integrated into the hereditary material of the reproductive cells, causing the alteration to be passed to the offspring. The problem becomes all the more difficult

when merely classifying the treated animal as genetically modified, irrespective of whether it has been approved for deliberate release or not, complicates the marketing of the product. Caution must, therefore, be exercised when manoeuvring in such a minefield, and the regulation of DNA-treated animals must be thoroughly assessed and well founded – for environmental, ethical as well as socio-economic reasons.

A variety of arguments have been put forward in the debate on GMO releases in defence of a restrictive approach. Some place emphasis on safe food, others on preventing threats to ecosystems, whereas yet others are concerned about the power balance between developing countries and large multinational companies. DNA vaccination and gene therapy of animals is an area where the benefit to society may be high and where a balancing of different considerations becomes apparent. Considerations that are given the greatest emphasis will underpin the preferred definition of GMOs. If emphasis is placed on preserving the species, the borderline might be determined by whether the alteration is heritable or not. If this is a vital matter of principle, significant importance might also be attached to the small possibility that exists of a naked DNA being spread throughout the body and integrated into the chromosomes of reproductive cells. If the animal's intrinsic value is what counts, any alterations that the introduced gene entails will be of crucial importance, whether it be heritable or not. If the spread of genetic material to other organisms is considered the most important aspect, the deciding factor might then be whether a foreign DNA is still present when the animal dies/is eaten, and perhaps

one might then be more concerned about added, free DNA molecules than about any alterations in the animal's chromosomes. If economics and trade are deemed the most important, it might be appropriate to focus on applying the same regulatory system as our most important trading partners. In addition to all these considerations, it is vital that any regulatory method is biologically well-founded and possible to implement legislatively and in practice.

Since both practical aspects and matters of principle must be considered, there are many ways of looking at the regulation of DNA vaccines and gene therapy on animals. Biologically speaking, one could look at how the genetic material enters, what becomes of it, its function, the techniques applied or what the purpose of the treatment is. In the eyes of public authorities, it might be useful to look at the laws that must be complied with, which mechanisms that are available and what is achievable in practical terms. From a societal perspective, it might be expedient to consider what the consequences of the different regulatory alternatives might be and what is useful and ethically justifiable.

In this document, the biological and legislative framework of the problem have been described first - in Chapters 3 and 4 respectively - followed by a review of possible regulatory methods in Chapter 5. Important considerations that should be assessed and how these are addressed by the different regulatory methods are described in Chapter 6. Chapter 7 provides a summary of the different regulatory methods, with the consequences and challenges involved.

3. Biology: DNA vaccines and gene therapy

3.1 Definitions

The definitions of DNA vaccines and gene therapy vary in literature. Often, gene therapy also encompasses the use of DNA vaccines. The Norwegian Biotechnology Act, which regulates gene therapy on humans, applies this type of broad definition of gene therapy. When discussing DNA vaccination and gene therapy on animals, it might be useful, however, to distinguish vaccine purposes from other purposes. It might also be appropriate to use a specific term to describe the transfer of genetic material not involving the use of genetically modified microorganisms. In this document, therefore, the terms have the following meanings:

DNA vaccine:

The intentional transfer of genetic material (DNA or RNA) to somatic cells for the purpose of influencing the immune system.

Gene therapy:

The intentional transfer of genetic material to somatic cells for purposes other than influencing the immune system.

DNA treatment:

The intentional transfer of genetic material to somatic cells, either in the form of DNA vaccines or gene therapy, in ways that do not entail the use of genetically modified microorganisms.

In gene therapy as with DNA vaccines, genetic material is transferred to some of the animal's cells for the purpose of carrying out a specific function. This function may be fulfilled by the cells producing proteins from the added genes, or by the added genetic material directly influencing genetic material or other molecules in the cell. Genetic material may be transferred either as naked DNA, as encapsulated DNA or via genetically modified viruses, bacteria etc.

In general, the same molecular tools are used in DNA vaccination, gene therapy and

heritable genetic modification. The objective, however, varies, and this is reflected in the choice of elements built into the new genetic material, where and how the genetic material is added and what is focussed on when results are measured.

3.2 DNA vaccines

For some time, it was thought that naked DNA outside living cells would rapidly be degraded. But surprisingly enough, it has been seen that cells in the body are capable of taking up naked DNA and expressing genes encoded by this DNA (2). This discovery has encouraged the development of vaccines based on naked DNA.

Properties of DNA vaccines

DNA vaccines consist of a DNA molecule, generally a circular plasmid, with a gene that codes for the protein against which an immune response is desired. The protein-coding entity is surrounded by regulatory sequences that ensure good protein production. Plasmids will also have a sequence allowing replication in bacteria and often a gene for a selectable marker. The future may see the replacement of antibiotic resistance genes by other less controversial selectable marker genes. DNA vaccines may be administered by a variety of methods. In present day trials, injection is the most efficient method, but other means of delivery are in the process of being developed based on, for example, immersion, spraying, gene gun and electroporation.

DNA vaccines possess new, promising properties compared to earlier vaccines. They are capable of providing a broad, long-lasting immune response, they do not require complete knowledge of the pathogenic organism, they are relatively simple, cheap and quick to produce and they are stable at room temperature and therefore easy to transport and store. To achieve a good vaccinating effect, the DNA vaccine should be present and active for only a short period

of time. During this period, a large amount of protein will be formed, giving rise to an immune response.

Vaccine principles

DNA vaccines are a type of subunit vaccine, in the sense that they produce only a selected protein from a microorganism. In other forms of subunit vaccines, the protein may be purified from the microorganism itself, or it may be produced by means of gene technology by cloning the gene for the subunit from the heritable material of the pathogenic microorganism. Selecting only one component of a microorganism as a vaccine, involves certain limitations. The immune response generated by DNA vaccines is limited to targeting proteins and not other types of complex molecules on the surface of the microorganism. On the other hand, there is little risk that the vaccine itself will cause disease, as it does not contain the other components of the microorganism.

Traditionally, vaccines have been developed in two different ways: either by using dead microorganisms or with the help of attenuated (weakened), living microorganisms. A vaccine consisting of dead or inactivated microorganisms will normally generate an immune reaction against structures on the surface of the microorganism, which in turn will provide protection against later infections. Alternatively, vaccines can be based on variants of living bacteria and viruses that are less pathogenic than those against which protection is required. Variants can be closely related pathological organisms that prefer other host animals (e.g. cow pox) or the pathogenic organism may be attenuated through breeding and selection. For many decades, microorganism attenuation has been used to develop new vaccines in the form of mutant strains. One example is the BCG-vaccine against tuberculosis. There is, however, a certain risk that living vaccines may revert to their pathogenic variant. Today's incidences of polio in the western world are caused by reversion of a living, attenuated vaccine.

Genetic alterations in deliberately attenuated strains are normally unknown or

uncharted in detail, and the microorganisms are classified as not genetically modified. The genetic alterations involved may, however, be fairly extensive. Recently, a comparison was made of the heritable material of the BCG-vaccine with that of the tuberculosis bacterium, and an area of nine genes was identified as missing in the vaccine (3). With the advent of gene technology it is now possible to deliberately alter or remove pathogenic elements in the heritable material of microorganisms. This method is much used for viruses in particular. Genetically modified viruses may be used as vaccines. These are termed *homologous* viral vaccines when the pathogenic virus itself has been modified. Genetically modified viruses may, however, also be used as vectors to produce an immune reaction against proteins from *other* microorganisms. In this instance, the gene for the desired protein is introduced into the heritable material of the vector virus. These are then called *heterologous* viral vaccines or viral vectors.

How vaccines work

Live vaccines will often provide better protection, as they activate a broader part of the immune system than dead or inactivated microorganisms do. Although DNA vaccines are not living, they are more closely related to genetically modified viral vaccines than their name indicates. This is an important aspect to be borne in mind when considering how such vaccines should be regulated. DNA vaccines and viral vaccines both possess certain traits of an ordinary viral infection in the way in which they work. They provide better and more long-lasting protection than vaccines consisting of inactivated microorganisms, since DNA vaccines and viruses both result in genetic material entering *into* the cells, thereby triggering the new production of proteins. Such proteins retain their natural form and are not deformed, as is often the case when microorganisms are inactivated. This leads to the activation of B cells and an antibody response ("humoral immune response") that more readily recognizes naturally existing microorganisms. Moreover, DNA vaccines and viral vaccines activate another branch of the immune system, i.e. the T cells, also called the "cellular immune response".

T cells keep track of what is going on inside the cells of the body by means of a mechanism where fragments of the cell's contents are transported with the major histocompatibility complex (MHC) to the cell surface and presented to the immune cells. In this way, virus-infected cells can be detected and the infection stopped by the T cells killing off the infected cells.

Similarities between DNA vaccines and viruses

Although viruses are, in many instances, called microorganisms, their structure is exceedingly simple and they are dependent on the machinery of host cells to reproduce. Generally, they only consist of heritable material encapsulated by proteins and in some cases a membrane. In the heritable material, many viruses have genes for enzymes that are necessary for the multiplication of the virus. With certain viral infections, therefore, the virus' heritable material alone is sufficient to produce new viral particles. Hence, this type of viral infection can also be formed by the cell taking up naked viral heritable material. A DNA vaccine consisting of complete heritable material from such viruses could, therefore, trigger a new viral infection. Recently, researchers have succeeded in manufacturing infectious poliovirus by means of chemically synthesizing the genetic material (4). This has subsequently raised the question of when naked genetic material is to be classified as an organism. Inversely, it is conceivable that DNA vaccines could be given a viral form by encapsulating the DNA in a viral particle. Since there is the chance of an indistinct borderline between virus and DNA, it is important, when considering appropriate regulatory mechanisms, that DNA vaccines and genetically modified viral vaccines are viewed in the same context.

3.3 Gene therapy

Contrary to DNA vaccination, which aims to produce large amounts of protein in a short span of time so as to generate an immune response, gene therapy is often aimed at achieving a long-lasting, physiologically matched expression of the gene, without activating the immune system. In certain

forms of gene therapy, the aim is even to integrate the genetic material into the chromosomes.

Gene therapy often requires a more targeted and finely tuned technology than is the case for DNA vaccines. In gene therapy, the genetic material must reach the right cells, as well as generate the desired degree of activity. For this reason, the development of gene therapy has not advanced as far as the development of DNA vaccines.

Gene therapy may aim at different objectives. One objective might be to add genes coding for desired proteins, which can either contribute to a new function in the cell or replace proteins that are no longer effective due to harmful mutations. It is also possible to add genetic material that specifically affects the expression of a protein. In this way, genes that code for undesirable or harmful products may be neutralized by inhibiting or preventing the production of the protein. When adding small DNA or RNA molecules that correspond to the desired gene and therefore attach themselves to the gene as antisense, the gene's transcription may be directly inhibited or the gene's mRNA may be prevented from serving as a template for protein production. Some RNA molecules (ribozymes and siRNA) may even be designed so that the gene's mRNA molecules are specifically fragmented.

In order to introduce new genetic material into cells, a series of vector systems have been developed. As for vaccines, the new genes may be delivered with plasmids or viral vectors. Small DNA molecules (oligonucleotides) may be introduced in their existing form, or they may be wrapped into appropriate molecular packages, e.g. liposomes or other vesicles. RNA molecules as well may be delivered directly, but they may also be introduced in the form of a gene that will be transcribed to RNA inside the cell.

The challenges facing gene therapy today reside in the need to achieve good biological and therapeutic effects. To do so, the genetic material must be able to reach the right cells, they must remain there and be precisely as active as required. Systems for the delivery

and targeting of genetic material are being continuously developed and, so far, there are few good strategies for gene therapy.

3.4 Stability of the added genetic material in the animal

DNA vaccines are distinct from gene therapy in that a short-term presence of DNA in the animal is the desired result, whereas gene therapy often aims at ensuring the presence of the added genetic material over a longer period of time.

When DNA vaccines have been added to the body, either by intramuscular injection or other means, most of the added DNA will normally be degraded in a short space of time, while a portion will be absorbed by the cells. Some of the DNA may, however, transfer into lymph and blood and thereby spread to the rest of the body. Spermatozoa are capable of taking up foreign DNA, a phenomenon that is currently being used to develop new methods for the genetic modification of animals by treating spermatozoa with DNA (5) and by injecting DNA into animal testes (6).

In gene therapy, genetic material is often meant to reach a specific type of cell in the body and it may need to move to its destination via the blood. Work is currently ongoing to develop specific molecular tags so as to ensure that the DNA is taken up only by the target cells. Until this problem has been resolved, methods are being used where target cells are more easily accessible. One such example is the trial gene therapy in cancer treatment, where immune cells are extracted from the body, given gene therapy, selected for DNA uptake and thereafter reintroduced into the body.

