

Gene medication or genetic modification? The devil is in the details

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Medication based on the transfer of genes, like gene therapy and DNA vaccines, holds the promise of combating diseases both in humans and animals. Similar methods of gene transfer are used when making genetically modified (GM) animals. When exactly is a 'gene-medicated' animal also a genetically modified organism (GMO)? In Europe and elsewhere, GMOs are subject to limited release and to rules of labeling; therefore, the answer could have implications for pharmaceutical companies, veterinarians, food producers, consumers and even pet owners.

The overlap of the fields of gene medication and genetic modification is a challenging area where two distinct cultures and regulatory systems hold sway: medicine