Once inside the cell, many partly unknown factors will affect the DNA's stability. Without elements enabling DNA replication, it will remain active for a certain period of time and subsequently degrade. How long this will take will depend on both DNA sequence, DNA structure and cell type. To achieve the best effect of gene therapy, work is in progress to optimise the stability

and long-term expression of the genetic material.

If retention of the genetic material in the cells is desired, elements allowing replication in the host cell may be built into the genetic construct. Most plasmids contain an element enabling replication in bacteria, but this element does not normally work in animal cells. Many viral vectors are capable of amplification in animal cells. Some will cause an infection, which will transfer the added genetic material into nearby cells, as well as into the surroundings in the form of viral particles. The most common method for achieving long-term presence in the cell is, however, to use a mechanism that integrates the genetic material into the cell's chromosomes.

3.5 Possible integration into chromosomes

In gene therapy, viral vectors are occasionally used to ensure the incorporation and lasting presence of genetic material in the cell. One viral vector used (adeno-associated virus) even possesses a mechanism enabling its relatively precise integration into a specific area of the human chromosome 19. However, it has been seen that it is also capable of integrating into other areas (7).

There is, however, always a slight probability that added DNA will be integrated into the chromosomes of the cell, independently of whether such integration is intended or not. The probability may vary according to the type of tissue, means of delivery and amount of DNA introduced. The traditional method for producing heritably genetically modified (transgenic) animals makes use of this probability. In such instances, many plasmid copies are injected into a series of fertilized eggs and the DNA will be integrated into only a small proportion of the eggs and thereby produce transgenic offspring.

It is impossible to predict the effects of incidental incorporation. The added gene may be introduced into an area of no consequence or it may end up in the middle of another gene and disrupt it. Hence, receiving gene

therapy and DNA vaccines will involve a certain risk of developing cancer or other diseases, as a result of the effect of the genes at the site of integration. Cases of cancer due to integration have recently led to the halt of several gene therapy trials on humans (8). Such a possibility will exist, irrespective of the type of DNA added. Many integrative mechanisms and transposable elements are based on relatively short sequences, so the use of short DNA molecules provides no guarantee against integration. The likelihood of integration may be reduced by avoiding elements that are known to promote integration and by conducting further research on the stability and properties of genetic materials in the target organism.

If the added genetic material circulates in the body, is taken up by reproductive cells and also is integrated into the chromosomes there, the DNA-treated animal could theoretically produce heritably genetically modified offspring. Gene therapy could conceivably allow the administration of DNA capable of translocating to the reproductive cells and the subsequent selection of offspring possessing properties attributable to integration and heritable genetic modification. Furthermore, such a method might possibly be resorted to if someone wished to misuse a regulatory system that is more liberal where gene therapy is concerned, compared to heritable genetic modification.

Using RNA instead of DNA might possibly avoid the problem of unwanted integration into chromosomes. In the cell, mRNA serves as the link between genes and the machinery for protein production. By adding RNA that functions as mRNA, it would be possible to enter at the post-DNA step of the information ladder and still achieve the required protein production. After DNA vaccines, RNA vaccines appear to be the next step in the field of vaccine development. RNA is already in use in the field of gene therapy. One disadvantage of using RNA is that it is more complicated to produce and less stable than DNA. RNA molecules for use in gene therapy are now being chemically modified to improve their stability. Although RNA is not the heritable material in the animal cell, it still

functions as heritable material in other contexts. Many viruses have RNA as their heritable material instead of DNA. Some of these (retroviruses) possess a gene for the enzyme reverse transcriptase that converts RNA into DNA following infection. In a subsequent phase, the virus may ensure that the DNA version of the heritable material is integrated into the host cell's chromosomes. However, retroviruses require quite specific sequences for conversion from RNA to DNA, as well as for integration. The likelihood of RNA vaccines being integrated while a cell is simultaneously infected with a retrovirus is, therefore, exceedingly small, as long as integrative sequences are avoided.

3.6 New properties of DNA-treated animals

Even if DNA vaccination and gene therapy results in DNA being taken up by only a few cells, it might still be enough to give the animal new physiological properties, in the same way as for genetically modified animals. One such example is the introduction of a growth hormone gene into fish, where the cells taking up the gene secrete hormones that affect the entire animal, producing fish that grow significantly faster. A similar effect could also be achieved without the use of DNA, by giving the fish hormone injections. The difference is that the use of DNA moves the hormone production into the animal itself.

The concept of vaccine may, moreover, be extended to have effects above and beyond that of disease prevention. Immune reactions may be used to alter the hormone balance of animals and change the animal's natural characteristics. But the same effects could also be achieved by means of traditional vaccine methods and without the use of DNA.

Some of the novel properties that could be introduced by means of DNA vaccines and gene therapy might conceivably lead to a selective advantage in the animal's ecosystem, if such properties are inherited. The fact that there is a slight possibility that the added DNA could be integrated and passed on to the next generation could,

therefore, play a role when choosing the type of genes that should be permitted for the DNA treatment of animals. The consequences of DNA treatment using genes that introduce a selective advantage for the animal could

be the same as those of heritable genetic modification, even though their likely occurrence is significantly smaller. With repeated releases, non-heritable properties could also have an ecological effect.



Photo: Stuart McEvoy, EPA / Scanpix

4. Current regulatory framework – national and international

4.1 GMO and DNA under current Norwegian legislation

When defining more precisely the regulation of DNA vaccines and gene therapy on animals, it is important to have a clear picture of what the Gene Technology Act provides for in these areas today. But the Gene Technology Act is not the only piece of legislation dealing with genetically modified organisms.

Choices made in current legislation

The Act relating to the production and use of genetically modified organisms (Gene Technology Act) regulates living, genetically modified organisms in Norway. In this context, GMOs are defined as "micro-organisms, plants and animals in which the genetic material has been altered by means of gene or cell technology". Human beings are not covered by the Gene Technology Act.

As long as a GMO is alive, the Gene Technology Act applies. For dead GMOs or for products produced from GMOs, other legislation applies, depending on the purpose involved. Once a dead GMO becomes food, it is regulated by the Food Act. If used for animal feed, the Animal Feed Act applies. Medical and veterinary medicinal products manufactured with the help of gene technology are subject to the Norwegian Medicinal Products Act. Furthermore, the Animal Welfare Act restricts the type of genetic modifications that may be performed on animals.

Naked recombinant DNA is regulated by the Gene Technology Act solely when the genetic material is included in the production of a GMO. Furthermore, the health and environmental risks of spreading genetic material from the dead organism must be considered when applying for the deliberate release of a living GMO. The Animal Feed Act has introduced a ban on the presence of antibiotic resistance genes in animal feed.

When naked recombinant DNA is used as a medicinal product, it is governed by the Medicinal Products Act.

The Gene Technology Act is restricted to genetic modifications using gene and cell technology. Radiation and chemical mutagens have long been used to produce new, improved strains of species, in research as well as in production, and this has given rise to heritable alterations in the form of genetic mutations. Some of these mutations present altered properties – in a positive or negative way – whereas the majority of such mutations are not apparent. The use of mutagens or radiation is not regarded as genetic modification, even though the purpose, in these instances as well, has been to achieve alterations in heritable properties.

Below follows a review of other legislation that is particularly relevant to the regulation of DNA vaccines and gene therapy on animals. The Gene Technology Act itself is dealt with in sub-chapter 4.2.

Food Act

When mentioning the regulation of genetically modified foodstuffs, the Food Act refers to the Gene Technology Act's definition of a GMO. It seems logical, therefore, that the administration of the Food Act should comply with the regulatory system applying to DNA-treated animals as stipulated in the Gene Technology Act. In consequence, an interpretation of DNA-treated animals as GMOs would require the approval and labelling of products from such animals in Norway. When importing similar foodstuffs from abroad, these too would in principle have to be labelled as GMOs, but, in that case, only after the product has been approved by the Norwegian Food Control Authority (SNT). Such approval may, however, be granted without the same comprehensive impact study that is required for the deliberate release of living GMOs. When applying for approval, health

effects will be examined, in addition to other societal considerations.

The Norwegian Food Control Authority also administers the Regulation on maximum residue limits for veterinary medicinal products in foodstuffs of animal origin, which includes “provisions on the determination of maximum residue limits for veterinary medicinal products in all foodstuffs of animal origin, including meat, fish, milk, eggs and honey. The Regulation does not apply to active substances of biological origin that are intended to produce active or passive immunity or to diagnose a state of immunity, and that are used in immunological veterinary medicinal products”. Here, an exemption has been made for vaccines, and hence the Regulation applies to gene therapy products, but not to DNA vaccines.

Animal Feed Act

Genetically modified animal feed products must be labelled for sales purposes, as well as when they are ingredients of feed mixes. Here too, it would be logical to rely on the definitions set out in the Gene Technology Act. Furthermore, it has been established that the use of genetically modified feed in production does not require the labelling of fish or meat products, as long as the genetic composition of the end product remains unchanged (9).

Biotechnology Act

Gene therapy on humans is regulated by the Act relating to the application of biotechnology in medicine. The conditions thereof are set out in Section 7-1:

“The human heritable material may only be altered by means of somatic gene therapy for the purpose of treating serious disease or preventing serious disease from occurring. Germline gene therapy is prohibited.” Although humans who have undergone gene therapy treatment cannot be classified as genetically modified organisms, environmental, as well as other concerns will be assessed for every individual application for gene therapy. The definition of gene therapy set out in the Biotechnology Act also covers any use of DNA vaccines on humans.

Animal Health Act

Section 9 of the Animal Health Act states that “vaccines for the vaccination of animals (livestock, game) may be used only when the vaccines and vaccinations have been approved by the Ministry. The Ministry may issue regulations on the use of vaccines for the vaccination of animals (livestock, game).” All DNA vaccines for livestock and game animals are, therefore, subject to the approval of the Norwegian Medicines Agency and the Norwegian Animal Health Authority before use.

Animal Welfare Act

The Animal Welfare Act was amended when the Gene Technology Act entered into force. Section 5 of the Act provides for restrictions on the genetic modification of animals for breeding purposes:

“It is prohibited to alter the heritable material of animals by means of gene technology methods or by means of traditional breeding methods if:

- 1. it makes the animal unfit for carrying out normal behaviour or if it adversely affects its physiological functions;*
- 2. the animal is caused unnecessary suffering;*
- 3. the alterations arouse general ethical concerns.*

It is prohibited to breed animals covered by the first paragraph.”

The animal’s natural characteristics are thereby safeguarded by the Act as far as heritable alterations are concerned. The same does not apply, however, when altering the individual animal without affecting its genome. However, if the DNA in the treatment should prove to be heritable and the alteration affected the animal’s natural characteristics, the final paragraph of this Section would then prohibit any further breeding of the animal.

The use of animals for research purposes is regulated under Section 21 of the Act, Use of animals for research purposes:

“It is prohibited to perform biological experiments on animals without specific authorisation. Such authorisation may be

granted if the purpose is to determine the type of disease that animals or humans are suffering from, or if the purpose is to prevent or eradicate disease. Authorisation may also be granted when the purpose is related to research, manufacture or testing of medicines, medications, preparations, toxins, etc. for use on humans, animals or plants. Such trials must be conducted in such a way as to prevent any risk of the animal suffering more than is strictly necessary for the purpose in question". More detailed guidelines and authorisation procedures are available in the Animal Welfare Act's Regulation on animal trials. Here, however, an exemption has been made for *"treatment and interventions conducted in clinical veterinary activities in accordance with recognized methods and trials relating to breeding/farming, feeding and the environment (livestock and aquatic organisms), unless there is reason to believe that the trials will result in an abnormal physiological condition for the experimental animal."* Gene therapy trials causing such conditions for the animal require, therefore, permission from the Experimental Animals Committee, whereas trials with vaccines according to recognized methods require no such permission under the Animal Welfare Act.

Medicinal Products Act

Section 2 of the Medicinal Products Act defines what is considered to be a medicinal product:

"For the purpose of the present Act, medicinal products are defined as substances, drugs and preparations that are intended for or presented for use to prevent, heal, cure or alleviate disease, disease symptoms or pain, to influence physiological functions in human beings or animals, or, through internal or external use, to detect disease. The King may issue more detailed regulations defining what is to be considered a medicinal product. Such regulations may stipulate that certain substances, drugs or preparations are always to be considered medicinal products, regardless of whether they might have other applications, and that certain other substances, drugs or preparations, falling within the scope of the provision set out in the first paragraph above, may still be considered to be non-medicinal products."

Most DNA vaccines would be defined as medicinal products, since they prevent disease in animals. Also gene therapy, which is not disease-related, but which affects physiological functions, would fall within the definition of a medicinal product. Furthermore, the wording allows the Norwegian Medicines Agency to determine which products are to be classified as medicinal products and which are not. Section 4-6 of the Medicinal Products Regulation stipulates that any application for authorisation to place on the market a medicinal product for animals should include *"an assessment of the possible risk to the environment and to the health of humans and animals with normal use of the medicinal product, as well as all documentation on which said assessment has been based"*. Medicinal products based on gene technology are granted market authorisation by way of a common European application procedure.

The Norwegian Medicines Agency is also responsible for assessing the clinical testing of medicinal products on animals. Specific guidelines have, for example, been drawn up for the clinical testing of vaccines on fish. On the other hand, animal trials involved in the development of medicinal products for humans are not subject to prior assessment by the Norwegian Medicines Agency.

4.2 Definitions and intentions of the Gene Technology Act

Today, the definition of a GMO under the Gene Technology Act is as follows: *"Microorganisms, plants and animals in which the genetic material has been altered by means of gene or cell technology."*

The individual concepts are further defined as follows:

"Microorganisms: any cellular or non-cellular microbiological entity that is able to reproduce or transfer genetic material"

"Gene technology: techniques that involve heritable material being isolated, characterized, modified, and introduced into living cells or viruses"

"Cell technology: techniques for the production

of living cells with new combinations of genetic material by the fusion of two or more cells.”

Expanding on the definitions

Proposition No. 8 to the Odelsting* (1992-93), in which the draft of the Gene Technology Act was submitted, provides further details on how legislators have worked their way to a definition of GMOs. This might shed some light on the possible interpretations of how DNA-treated animals are to be regulated.

Could naked genetic material per se be regarded as a GMO?

One possible interpretation of the definition of microorganisms might be that naked DNA, when self-replicating, is a “non-cellular, microbiological entity that is able to reproduce”, and consequently might per se be defined as a GMO. However, the preparatory work provides no support for such an interpretation. Here, endorsement was instead given to the then EC’s interpretation of what the concept of “non-cellular microbiological entity” meant (Proposition No. 8 to the Odelsting, page 70):

“An interpretation was reached which meant that the definition covered viruses, including bacteriophages, but not plasmids or other naked genetic material. The Ministry endorses this delimitation. Hence, the definition of microorganisms includes viruses, bacteria, unicellular plants and animals, plant and animal cells (including human cells) in culture and microscopic yeast and mould fungi.”

In consequence, naked genetic material per se falls outside today’s definition of a GMO. (Entire viral genomes are defined as viruses.)

Would an organism to which naked genetic material has been added be classified as a GMO?

The Gene Technology Act applies to living organisms whose genetic material has been altered by means of gene or cell technology.

*Note: Odelsting: one of two divisions of the Norwegian Parliament

What is meant by the term “genetic material” is not further developed in the Proposition to the Odelsting. It is not entirely clear whether this applies to all addition of new genetic material or only when the added genetic material is heritable.

However, reference is made to examples that fall outside the scope of the Act (page 68 of Proposition No. 8):

This means that work with genetic material that has been extracted from an organism or is synthesized, as well as biochemical research on polynucleotides, fall outside the scope of the Act when the direct aim is not to introduce heritable material into a living cell or virus.”

This statement could indicate that it would suffice that the genetic material was introduced and that there is no requirement as to the material being inherited.

Moreover, the meaning of the concept of “genetically modified organism” is further expanded (page 70):

“A genetically modified animal or a so-called “transgenic animal” also refers to the progeny of a crossing of a transgenic animal with a non-modified animal, as well as animals with transplanted transgenic tissue.”

Transplanted transgenic tissue would not normally lead to a heritable alteration, which might indicate that the idea was that genetic modification did not have to be heritable to be covered by the current Gene Technology Act.

Is the method used for adding naked genetic material important?

What the Act’s definition of “gene technology” (see above) actually implies may be somewhat unclear. The definition could be read to mean that genes are *either* isolated, *or* characterized, *or* modified, *or* introduced into living cells or viruses. Alternatively, the definition of gene technology could mean that genes are isolated, *as well as* characterized, *as well as* modified, *as well as* introduced into living cells or viruses. These different meanings could have an impact on which vaccine technologies might today be

considered as gene technology.

On page 70 of the Proposition to the Odelsting, there is further emphasis on the importance that the uptake of genes has for the definition of “gene technology”: *“One absolute condition is that the aim is the uptake of heritable material in a living cell or in a virus. There is no condition that the gene must be isolated, as well as characterized, as well as modified. One of these work operations, combined with the introduction of the heritable material into a living cell or virus (see above), would suffice.”*

However, it is still not entirely clear what is meant by the terms “introduction” and “uptake” and whether this entails incorporation into chromosomes or not.

In gene therapy, there are several possible delivery methods for the genetic material. When considering how relevant the method of introduction is, it is important to bear in mind that the Act’s technical area of application covers production, in addition to use: *“The Act applies to the production and use of genetically modified organisms. The provisions of the Act relating to genetically modified organisms also apply to substances and products that consist of or contain genetically modified organisms.”*

This is further expanded on page 68 of the Proposition to the Odelsting:

“The term “production” means all the steps in a process that specifically lead to an organism being genetically modified”.

Hence, there is no requirement as to how the genetic material is introduced. For substances or products consisting of or containing genetically modified organisms, the requirement is that the GMOs must be living: *“The Act does not apply to products that are produced by means of genetically modified organisms when the end product does not contain living organisms.”*

This review shows that even when the wording of the Act is examined in the light of Proposition No. 8 to the Odelsting (1992-93), it is still not clear whether or not the use of

DNA vaccines and gene therapy on animals should be defined as genetic modification. It is possible, by relying on various sentences in the wording of the Act and of the Proposition to the Odelsting, to find support for the interpretation that DNA-treated animals are GMOs and as well to interpret the wording to mean that they are not to be considered as GMOs. The picture might possibly be clarified by examining the intentions behind the Gene Technology Act.

Intentions of the Gene Technology Act

In the context of a regulatory system for GMOs, many considerations have been underscored. These are reflected in the recommendation that the Standing Committee on Local Government and the Environment of the Norwegian Storting (parliament) tabled in May 1991:

“When deliberately releasing genetically modified organisms into nature, the majority of the Committee, like the Government, believes that the regulatory framework should be restrictive [...] A prerequisite for permission for deliberate release must be that there is no danger of unwanted ecological or health effects and of the unwanted spread of the organism or its genetic material. The majority would also stress that permission must be contingent on the utility value involved and the ethical, health and ecological issues that deliberate release raises following controlled trials and impact and risk assessments.”

In the interests of the environment, any detrimental spread of either GMOs or their genetic material is unwanted. An important factor to be borne in mind when considering DNA vaccines and gene therapy is, therefore, how the added genetic material is treated by the body and any possible environmental effects the naked genetic material might have when liberated from the animal. The intention of the Act provides no clarification on the status awarded to the treated animal. It might still be considered either as a GMO *per se*, or it may be regarded and evaluated as a part of the environment into which the genetic material has been deliberately released.

4.3 New EU Directive on the deliberate release of GMOs

The EU Parliament has approved a new directive (2001/18/EC) for the deliberate release of genetically modified organisms. The Directive states that the deliberate release of GMOs must be based on the precautionary principle. DNA vaccines and gene therapy are not specifically mentioned in the new Directive, but its definitions do provide indications of how the EU will regulate DNA treatment and DNA-treated animals.

Definition of a GMO in EU Directive 2001/18/EC

In the English version of the Directive, organisms and GMOs are defined as follows:

1) *“organism” means any biological entity capable of replication or of transferring genetic material;*

2) *“genetically modified organism (GMO)” means 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;*

Within the terms of this definition:

(a) *genetic modification occurs at least through the use of the techniques listed in Annex 1A, Part 1;*

(b) [...]

The definition of organism is very similar to the one used in the Norwegian Gene Technology Act and it is not specified whether replicating plasmids are covered by the definition. In the preparatory work of the Norwegian Act, the then EC definition was used as a basis when excluding plasmids from the definition of an organism. During the negotiation of the Cartagena Protocol, the EU Commission stated that it did not consider plasmids and other naked genetic material to be organisms.

However, treating an animal with naked DNA could conceivably lead to the animal becoming a GMO. Attached to the definition of a GMO is an Annex in which techniques

for genetic modification are mentioned:

Annex 1A, Part 1: Techniques of genetic modification referred to in Article 2(2)(a) are inter alia:

1) *recombinant nucleic acid techniques involving the formation of new combinations of genetic material by the insertion of nucleic acid molecules produced by whatever means outside an organism, into any virus, bacterial plasmid or other vector system and their incorporation into a host organism in which they do not naturally occur but in which they are capable of continued propagation;*

2) *techniques involving the direct introduction into an organism of heritable material prepared outside the organism including micro-injection, macro-injection and micro-encapsulation;*

3) [...]

It is conceivable that DNA treatment could be covered by item 1 in those instances where the inserted genetic material could propagate in the organism. In that case, it would apply to a greater degree to gene therapy than to DNA vaccines. However, there is still room for other interpretations based on what the term “propagation” entails.

DNA treatment appears, moreover, to fall under item 2, which mentions the direct introduction of heritable material into an organism. However, it is not clear whether “heritable material”, in this context, means nucleic acids in general or whether it means that the material indeed must be heritable. Under item 1 of the Annex, the expressions “nucleic acid molecules” and “genetic material” are used instead of “heritable material”. The same distinction is also to be found in the Danish and French texts. This could indicate that the EU’s definition of genetic modification does not include the direct introduction of nucleic acid molecules that are not heritable, but this is not explicitly stated. An alternative explanation might be that the term is also meant to cover other types of molecules that are capable of transferring properties, such as prions.

Hence, the new EU Directive does not appear to be entirely unambiguous as to whether DNA-treated animals in general are to be considered as genetically modified. Here,

there is room for discretion and different interpretations.

There are few international statements that explicitly take a position on the status to be given to DNA-treated animals. However, the Agriculture and Environment Biotechnology Commission (AEBC) of Great Britain published the report "Animals and Biotechnology" on 3 September 2002. On page 13, DNA-vaccinated animals are mentioned: *"Importantly, the foreign DNA is not expected to integrate into the host's genome and so the vaccinated animal is not genetically modified."*

Applying this criterion, the majority of DNA-vaccinated animals would not be genetically modified, whereas gene therapy could imply genetic modification.

Special rules for genetically modified medicinal products

In the EU, the aim is that a single application should suffice in order to assess the deliberate release of a GMO and to approve products produced from this GMO as food or animal feed. In conjunction with the Directive, therefore, new regulations have been issued on the traceability and labelling of genetically modified food and feed. This is formulated in Regulations 2001/0173 and 2001/0180. In these documents, approval and labelling requirements are linked to the food or feed, or the ingredients of these, that have been *produced from* a GMO, but not to those that have been *produced with* a GMO. The criterion is whether the material from the GMO is present in the product. It is specified that products from animals having received genetically modified feed and genetically modified medicinal products are not covered by the Regulation:

"Thus, cheese produced with a genetically modified enzyme that does not remain in the final product and products obtained from animals fed with genetically modified feed or treated with genetically modified medicinal products would be subject neither to the authorisation requirements, nor to the labelling requirements laid down in the proposed Regulation."

Since the aim is that a single application

should apply to both deliberate release and product approval, the Directive with its related Regulations could be interpreted to mean that the treatment of animals with genetically modified medicinal products not even makes the animals genetically modified while alive, even though the genetically modified product is present in the animal for a certain period of time.

A further exception has been made for genetically modified medicinal products, and this applies to the product itself. In recital 31 of EU Directive 2001/18/EC, it is stated that genetically modified medicinal products that are to be placed on the market are not covered by the Directive, but that an environmental risk assessment should, nevertheless, be carried out:

"(31) Part C of this Directive does not apply to products covered by Council Regulation (EEC) No. 2309/93 of 22 July 1993 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products, provided that it includes an environmental risk assessment equivalent to that provided for by this Directive."

(Part C: Placing on the market of GMOs as or in products; Part B: Deliberate release of GMOs for any other purpose than for placing on the market.)

A GMO that is to be placed on the market as a veterinary medicinal product is, therefore, not directly covered by the deliberate release Directive. The exemption presupposes, however, that an equivalent environmental risk assessment is evaluated by the same body that considers other deliberate releases of GMOs. This type of environmental risk assessment includes the species on which the medicinal product is to be used. As a result, the animals will be covered by a risk assessment, by being a part of the environment into which the medicinal GMO is to be released.

The exemption set out in recital 31, entailing the requirement of an environmental risk assessment, applies to medicinal products where a GMO is the product or is an

ingredient of the product. This applies, therefore, to genetically modified viruses for use in vaccines and gene therapy. However, it is unclear whether DNA treatment products are to be considered as genetically modified medicinal products, as no organism constitutes the product or is an ingredient of the product.

If products for DNA treatment are not to be considered as GMOs or genetically modified medicinal products, there is no requirement that they be assessed in terms of their environmental risks by the same body that evaluates GMO releases. Such an environmental risk assessment could, on the other hand, be relevant at the next stage, when assessing whether the animal treated with such products is to be regarded as genetically modified.

The European Agency for the Evaluation of Medicinal Products (EMA) has drawn up guidelines for medicinal product development, where DNA vaccines for animals are covered by the following:

“DNA vaccines non-amplifiable in eukaryotic cells for veterinary use”

“Environmental risk assessment for immunological veterinary medicinal products”

Here, there are requirements as to safety and documentation on the spread of the DNA in the animal, integration into chromosomes and toxicity for the animal itself and for the animal's reproduction.

In the US, gene therapy and the heritable genetic modification of animals are both covered by the concept of drug. The area is controlled by the Center for Veterinary Medicine (CVM) under the Food and Drug Administration (FDA). On the FDA's home page, this is expanded under "Q&A":

“Most, but probably not all, gene-based modifications of animals for production or therapeutic claims fall under CVM regulation as new animal drugs.” “The animal drug provisions of the Federal Food, Drug, and Cosmetic Act best fit the transgenic animals that have agronomic traits now being investigated and developed. Other transgenics will no doubt come along that could be viewed as containing food additives,

color additives, and vaccines.”

The Pew Initiative on Food and Biotechnology in the US pointed out in a recent report that the regulatory system in the US was ambiguous as far as genetically modified animals for food purposes were concerned, and that genetically modified salmon, for example, could not be regulated on the basis of environmental considerations alone (10).

4.4 Cartagena Protocol on Biosafety

When drawing up a Norwegian regulatory system for DNA vaccines and gene therapy on animals, consideration should be given to international agreements that Norway has signed.

The Cartagena Protocol applies to the biosafety of GMOs in the environment and it is part of the Convention on Biological Diversity. The Protocol has been ratified by Norway, the EU Commission and several EU member states. It entered into force 11 September 2003.

The objective of the Protocol is to take account of biological diversity in the context of the trade in and use of living, genetically modified organisms. It is worded as follows:

“In accordance with the precautionary approach contained in Principle 15 of the Rio Declaration on Environment and Development, the objective of this Protocol is to contribute to ensuring an adequate level of protection in the field of the safe transfer, handling and use of living modified organisms resulting from modern biotechnology that may have adverse effects on the conservation and sustainable use of biological diversity, taking also into account risks to human health, and specifically focusing on transboundary movements.”

In the Cartagena Protocol, the term "LMO", living modified organism, is used for GMOs: *“Living modified organism” means any living organism that possesses a novel combination of genetic material obtained through the use of modern biotechnology; “Living organism” means any biological*

entity capable of transferring or replicating genetic material, including sterile organisms, viruses and viroids;

"Modern biotechnology" means the application of:

a. In vitro nucleic acid techniques, including recombinant deoxyribonucleic acid (DNA) and direct injection of nucleic acid into cells or organelles, or

b. Fusion of cells beyond the taxonomic family,

that overcome natural physiological reproductive or recombination barriers and that are not techniques used in traditional breeding and selection."

The Protocol uses the term "novel combination of genetic material", but it is not specifically stated whether the novel combination has to be heritable. Hence, it is possible to interpret DNA treatment as a method of genetically modifying an organism, and the animal as an LMO, for as long as the novel combination is present. However, the Protocol is only applicable as long as the animal is alive, and separate rules apply for organisms that are to be used directly as food or animal feed.

The Cartagena Protocol, too, provides exemptions for medicinal products, but as far as veterinary medicinal products are concerned, there is a difference compared with the EU Directive. In the Cartagena Protocol, medicinal products intended for human use are exempted, whereas veterinary

medicinal products are not (Article 5):

"Notwithstanding Article 4 and without prejudice to any right of a Party to subject all living modified organisms to risk assessment prior to the making of decisions on import, this Protocol shall not apply to the transboundary movement of living modified organisms which are pharmaceuticals for humans that are addressed by other relevant international agreements and organisations."

The Protocol's definition of an organism includes biological entities that are capable of transferring or replicating genetic material. This definition is similar to that used in the new EU Directive, but it mentions, in addition, sterile organisms, viruses and viroids in particular. In the New Penguin Dictionary of Biology, viroids are explained as follows:

"Small naked RNA loops, 300-400 nucleotides long. Replicated by host enzymes as their genomes do not encode any. Lacking capsids, only able to pass from one damaged cell to another. Analogous to plasmids."

The fundamental difference between viroids and self-replicating plasmids is not that significant, but plasmids are not explicitly included in the definition of a living organism. Living, genetically modified viral vaccines for animals are, therefore, included in the definition of an LMO, whereas DNA-treatment products based on plasmids do not, according to the Protocol, appear to be LMOs *per se*.

5. Possible regulatory methods

There are two principal methods for regulating DNA vaccines and gene therapy on animals: regulating the animal that has undergone treatment or regulating the treatment itself. A combination of both is, of course, a third option.

5.1 Regulating the animal

Regulating DNA-treated animals under the Gene Technology Act could mean that the animal would, under certain circumstances, be classified as genetically modified. The key question would then be what the term “genetically modified” implies and, more specifically, the concept of “genetic material”. Alternatively, a new category could be introduced or DNA treatment could be regulated under other legislation. The term “genetically modified animal” has traditionally been used to designate animals that have been produced by altering the chromosomal DNA of a fertilized egg or embryo by means of gene technology. But what should be the criteria to apply when determining whether DNA treatment of a developed animal makes it genetically modified? In this respect, there may be several alternative approaches:

1a. GMO if genetic material has at any time been added to the animal

Animals that have received genetic material, either in the form of a vaccine or for other purposes, would be classified as genetically modified forever. A relevant consideration is then whether this should also apply to the offspring of such animals.

1b. GMO as long as the added genetic material is present

The animal will be classified as genetically modified only for as long as the genetic material added remains present in the animal. In this case, it would have to be shown probable that the DNA is no longer present before the animal could be declassified as genetically modified.

1c. GMO when the added genetic material is likely to become heritable

Some genetic constructs might entail a genetic alteration of reproductive cells. The animal would be classified as genetically modified only when it is likely that the genetic material added could be inherited. Here, an assessment would have to be made of what is an acceptable risk for incidental integration in the chromosomes of reproductive cells.

1d. GMO when the new genetic material has particular characteristics

This alternative would provide guidelines specifying when the genetic material is of such a nature that it would render the animal genetically modified, and when this is not the case. It might apply to combinations of the criteria set out in the alternatives above or if the animal acquires new properties that alter its natural characteristics. In cases of doubt, the considerations should be made on a case-by-case basis.

1e. DNA-treated animals are given an entirely new designation

Rather than establishing a sharp distinction between genetically modified and non-genetically modified, it might be possible to grade genetic modification by introducing one or more new categories, e.g. “DNA-treated” as a term to describe animals that have received DNA vaccines or gene therapy.

1f. The term “GMO” is reserved for deliberate, heritable modifications

Another option might be to refrain from regulating DNA-treated animals under the Gene Technology Act, but instead reserve the term “GMO” for organisms that have undergone deliberate, heritable genetic modification.

5.2 Regulating treatment

DNA vaccines and gene therapy on animals might conceivably be controlled by regulating treatment instead of, or in addition to the DNA-treated animal itself.

2a. Genetic material for DNA treatment is regulated under the Gene Technology Act

The Gene Technology Act's current definition of organisms includes viruses, but not naked DNA. The definition could be extended to apply also to naked genetic material when such material is a replicating entity or fulfils other selected criteria.

2b. Specific legal provisions regulating the DNA treatment of animals

DNA treatment of animals could be regulated in a separate act or in a separate chapter of the Gene Technology Act, where no definite position on the definition of GMO would necessarily have to be adopted.

2c. DNA treatment of animals is covered by other legislation

DNA vaccines and gene therapy on animals will, in most instances, fall within the scope of other acts. Veterinary medicinal products are, for instance, covered by the Medicinal Products Act and their use by the Animal Health Act. Any amplification of the Gene Technology Act in these areas would, therefore, be superfluous, but additional provisions could be introduced under other legislation.

Which of these regulatory systems would provide for appropriate regulation of DNA-treated animals? It would depend on the

values on which they have been founded, the considerations that regulators wish to make and how opposing considerations are balanced.

Since DNA treatment of animals moves in a grey area of the Gene Technology Act and since a restrictive regulation of GMOs is widely accepted in today's society, it is important to determine whether the considerations on which this Act is based should also apply to DNA-treated animals. According to the intentions of the Gene Technology Act, the production and use of GMOs should be without detrimental effects on health and the environment. Furthermore, they should take place in an ethically and socially justifiable way, in accordance with the principle of sustainable development. Any evaluation of these overriding considerations depends, however, on the values that underpin them and how these are expressed. Hence, focus should be placed on considerations that might be important in such an evaluation, such as animal welfare, consumer interests, business interests and international cooperation. Furthermore, it is important that any regulation of DNA-treated animals is biologically well-founded and that it is possible to implement in legislation as well as in practice.

The next chapter presents a discussion of the most important considerations that must be made. The considerations mentioned have been selected in the light of the current situation, but, to the extent possible, also with a view to the consequences of future developments. For each specific consideration, it is discussed whether the different regulatory alternatives provide appropriate safeguards.

6. Considerations to be made when selecting regulatory method

6.1 Environment

Environmental considerations

Environmental considerations represent a core element of any regulation of genetically modified organisms, and they are, therefore, important to any evaluation of how DNA-treated animals should be regulated.

Ethical principles related to the environment

The value of the environment will, for many people, mean the value that the environment holds for human beings – for people alive today, as well as for future generations. The interests of future generations are central to the concept of “sustainable development”. When assessing benefit to the society, environmental considerations will be weighed against other considerations, in such a way that we feel able to answer for any balancing of the interests of today’s society against the importance of the interests of coming generations. However, the environment may also represent a value that goes beyond that of its worth to human beings. In this instance, the environment is said to hold an inherent value. Thinking along these lines, many could argue that we have no right to misuse nature, regardless of how useful it might be to us. Both these ethical principles could form the basis of an evaluation of the different environmental considerations involved, and they will often lead to the same conclusions.

Integration and ecological balance

Long-term effects of DNA treatment might occur when humans repeat the same actions over a long period of time, like when vaccinating farmed fish, or when new characteristics become heritable. For DNA-treated animals, heritable characteristics could arise as a result of the intentional integration of genetic constructs into chromosomal DNA, or they could be caused by unintentional integration. The use of integrative genetic elements may be

restricted, but incidental integration can occur independently of the sequence. The development of transgenic animals mostly depends upon incidental integration. Even if genetic sequences are as “innocuous” as possible and do not contain any known integrative sequences, it is impossible to control where in the genome such incidental integrations may occur. They can occur in various locations in the genome and give rise to different effects. In this respect, there will always be an element of uncertainty. What kind of effects could this produce? In many cases, it will affect the animal itself, in the form of cancer development or other diseases. In rare instances, an alteration may occur giving rise to a selective advantage for the animal in the ecosystem, something that will often be unwanted.

Spread of genetic material and recombination

Genetic material may spread accidentally, e.g. by the transfer of plasmids to other species when the animal dies or via body fluids secreted by the animal (11). A recombination with natural viruses could, moreover, occur inside the animal’s cells, especially with the use of viral vectors (12). With free plasmids there is a greater likelihood of mobility than with a genetic alteration in the chromosomes. It is conceivable, therefore, that added genetic material might be taken up by microorganisms living in the animal.

Risk assessment and the precautionary principle

According to the Gene Technology Act, deliberate releases should have no detrimental effects on the environment. All applications for the deliberate release of a GMO must, therefore, include a risk assessment accounting for its possible effects on the environment. The harmful environmental effects that are feared include the disproportionate and irreversible effect on non-target organisms, gene flow to wild congeners or closely related species, recombination and the creation of, for

example, new viral strains, and the spread of properties such as antibiotic resistance via horizontal gene transfer. Many of these aspects are difficult to assess, due to complex systems and unknown risks. Especially difficult is any estimation of the long-term effects, since small and perhaps unknown selective advantages can have major consequences in the long term. The precautionary principle should, therefore, form the basis of any deliberate release of GMOs into the environment.

The probabilities of DNA-treated animals spreading the genetic material and having effects on the environment will differ from those for heritably genetically modified animals. Since risk is defined as probability times consequence, differing probabilities will alone affect the risk. There might possibly be a greater likelihood of spread of genetic material to microorganisms following DNA injection than when the DNA is integrated into the chromosomes. For DNA treatment, there are four circumstances that all have to occur for the genetic material to become heritable; the DNA added has to translocate inside the body, it must be taken up by reproductive cells, it must be integrated into the chromosomes of reproductive cells without these cells dying, and the cells must subsequently lead to live offspring. Furthermore, added genes may – perhaps to a lesser degree than for intentional, heritable modification – give the animal a selective advantage. But even though the probabilities of such events differ, the unwanted environmental consequences may still be the same, and the risk correspondingly high. What an acceptable risk limit is, or whether the precautionary principle should be applied, will have to be evaluated on a case-by-case basis.

In order to ensure that the possible effects on the environment following the use of DNA vaccines and gene therapy are taken into consideration, public authorities need to be able to assess potential environmental effects. A risk assessment that also includes environmental impacts will therefore be required. Since different animal species have different physiologies and genetics, trials are needed to show the effects on the specific

animal species that is to be treated. In that case, documentation for every new animal species and every new type of treatment will be required. Depending on the environment in which the animal lives, it might also be relevant to analyse possible impacts on the environment surrounding the treated animal and to consider limiting its freedom of movement.

Safeguarding environmental interests by regulating the animal

If DNA-treated animals are to be regulated as GMOs under the Gene Technology Act, animals that are not meant for contained use will be considered in the same way as deliberate release of GMOs, involving a comprehensive study of the environmental impact in each individual case. Such a study would also include the possible consequences of any spreading outside the release area, the possibility of transfer of genetic material to other organisms, the likelihood of other interactions with the environment and the possibility of pathogenic or harmful effects to health by living or dead GMOs. Furthermore, safety measures would be required to avoid spreading, as would methods for traceability and internal control. Environmental interests would, therefore, be safeguarded under the rules applying to the deliberate release of GMOs.

Defining all animals that have ever received DNA treatment as GMOs would ensure that the animal's local, ecological environment is taken into account, and it would be possible to say “no” when required. This approach would also presuppose a precautionary attitude, based on the assumption that it is impossible to rule out that some of the added genetic material may still be present in the animal and that it *might* have been integrated into its reproductive cells and lead to offspring with a heritable genetic modification.

The precautionary principle would be somewhat toned down if the possibility of a temporary genetic modification of the animal is allowed for. In that case, trial results would have to be produced showing that the genetic material is degraded and no

longer present in the tissue. Furthermore, a time margin would have to be set before an animal would no longer be termed a GMO.

In some gene therapies, the aim might be to integrate the genetic material into the chromosomes of target cells. In such cases, there is a significant possibility that the gene construct might also be integrated into the chromosomes of reproductive cells. In a regulatory context, therefore, primary emphasis might be placed on the likelihood of genetic material giving rise to a heritable genetic modification and less emphasis might be given to the presence of genetic material. Since integration rarely can be completely ruled out, documentation must be required showing that the method has minimized the probability of such an event.

A more detailed specification of the criteria for classification as a GMO, with the subsequent requirement of prior approval for each individual release, might be an alternative approach. Here, factors other than environmental considerations could be included, such as the genetic material's effect on the animal's natural characteristics.

The difference in environmental risk between DNA-treated animals and heritably genetically modified (transgenic) animals would be made more apparent if the term "DNA-treated" (or the like) was introduced as a separate category, in addition to "genetically modified". As is the case for GMOs, an impact study and approval can be required before DNA-treated animals could be released into the environment. In this situation, it is also possible to evaluate, on a case-by-case basis, whether or not the animal should be termed GMO and relate the environmental risk assessment to that evaluation.

If a DNA-treated animal already has been defined as a non-GMO, an environmental risk assessment of the treatment given to the animal could still be introduced. The animal could be regarded as part of the environment in which the genetic material is released (see below).

Safeguarding environmental interests by regulating treatment

By including plasmids and perhaps even other genetic constructs, in the definition of a GMO, the spread of genetic material and its effect on the environment could be assessed before proceeding with DNA treatment. This type of assessment could also include the animals that receive DNA treatment, and the effects that the genetic material might have on them. On the other hand, an assessment of the local environment is difficult, as authorisation will have been granted before having knowledge of the local environment of application.

It is also possible to require an environmental risk assessment of DNA treatment without extending the concept of GMO, regardless of whether the regulatory system is formulated as a separate act (or a separate chapter of an act) or whether DNA treatment is merely to be covered by existing legislation. In the latter alternative, however, it is important for the safeguarding of environmental concerns that DNA treatment, for all purposes whatsoever, is subject to regulation, and not only when used for medicinal product purposes.

6.2 Animal welfare

Vaccines and disease treatment of animals are important for the welfare of the animal, as well as to prevent the loss of production efficiency when the animal is a production animal. At the same time, a key argument often used against the genetic modification of animals is that modification might be at the expense of the animal's natural characteristics and health. The use of DNA vaccines and gene therapy on animals entail methods that are similar to genetic modification, but their purpose is often to improve the animal's health and welfare. Hence, it is important, when drawing up a regulatory system for DNA vaccines and gene therapy, to consider possible animal welfare interests, as well as the consequences that alternative regulatory regimes may lead to.

Animal welfare interests

As in the case of assessing environmental interests, different values may underpin the considerations that one might wish to make in respect of animal welfare. Throughout the ages, human beings have made use of animals, and different animals could be said to represent greater or lesser value to humans. However, there is a difference between the purely utilitarian view of an animal, where the animal is regarded exclusively as a creature for human use, and attributing to the animal a value that represents an end in itself. Our wish to preserve an animal's natural characteristics may be based either on the view that it is of value to us that the animal preserves its natural traits and characteristics, or because we attribute an inherent value to the animal. If the animal is attributed an inherent value, it should be our duty to take account of this in our treatment of the animal, above and beyond any value that we as humans might draw from such treatment.

Influencing the natural characteristics of animals

Wild animals have developed through evolution into the animals we see today. Over a long period of time, humans have performed deliberate breeding of livestock, and, as a result, these animals are today vastly different from their wild ancestors. The genetic modification of animals could be viewed as a continuation of this process, but there are certain differences. The time scale is different – with genetic modification, major alterations may be achieved from one generation to the next. Furthermore, entirely novel characteristics may be introduced from other species, so the range of possible alterations is significantly broader. Gene technology offers, moreover, greater opportunity for carrying out intentional alterations and the control that humans have gained over the natural characteristics of animals is, therefore, much greater. In contrast to heritable genetic modification, gene therapy and DNA vaccination will, in principle, have an impact on the individual animal and not on its offspring. However, there is the slight probability of a transfer of added genetic material to offspring through reproductive cells. For example, vaccine DNA

has been found in the spermatozoa of pigs vaccinated with DNA (13). Some types of added genes might be capable of altering the individual animal's natural characteristics, whereas vaccination against disease is not perceived as a means of influencing the animal's natural characteristics.

Animal health following genetic modification or DNA treatment

With many forms of genetic modification of animals, the animal will notice little or nothing of the genetic modification. In other instances, for example when animals are used for research on human genetic diseases, the animal may suffer as a result. The aim of animal vaccination, including DNA vaccination, will generally be to *avoid* disease, thereby contributing to improved animal health. With the gene therapy not aimed at preventing disease, an evaluation would depend on the characteristics that the animal acquires from the added genetic material (see below). Furthermore, DNA vaccination and gene therapy will always present a slight possibility of integration of the added genetic material into an adverse site in the chromosomes, leading to the development of cancer or metabolic disorder in the animal.

Choice of method for disease prevention and treatment

Many considerations come into play when selecting the type of treatment for an animal, and much will depend on the role played by the animals for human beings. For farmed fish, a certain level of mortality is calculated into production costs. Quite different considerations may prevail when a pet is taken to the vet.

Many of today's vaccines have side effects for the animal. Fish may, for example, suffer adhesions at the injection site when an oil adjuvant is used in the vaccine mixture. An adjuvant is necessary to achieve high efficacy of vaccines based on inactivated microorganisms. Viral vaccines and DNA vaccines may be administered without the use of an oil adjuvant. DNA vaccines and other subunit vaccines are also safer than attenuated viral vaccines, because disease

breakout caused by incomplete attenuation or reversion can be avoided.

Vaccines administered in the form of an injection entail stress for the animal. Immersion as a delivery method for fish and nose spray or edible vaccines for other animals would represent better vaccination methods for the animals. Work is currently in progress to develop such delivery methods for DNA vaccines.

When treating disease in animals, as in humans, it is always an advantage to have the opportunity of choosing the treatment that is best for the animal in terms of good effect and few side-effects. In all likelihood, owners of pets or production animals alike would prefer to use the best vaccines and medicinal products available. With a more restrictive regulation of DNA treatment in Norway than in other countries, there is the possibility that the best treatment may not be available here in Norway.

Disease in animals may also be limited by means other than vaccination. The animal's resistance to attack may be improved with correct nutrition and good living conditions, and it may be better protected from sources of contagion if such sources are identified and avoided. It is important, therefore, to look at all the different aspects of vaccination. It is conceivable that an animal's conditions of life might, in certain instances, be worsened as a result of good vaccines, as the animal might then be pushed even further without falling ill. This aspect might be particularly relevant in the fish-farming industry.

DNA treatment of animals for other purposes

When choosing a regulatory system for DNA vaccines and gene therapy on animals, it is important to consider the fact that DNA treatment may have applications beyond those of disease prevention and treatment. Here, there may be areas that might conflict with the intentions on which the Gene Technology Act is founded.

Some of the vaccines of the future may aim at controlling the animal's reproductive

capacity and metabolism. Vaccine trials have already been conducted to eliminate the boar taint in pigs and to increase the number of lambs in ewes. By using vaccines against certain molecules on fat cells, the fat deposit in slaughter animals may be reduced, and the colour of the fat may also be influenced through the immune system (14).

Many of these objectives could also be achieved by means other than DNA treatment, for example with the use of protein-based medicinal products. Instead of injecting fish with a growth hormone gene to increase its size, the fish could receive the growth hormone directly, in the same way as cattle do in the US. Immune reactions against the animal's own proteins may also be achieved by using other types of vaccines than DNA vaccines. At present, vaccines and the use of these are regulated by the Animal Health Act, the Animal Welfare Act and the Medicinal Products Act, and DNA treatment would also fall within the scope of this legislation.

In several contexts, proposals are currently being made to genetically modify animals for useful purposes. In Australia, there have been proposals to use genetically modified viral vaccines to inhibit the fertility of rabbits by means of an immune response against the rabbit's own egg cells (15) and to genetically modify carp so as to produce male offspring only (16). The aim of both these proposals is to limit the spread of these species in Australia. The future may see many more similar proposals involving gene technology, and it might be easier to gain acceptance for treatment with only a temporary effect than for heritable, lasting alterations. In certain cases, therefore, DNA treatment could gain relevance as an alternative to heritable genetic modification. DNA treatment may be simple to develop and cheap to use and may thus contribute to a further instrumentalisation of animals. Any selective advantage resulting from such treatment might conceivably manifest itself in the species in the long-term, should the added DNA become integrated and be inherited by offspring. Any regulation of DNA treatment must also take these perspectives into account.

Safeguarding animal welfare interests by regulating the animal

Classifying all DNA-treated animals as GMOs will require that an application is made for deliberate release both of production animals and of pets following treatment. The use of DNA treatment would then be significantly restricted, including those instances where such treatment would be in the animal's best interests. Even introducing the concept of "temporary GMO", would require the approval of a deliberate release, unless the animal's freedom of movement was so strictly limited that it could be termed "contained use" during the period when the animal is considered a GMO. It is conceivable that a period of contained use could be implemented for farmed fish, as well as for production animals, but hardly for all pets.

If an animal is termed a GMO only when and if it has been shown probable that the added genetic material will become heritable, the use of DNA vaccines might, to a greater degree, become practically viable, whereas many forms of gene therapy will be restricted by the approval requirement for deliberate release. The interests of preserving the animal's natural characteristics will be safeguarded if the regulatory system sets up criteria for the type of alterations that the added genetic material is permitted to produce.

If DNA-treated animals are not termed GMOs as a result of their treatment, they may be freely treated with DNA vaccines and gene therapy, provided that treatment is approved according to regulations in force. This would give producers of animal food greater freedom in their choice of veterinary medicinal treatment for their animals, since they would neither be required to apply for approval of deliberate releases, nor to label their products as GMOs.

Safeguarding animal welfare interests by regulating treatment

With a concept of GMO that includes many of the DNA constructs of vaccines and gene therapy, the animals themselves

would represent an arena for the deliberate release of GMOs. For a certain period of time after treatment, the animal may contain the modified DNA, and restrictions on the animal's freedom of movement might become one of the criteria for releasing the DNA.

With specific legislation regulating DNA vaccines and gene therapy, animals treated with such methods could be subject to requirements limiting the possible spread of genetic material, for example, that such animals might be banned from being used for breeding purposes. This might influence the treatment given to the animal and perhaps even prevent it from receiving the best treatment available. On the other hand, it might also pave the way for the development of good DNA vaccines for animals. At the same time, special criteria could be formulated ensuring that DNA treatment does not adversely affect the animal's natural characteristics.

The treatment of animals and veterinary medicinal products are areas regulated by other legislation. From an animal health perspective, the pros and cons of DNA treatment could be taken into account in such legislation, in the way in which the genetic modification of animals is currently restricted under Section 5 of the Animal Welfare Act related to breeding.

6.3 Health

Health considerations

Safe food

The food we eat must be safe. This is an essential principle of food control. The health hazard of novel foods is assessed in terms of whether the food is substantially equivalent to existing foodstuffs. The Norwegian Food Control Authority has issued rules that apply in this area. Genetically modified food is to be assessed with regard to new components, possible antibiotic resistance genes and allergenic substances. Analyses of nutritional and physiological effects may also be required, which mostly are carried out in the form of animal feed trials.

If DNA-treated animals are used for food production purposes, new components and foreign genes might also be present in the food. There might conceivably be a greater likelihood of intestinal uptake of plasmids than uptake of chromosomal fragments from transgenic animals. Also products from DNA-treated animals should, therefore, be assessed with regard to the possible health hazard of the added genetic material and of direct and indirect alterations caused by the genes.

In line with EU regulations, Norway also applies rules on the residual quantity of veterinary medicinal products in meat and fish. Instead of zero tolerance, limit values have been set for the various medicinal products, based on the principle that they must entail no hazard to health. This also applies to products from animals that may become food, but that are not production animals themselves, such as race horses, for example. These rules would also apply to veterinary medicinal gene therapy, but they do not apply to vaccines.

Protection against infections

Animals may also involve a hazard to human health beyond their role as food. Interaction with animals may lead to infections and disease (zoonoses). Hence, any treatment of animals must also be considered in the light of how such treatment may affect humans. For example, the influence of host specificity in the development of viral vaccines for animals may have an impact. Possible health effects on humans in general, and for veterinarians and animal producers in their working environment in particular, are assessed before vaccines for animals are approved. However, the use of vaccines may also lead to the development of mutated pathogenic organisms that might be transferred to humans. On the other hand, less disease in animals in general might also lead to fewer cases of animal diseases in humans.

Prospect of good medical treatment

Several DNA vaccines are currently being developed for humans, including vaccines against malaria and HIV. In addition, work

is progressing to develop gene therapies. So as to ensure the best possible medical treatment of humans, it is important that the development of DNA vaccines and gene therapy for humans is not hampered by an excessively restrictive regulation of DNA-treated animals. This might become the case if potential DNA vaccines and gene therapy methods for humans were difficult first to test on animals. A severe restriction of DNA treatment on experimental animals in Norway would mean that the development of DNA vaccines and gene therapy for humans would be dependent on animal trials conducted abroad. The bulk of animal trials, however, would be contained use and would not entail a deliberate release of the animal into the environment. Distinguishing between contained use and deliberate release in the context of DNA treatment could, therefore, provide the appropriate safeguards in the interests of research. Moreover, the development of animal vaccines would lead to increased research on vaccines in general and, in consequence, enhanced competence in this field.

When assessing DNA vaccines and gene therapy for the medical treatment of humans, the interests of human health and benefit to the community would be weighed against environmental considerations. Hence, it might be possible to defend a policy where humans are allowed DNA treatment, whereas a restrictive approach is chosen for the DNA treatment of animals in the environment. It is, of course, possible for patients to choose not to receive DNA treatment if they so wish.

Safeguarding health aspects by regulating the animal

Since food is assessed from a health point of view with regard to its components and residual medicinal products present, the designation "GMO" or "non-GMO" should, in principle, have no decisive impact on the health aspect of the food product. Nevertheless, it is conceivable that more work would be devoted to demonstrating that a food product produced from a DNA-treated animal is non-hazardous to human health, if specific labelling was required for such a product.

Any regulation of the DNA treatment of animals that is so restrictive as to obstruct the build-up of research and competence could have an adverse effect on medical competence in the field of DNA vaccines and gene therapy for humans. A more subtle regulatory system, setting up requirements for the characteristics of the genetic material involved, could, on the other hand, help in the development of DNA treatment for medical use in humans.

Safeguarding health aspects by regulating treatment

New veterinary medicinal products based on biotechnology and gene technology must all be assessed for health risk – for the veterinarian using them, but also for possible effects on others. This holds true irrespective of whether the medicinal product is classified as a GMO or not. However, if the GMO concept is extended to also apply to genetic constructs used in DNA treatment, gene therapy products and DNA vaccines for human use would have to be approved as deliberate releases of GMOs prior to use. Human beings themselves would not, however, be regarded as GMOs.

6.4 Consumers

Consumer interests

Good information and freedom of choice

The introduction of labelling requirements for genetically modified food is a consequence of the fact that people have different views on such products. The same might also be relevant for products produced from DNA-treated animals. Consumers are largely able to influence the market, and a labelling of salmon as genetically modified as a result of DNA vaccination, could lead to a decline in the sale of fish. If the labelling requirement is also to cover imported products produced from animals that have received DNA vaccines, the number of GMO products may become so vast that many consumers could gradually resign and end up thinking that "everything" is genetically modified.

The introduction of a new labelling category, e.g. "DNA-treated" would provide more balanced information, but also make it more difficult for consumers to react to labelling. Furthermore, for many consumers it would be important to have access to information about production methods; this is the reason for the introduction of process labelling of GMOs in Norway and the EU. An alternative could be to make information available to consumers in other ways than by labelling.

Wide selection, good quality and low prices

Consumers are also interested in having a wide selection in the supermarkets, good quality products from healthy animals and low prices. Effectively combating disease in animal production for food purposes is an important factor in this respect. Hence, it is also in the consumer's interests that production runs as smoothly as possible and that producers are allowed a choice of the medicinal products they believe to be the best for their animals. On the other hand, highly intensive animal production may lead to poor conditions of life for the animals and to poorer quality of the products. Good business development may contribute to added value in society and improved purchasing power for the individual consumer.

Confidence in the authorities

It is natural to feel scepticism towards new and unfamiliar technologies, and perceived risk may often deviate from actual risk. It is important that a regulatory system creates confidence among consumers and that they feel that their interests are being safeguarded. This applies not only to objective information, but also to control measures and risk research and is helped by ensuring that the regulatory system coincides with the ethical principles of the general public. If the principle objection to GMOs is founded on resistance to intentional heritable alterations, a concept of GMOs that also includes DNA-vaccinated animals might be perceived as an unfortunate watering-down of the concept, so that it loses much of its force.

Safeguarding consumer interests by regulating the animal

With a regulatory system where DNA-treated animals are considered as GMOs at their time of slaughter, the products would be labelled "genetically modified". Consumers may either feel that their confidence in the public authorities is enhanced as a result, or there might be an unworkable watering-down of the concept if *too* many products would be given this labelling. Reduced confidence with certain consumers can be the result if the regulatory system runs contrary to their arguments for wanting GMO products to be labelled. The supply of food products could also decrease and prices rise, as a result of import restrictions.

If choosing the term "DNA-treated" to designate animals that have received DNA vaccines or gene therapy, and by labelling the products accordingly, consumers would have to deal with a new category of products. Sound public information would be required, and it is not entirely evident how consumers would react. Furthermore, the supply of food products might be limited, due to import restrictions, depending on the rules that apply to the import of products from DNA-treated animals and on whether these rules deviate from those of our trading partners.

If DNA-treated animals are not regarded as GMOs and are not labelled in any particular way, it will be up to the individual consumer to obtain information about any medicinal treatment of the animals and otherwise trust that residual medicinal products are well below the level involving health risks. This alternative would entail few import restrictions on animal products.

Safeguarding consumer interests by regulating treatment

By regulating treatment and not the animal, consumers would be allowed no choice from shop shelves based on personal opinion. However, an appropriate regulation of treatment could contribute to good quality of the products.

6.5 Business interests

Taking account of business interests

In the interests of business development, it is generally important to have clear-cut, precise guidelines so that companies can avoid making unsound investments. At the same time, there is a case for avoiding an excessively complicated and laborious bureaucracy that might give rise to serious practical difficulties.

Today's markets strive to achieve a level playing field in order to promote competition between companies. In this respect, Norway is part of the EEA and free competition applies across national borders. For Norwegian producers wishing to be part of this market, it will be important that Norway's rules are no more restrictive than those of our trading partners in the fields of natural resource use and the development and sale of products.

Development of veterinary medicinal products

Norway has approximately half of the world's market for fish vaccines, and there is a large potential market in the aquaculture industries. Firms and research environments in Norway are in the forefront of developments of medicinal products for fish. This has given rise to high-competence environments that, in turn, provide good breeding grounds for further growth in the industry. Most firms have been bought up by large, international pharmaceutical companies that have seen the potential of the fish-farming industry. These are companies capable of contributing with their experience and financial power to ensure that new medicinal products are approved through centralised procedures.

DNA vaccines are relatively simple to develop, since finding the right culture conditions for new pathogenic organisms is not needed. The vaccines are cheap to produce, since standard methods for purification may be used. Furthermore, DNA is stable at a wide range of temperatures and

does not require refrigeration. In addition, if the vaccine can be administered orally or by means of immersion instead of injection, the vaccination process becomes significantly cheaper. DNA vaccines seem, therefore, to hold a great potential as medicinal products.

Pharmaceutical manufacturers would like to see a liberal regime allowing for the development of the best vaccines or therapies, irrespective of the method used. On the international market, good effects and good prices would sell best. Specific medicinal products could replace the more general drugs that have side effects, in the same way as vaccines against specific diseases have replaced the use of antibiotics in the fish-farming industry. This is a trend that would benefit society and that might, therefore, pay off to focus on. Having national cooperating partners and users will encourage the development of medicinal products here in Norway. A more restrictive regulatory system in Norway compared to other countries might, on the other hand, hamper the development of such products in this country. But a strict regulatory system could also contribute to putting pressure on industry to produce even more environmentally-friendly medicinal products.

Aquaculture industry

A wide choice in the types of vaccine technologies offered would make it easier to combat disease efficiently in fish-farming facilities. Furthermore, if injections can be avoided, and the vaccines can be administered either orally or by means of immersion, the vaccination process would become cheaper to perform.

Medicinal products may also contribute to increasing production efficiency beyond that of combating disease, for example, by promoting rapid growth and other properties. In this way, a free choice of the best medicinal products, including DNA vaccines, living genetically modified viral vaccines and gene therapy, may contribute to increasing the production in fish-farming facilities.

Nonetheless, fish-farmers in Norway today want to offer “clean” products. This is in line with rising consumer awareness, which has also led to increased sales of organic food. Fish-farmers depend on the confidence of consumers and, at the present time, are, therefore, not interested in exploring the possibility of genetically modified products. If DNA treatment is regulated by means of a liberal regime, Norwegian farmed fish may face unwanted competition from, for example, imported fish that has received gene therapy in the form of growth hormone genes. A regulatory system for genetic modification and DNA treatment in Norway that takes due account of the environment could, on the other hand, be used in the marketing of Norwegian food products as more environmentally-friendly than products from many other countries.

Agrobusiness

For the agricultural sector, as for aquaculture, it is a matter of having a wide range of effective medicinal products capable of combating disease in livestock more efficiently and lower the production costs. New properties may contribute to the further development of products. Genetic modification, gene therapy and DNA vaccines could be used to achieve such aims. On the other hand, producers are best served if confidence among consumers is retained, and as long as there is resistance to products labelled as GMOs, many producers will seek to avoid this label on their products.

Wilderness sector

The development of medicinal products to combat disease in wild animal populations has also begun. One example is a genetically modified vaccine that was introduced into fox bait in Belgium to combat rabies. Recently, the first DNA vaccine in practical use was given to the endangered Californian condor to protect it against the fatal West Nile virus (17). Medicinal products of this type could also replace more unspecific measures, such as rotenone treatment of rivers aimed at eradicating the salmon parasite *Gyrodactylus salaris*.

Safeguarding business interests by regulating the animal

If DNA-treated animals are regulated as GMOs, developing and selling DNA vaccines will become a complicated matter. Many animal producers will refrain from using DNA treatment if they risk having to label the animal as a GMO, and their use will require authorisation for every new deliberate release. Restricted freedom of choice might conceivably hamper the fight against animal diseases and keep production costs at a higher level. By regulating DNA-treated animals as temporary GMOs, many DNA vaccines could be used, but there might be additional costs involved in keeping animals contained for a certain period of time. Also a labelling as "DNA-treated" would go against the wishes of many animal producers.

If DNA-treated animals do not need to be specifically labelled, and authorisation does not have to be applied for prior to each individual treatment, this will enable a much more liberal use of DNA vaccines and gene therapy in animal production. It might also contribute to growth in the development of veterinary medicinal products in Norway. If the criteria determining which treatments make an animal a GMO, are not clear, and applications are assessed on a case-by-case basis, pharmaceutical companies and users will need clear-cut guidelines and reasonably predictable approval procedures.

Irrespective of regulatory method, it will be possible for individual producers to continue to engage in the types of production that do not involve the use of DNA treatment, if they should so wish.

Safeguarding business interests by regulating treatment

By extending the GMO concept to include forms of naked genetic material, or if DNA treatment is subject to the same regulatory system, the authorisation procedures applying to DNA treatment will be the same as those applying to the use of living, genetically modified viral vaccines. Many major pharmaceutical companies will have the necessary funds and experience to carry through an authorisation procedure

in Norway. This depends, however, on whether the sales potential is considered significant enough, something that may, in turn, adversely affect price and supply, seen from a user perspective. Hence, users should also have the possibility of applying for the authorisation of a product.

When regulating DNA treatment in ways other than as a method for genetic modification, guidelines should be clear and should avoid imposing an unnecessary workload on producers and users. The import and use of medicinal products and the import and export of animals would be simplest if Norway and the EU practised the regulations in the same way.

6.6 International cooperation

Interests of international cooperation

Import and export agreements

If the definition of a GMO is interpreted differently in Norway compared to its surrounding countries, including the EU area, this may lead to difficulties for import and export activities. DNA treatment that in Norway would render the animal genetically modified, would perhaps, for this reason, not be practised here. In that case, some products might be outpriced by cheaper products from other countries. When importing animal products for food and animal feed, labelling of a product as genetically modified (or as DNA-treated) may be required, and if products are to be labelled, they must first be approved. If the products are not classified as GMOs in their country of origin, it might be difficult to obtain sufficient information to carry out a thorough evaluation here in Norway of every product prior to its import into the country. If the animal itself is classified as a GMO, the import of living animals will have to be considered as a deliberate release of a GMO. In this context, the necessary information might be more readily available in the form of vaccination certificates, etc. However, a regulatory system of this type would place strong demands on public authorities. Furthermore, in order to contribute to a

good climate of cooperation, unnecessary accusations of setting up trade barriers should be limited as far as possible.

Since the legal basis of the new EU Directive on the deliberate release of GMOs is founded on the Amsterdam Treaty and since it does not allow for stricter rules in the individual states, it will be up to Norway to negotiate, through the EEA Agreement, if the Norwegian authorities wish to apply a different regulatory system in this country. If Norway chooses to regulate DNA-treated animals as GMOs and the EU does not do so, the key question at the next juncture may be whether many animal products from EU states will have to be stopped at the border on the grounds of a lack of authorisation and labelling of the products as GMO products. Since DNA vaccines are so far not in use for production animals in the EU, it is unclear, however, whether the various EU member states will interpret and apply EU rules differently.

The sea as an arena of deliberate release

Norway's regulatory practice on issues of genetic modification and the DNA treatment of animals in nature may entail consequences for other countries beyond the regulatory scope of current trade agreements. This applies in particular to fish and other marine animals, but also to birds and insects.

Similarly, Norway will be affected by the practices of other countries. A regulatory system applying to this field should, therefore, be regarded as an international matter.

Possible means of influence

It is unclear whether authorised products for DNA treatment purposes are to be considered as genetically modified medicinal products in the EU and also whether DNA treatment that is non-medical will render the animal genetically modified. Different EU member states may interpret EU Directive 2001/18/EC differently. In this respect, Norway could contribute to clarifying the problem and work to achieve a regulatory practice that meets the challenges involved in a constructive manner. If Norway, on the

basis of sound justification, opts for a regime of clear regulation and argues well in favour of such a system, it might contribute to a debate on regulatory systems within the EU and in other countries as well.

Developing countries

The development of DNA vaccines may give rise to new vaccines for both human and animal use in developing countries, where thermal stability and reasonable production costs constitute essential aspects. A regulatory system that promotes the development of DNA vaccines providing a high level of security for health and the environment could, therefore, contribute to more efficiently combating disease in developing countries.

Safeguarding the interests of international cooperation by regulating the animal

The EU's deliberate release directive is open to differing interpretations of the concept of GMOs, and by linking the regulation of DNA-treated animals to an interpretation that agrees with the EU Directive, Norway could work to establish a constructive dialogue with its trading partners in the EU. If Norway chooses to retain the possibility of exercising discretion in the interpretation of the GMO concept, any divergent practice could be adjusted if trade conflicts arose.

Safeguarding the interests of international cooperation by regulating treatment

If the definition of GMO in Norway is extended to include plasmids, the import of many medicinal products could get complicated, because they would then be considered as GMOs. Viral vaccines from the EU will have undergone an environmental risk assessment as GMOs, but perhaps not DNA vaccines to the same extent. It also would influence relations between Norwegian and international researchers working with DNA vaccines and gene therapy for humans, since many of these genetic constructs would also be defined as GMOs. Furthermore, it would complicate Norwegian participation

in research projects in the field of molecular biology in general, where the exchange of plasmids constitutes an important element.

If a regulatory system is linked to the use of DNA treatment and not to the

product, this too might hamper trade with countries that have a different regulatory system. However, there would also be the possibility of contributing to the setting up of a common set of international rules for DNA treatment of animals.



Photo: Karin Beate Nøsterud, VG / Scanpix

7. Summary of regulatory alternatives

7.1 Regulating the animal

1a. GMO if genetic material has at any time been added to the animal

Considerations made:

- It would be impossible to rule out that some of the DNA might have reached the reproductive cells and been incorporated there. Furthermore, some of these animals might escape and the genes might be passed on.
- Naked, modified DNA might be transferred to other species without the consequences being known in advance. A precautionary attitude would indicate that this should be avoided as far as possible.
- With gene therapy, it would be possible to select (intentionally or unintentionally) animals where the DNA has been incorporated into the genome. Alternatively, it might be possible to select the offspring that have inherited the added genetic material. In that case, the method would be almost identical to the one commonly used to produce transgenic animals.
- It would be possible for consumers to avoid the products of DNA-treated animals, without having to deal with a specific category for such products.

Consequences:

- All animals that had received DNA vaccines or gene therapy would have to be classified as GMOs, thereby creating a labelling requirement for the products.
- It might lead to conflicts due to import restrictions, because our trading partners might have other labelling regulations. It might also become difficult to obtain information about the DNA treatment of imported animals and products from countries applying different labelling regulations.
- Different combinations of animals and vaccinations would have to be assessed as separate releases and this might hamper the development and use of such medicinal products.

- The development of DNA vaccines for use on humans might also be hampered.

Challenges:

- The concept of GMO might be watered down.
- There might be the possibility of methods for the indirect DNA treatment of animals not performed “by means of gene or cell technology” in the form of intentional “introduction into living cells”, e.g. in the form of animal feed additives.
- Animals having received live, attenuated viral vaccines have also had DNA or RNA introduced into the cells. It could therefore be considered whether these animals also should be termed GMOs. A genetic characterization of attenuated viruses might indeed lead to a situation where the requirements for being termed “gene technology” would gradually be met.

1b. GMO as long as the added genetic material is present

Considerations made:

- Genetic material might be spread to the environment and it would be important, therefore, to keep such material under controlled conditions until it was degraded. Hence, the animal would be regulated as a GMO until it could be assumed that the added DNA was degraded. Replicating and integrating genetic constructs will remain present for longer periods of time than short DNA molecules, so their use would be limited.
- It would be important not to water down the concept of GMO, and a distinction would, therefore, be made between the animals that were known to have undergone heritable alterations and the animals that had received DNA vaccine/gene therapy on somatic cells only. The likelihood of incorporation of added DNA in the chromosomes of reproductive cells would be considered so slight that it could be ignored.

Consequences:

- The animal would be termed genetically

modified when foreign genes are present in the animal's cells. Hence, it would only be classified as a GMO for a certain period of time and would, following an estimated DNA degradation period, no longer be considered a GMO.

- It would be possible to use DNA vaccines and at the same time take account of environmental considerations.
- In the event of a deliberate release, every vaccination case would have to be assessed separately. If vaccination took place within the context of contained use, involving subsequent release or sale, the duration of the GMO period would still have to be determined.
- Imported animals and products would have to be assessed, so as to determine whether or not the products would need labelling. This might lead to trade restrictions on certain products.

Challenges:

- It would be difficult to know at what point in time the added DNA was degraded.
- It might be difficult to obtain information about the DNA treatment of imported animals and products.

1c. GMO when the added genetic material is likely to become heritable

Considerations made:

- Emphasis would be placed on preserving the species, by regulating possible heritable genetic modification in the same way as deliberate, heritable genetic modification. At the same time, emphasis would be put on the likelihood of integration occurring.
- The use of DNA vaccines in animal production might combat disease more efficiently than traditional vaccines.

Consequences:

- This would enable the use of DNA vaccines where there was only a very slight probability that the genetic material would be inherited.
- Gene therapy on animals might, to a greater degree than for DNA vaccination, mean that the animal would be regulated as a GMO.
- When importing live animals, detailed

information on any DNA-treatment would be required.

Challenges:

- It would be difficult to estimate whether the added genetic material might be heritable, and trials would be required in order to show that it would not be integrated into reproductive cells.

1d. GMO when the new genetic material has particular characteristics

Considerations made:

- Consideration could here be given to the possibility that certain types of genetic material might give the animal entirely new properties affecting its natural characteristics.
- It would also be possible to take account of the risk of gene transfer, as well as of integration.

Consequences:

- This might enable the use of DNA treatment in the fight against disease, while restricting the use of gene therapy for other purposes.
- Detailed guidelines would need to be drawn up, taking into consideration the many different types of genetic constructs, and it would be logical to process applications on a case-by-case basis.
- It would be possible to exercise discretion, as well as to adjust practices en route, if so desired.

Challenges:

- The guidelines drawn up for manufacturers, producers and administrators would have to be clear-cut to avoid ambiguity.

1e. DNA-treated animals are given an entirely new designation

Considerations made:

- A distinction would be made between heritable genetic modification and DNA treatment, while simultaneously regulating DNA treatment.
- The animals would be given a designation that provided information about factual circumstances.

Consequences:

- Food products could be labelled specifically with “DNA-treated” or the like.
- The concept of GMO would not be watered down.
- It would be possible to draw up a separate regulatory system for DNA treatment.
- Imported food could be labelled in the same way, on the basis of information provided by the producer.
- Labelling requirements might have a price-raising effect.

Challenges:

- It might be quite challenging for consumers to have to deal with a separate category for DNA-treated animals.
- There might be more complicated rules regulating the use of gene technology on animals.
- A new labelling category might lead to trade barriers.

1f. The term “GMO” is reserved for deliberate, heritable modifications

Considerations made:

- The likelihood of heritable alterations following DNA treatment is very slight, and the concept of GMO should not be watered down.
- Animal producers should be given freedom to choose the treatment that is best for their animals and for production efficiency.

Consequences:

- Animals that have been treated with DNA vaccines or gene therapy as medicinal products would not be classified as GMOs.
- Nor would other types of gene therapy on animals be covered by the Gene Technology Act.
- Producers in Norway might experience favourable competitive conditions, but it might also reduce the possibility of specifically marketing “clean” products.

Challenges:

- Treatment with DNA that is not a medicinal product might approach methods for deliberate genetic modification, and clear-cut guidelines would have to be drawn up.

7.2 Regulating treatment

2a. Genetic material for DNA treatment is regulated under the Gene Technology Act

Considerations made:

- Account would be taken of the fact that certain genetic constructs may be replicated and spread in the surroundings, and the use of more environmentally-friendly genetic constructs would be encouraged.

Consequences:

- Certain DNA vaccines and gene therapy products for human use might also be classified as GMOs.
- If certain DNA constructs were defined as GMOs in Norway only, the import of many new medicinal products might become difficult.
- Norwegian participation in international research projects in the field of molecular biology might be complicated.

Challenges:

- Naked DNA has not been regulated under the Gene Technology Act in the past, and if any genetic constructs were included in the GMO designation, this would mean that the rest of the act would have to be reconsidered in light of this development.

2b. Specific legal provisions regulating the DNA treatment

Considerations made:

- The difference between heritable genetic modification and DNA treatment would be clarified in regulations and in terms of possible required labelling.
- A separate requirement for an environmental risk assessment might be specified.

Consequences:

- The GMO concept would not be watered down.
- The products could be developed and marketed, even though their use might be somewhat limited for Norwegian animal producers.

Challenges:

- New grey areas might be created between the statutory regulation of DNA treatment and the regulation of heritable genetic modification.

2c. DNA treatment of animals is covered by other legislation

Considerations made:

- Genetic modification would be considered to apply only to heritable properties, and the preservation of species and the ecosystem would not be considered threatened by DNA treatment that did not specifically aim at genetic modification.
- DNA vaccines and gene therapy would, in most cases, be covered by the Medicinal

Products Act and other legislation, and unnecessary double regulation could be avoided.

Consequences:

- DNA-treated animals and the products of such animals would not be classified as GMOs.
- There would be no additional regulation of the development and use of medicinal products based on DNA.

Challenges:

- DNA treatment that, with a reasonable degree of probability, might result in heritable genetic modification would not necessarily be covered by the other legislation. The grey area of the Gene Technology Act would, therefore, still need to be clarified.



Photo: Heiko Junge / Scanpix

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Regulation of DNA vaccines and gene therapy on animals

In its letter of 02.10.01, the Ministry of the Environment asked the Biotechnology Advisory Board to discuss how DNA vaccines and gene therapy on animals should be regulated and what should be the status of DNA-treated animals under such a regulatory system.

New and promising methods for preventing and combating disease are currently being developed, in the form of DNA vaccines and gene therapy, which are based on the transfer of genetic material to cells of the body. These methods are, therefore, approaching the methods used to genetically modify organisms. This raises the question of whether an animal is to be considered a genetically modified organism (GMO) when it receives DNA vaccines or gene therapy. In that case, the animal would be regulated under the Gene Technology Act.

The Biotechnology Advisory Board raised this issue for the first time at an internal seminar in Namsos on 05.09.2001 and has, following the enquiry made by the Ministry of the Environment, drafted a separate document highlighting the various aspects of the problem (see enclosure). The Board has subsequently discussed possible regulatory methods for the DNA treatment of animals in the light of the internal seminar and the discussion paper and has arrived at a recommended regulatory method.

The concept of “DNA treatment”

Vaccines and gene therapy may be administered in the form of genetically modified viruses and bacteria. However, the concept of “DNA treatment” is here used as the transfer of nucleic acids – either DNA or RNA – in ways that do not entail the use of genetically modified organisms. The term covers both DNA vaccines and gene therapy for purposes other than influencing the immune system. In the discussion on a regulatory system for the use of DNA vaccines and gene therapy on animals, it may be useful to apply a separate designation to define the transfer of nucleic acids that takes place without the use of genetically modified viruses or bacteria.

The Norwegian Biotechnology Act uses the term “gene therapy” to cover all intentional transfers of genetic material to cells in the human body. This use of the concept includes DNA vaccines and gene therapy in the form of naked or encapsulated DNA, as well as the transfer of genetic material by means of genetically modified viruses and bacteria. In the context of a statutory regulation of DNA vaccines and gene therapy on animals, the term “gene therapy” could be defined and used in the same manner, if conformity between the Gene Technology and Biotechnology Acts is required.

Regulating DNA treatment in a separate chapter of the Gene Technology Act

Since DNA treatment may give rise to a wide range of possible consequences, the Biotechnology Advisory Board, with the exception of two of its members, would like to see DNA treatment regulated in accordance with the principles laid down in the Gene Technology Act. Board members Grethe Evensen and Christina Abildgaard, however, maintain that it would be natural

for Norway to follow the same regulatory practice as that adopted by the European Union in respect of DNA vaccines and gene therapy as medicinal products (see below).

DNA treatment may entail serious environmental consequences, also when the genetic material is not inherited. Furthermore, since DNA treatment involves a series of different methods and genetic constructs, it is important to apply a system of case-by-case evaluation, ensuring a thorough environmental impact assessment. The majority of the Board's members recommends, therefore, that DNA treatment is regulated in the form of a separate chapter of the Gene Technology Act, specifying the rules that apply to DNA treatment. The Board believes that such a chapter could be drafted in such a way that it would apply to the DNA treatment of all types of multicellular organisms, including plants, and not only to animals. Board members Grethe Evensen and Christina Abildgaard support a system of case-by-case evaluation of applications, but argue that regulation through existing legislation would safeguard these aspects as far as medicinal products are concerned.

The production and use of genetically modified organisms is currently divided into contained use and deliberate release respectively, where the requirements applying to contained use must be fulfilled so as not to be considered a deliberate release. The Biotechnology Advisory Board suggests that this distinction is maintained. The rules and evaluations applying to contained use and deliberate release could, on the whole, be the same for DNA treatment as for the genetic modification of organisms, but the barriers against the spread of genetic material and the criteria for contained use could differ somewhat.

It might be useful to consider whether Section 5¹⁾ of the Animal Welfare Act should be amended to also cover DNA treatment, and not only genetic modification related to breeding.

Definition of a GMO

The Gene Technology Act's definition of a "genetically modified organism" leaves room for interpretation as far as DNA-treated animals are concerned. A similar room for interpretation is also to be found in EU Directive 2001/18/EC related to the deliberate release of genetically modified organisms.

The Biotechnology Advisory Board would not like to see the concept of "genetically modified organism" watered down and supports, therefore, the position that the use of DNA vaccines and gene therapy on animals should not, as a rule, be regarded as genetic modification. However, the Board would like to retain the possibility of exercising discretion in case-by-case evaluations and would, therefore, advise against stipulating an absolute requirement of heredity for the animal to be termed genetically modified. If it can be shown probable either 1) that the added genetic material will be inherited by the offspring, 2) that the genetic material will pose a risk to health or the environment if it is inherited, 3) that the genetic material, through recombination, can result in organisms with new, unwanted properties, or 4) that the genetic material will give the organism properties that will lead to a public outcry, the Board would recommend that one allows for the possibility of defining the organism as genetically modified, with the subsequent manda-

1) Section 5 of the Animal Welfare Act. *Breeding*

It is prohibited to alter the heritable material of animals by means of gene technology methods or by means of traditional breeding methods if:

1. it makes the animal unfit for carrying out normal behaviour or if it adversely affects its physiological functions;
2. the animal is caused unnecessary suffering;
3. the alteration arouses general ethical concerns.

It is prohibited to breed animals covered by the first paragraph.

tory application of labelling requirements. Subject to these criteria, most DNA vaccine plasmids would not render animals genetically modified, whereas certain forms of gene therapy would be covered by the criteria. Furthermore, DNA treatment, when used in the production of a genetically modified organism, would not be exempted from the rules currently in force.

The deliberate release of genetically modified organisms must be assessed for possible risk and, if necessary, the precautionary principle must be applied. This holds true under Norwegian law, the EU Directive 2001/18/EC and the Cartagena Protocol on biosafety. If Norway were to determine that the same rules should apply to DNA-treated animals, but without simultaneously classifying them as genetically modified organisms, this might be perceived as an exceptional regulation. Hence, the Board would recommend that the regulatory system is drafted in such a way that the requirement of risk assessment may be linked to the need to evaluate whether treatment would render the animal genetically modified or not. In this way, the risk assessment is covered by international rules currently in force.

The regulatory system could be worded in such way that it would also apply to the deliberate release of DNA-treated animals that have been imported alive after having undergone treatment. There should also be the possibility of assessing whether animals having received DNA vaccines and gene therapy in the form of living, genetically modified viruses or bacteria meet the criteria for a genetically modified organism, in order to avoid the use of genetically modified viruses instead of plasmids in instances where plasmids would involve a lesser environmental risk.

Regulating DNA treatment in relation to medicinal product regulation

The Biotechnology Advisory Board would recommend regulation of the treatment itself, i.e. the *use* of DNA vaccines and gene therapy on animals. Since Norway is linked to the EU's system for the evaluation and approval of medicinal products (EMA), Norway cannot impose restrictions on marketing permission for DNA vaccines and gene therapy products that have been approved as veterinary medicinal products. However, their use may be restricted, if required.

DNA vaccines and gene therapy may also be administered in the form of genetically modified viruses or bacteria. Medicinal products that are also genetically modified organisms are exempted from the provisions of EU Directive 2001/18/EC on the placing on the market of GMOs, but an equivalent environmental risk assessment is required. This type of assessment also covers the animals and environment in which GMO medicinal products are to be used. Furthermore, it is stipulated in the related food and feed regulation that animals treated with genetically modified medicinal products are not to be considered as genetically modified.

DNA vaccines and gene therapy products that are not GMOs are not covered by the same statutory requirement for an environmental impact assessment. Hence, the animals to be treated and other organisms in their environment would not be subject to an environmental risk assessment equivalent to that of the GMO medicinal products. The majority of the Biotechnology Advisory Board holds that it is important to establish in law the requirement for an environmental risk assessment that relates to medicinal products based on nucleic acids, and that such assessments should be conducted by the same bodies that today evaluate the deliberate release of GMOs. The Board's majority calls on the environmental authorities to strive to ensure that such a regime is implemented in the EU as well. This would ensure regard for the environment as well as confidence in producers.

Board members Grethe Evensen and Christina Abildgaard maintain that Norway, out of consideration for Norwegian trade and industry and its competitiveness, should await and follow the European Union's coming practice for the regulation of animals treated with EMA-authorized DNA vaccines and gene therapy products. A harmonized regulatory practice in Norway would be crucial to preserving the industrial competence that has been built up in Norway, as well as to

ensuring further efforts to develop products with the aim of obtaining permission for their use and marketing in Norway. Norway has a large fish-farming industry and approximately one half of the world market for fish vaccines. Hence, Norway should proceed with caution in this matter.

Application requirements

Applications for the deliberate release of DNA-treated animals or for the treatment of animals that are in the environment will, in principle, require an environmental impact assessment and will be subject to a case-by-case evaluation, in accordance with the same principles as for the deliberate release of genetically modified organisms. As experience with DNA-treated animals gradually accumulates, the requirements might possibly be adjusted by means of administrative regulations. So as to enable a practical, case-by-case evaluation of the use of marketed products, the Board would suggest that the producer, or the importer or the potential users should be allowed to apply for authorisation to use the product. To maintain proper control of the number of animals receiving treatment, a reporting system could be set up. For experimental activities and clinical trials using non-approved products, the project manager would be the applicant.

For DNA-treatments of animals, it is necessary to have information about the duration and spread of the DNA in the animal, the risk of integration, the number of animals receiving treatment, etc. Environmental impact assessment requirements in applications for DNA treatment could be based on the guidelines already developed by the EMEA, WHO and FDA for DNA vaccines and gene therapy, and on the environmental impact assessment applying to the deliberate release of genetically modified organisms.

Labelling

The Biotechnology Advisory Board wishes to avoid a “watering down” of the concept of GMO and favours, therefore, the position that animals having received DNA vaccines and gene therapy for veterinary medical purposes would not be covered by the GMO concept unless they fulfilled the criteria for classifying an animal as a genetically modified organism, as outlined above.

The introduction of a separate labelling category for DNA-treated animals might be a relevant option. In that connection, the Biotechnology Advisory Board believes that emphasis should be placed on the wish of consumers for relevant information – not only about the end product, but also about the production method. The implications of the EEA agreement should also be taken into account. It should further be considered whether a separate labelling category or a negative labelling ought to be internationally recognized before being implemented in practice. Information could also be made available to consumers in ways other than through direct labelling of the products. Furthermore, to ensure consumer confidence, requirements should be specified concerning the level of residual quantities of the added genetic material in the end product, similar to the rules on maximum residual limits of veterinary medicinal products in products of animal origin.

Yours sincerely

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Enclosure:
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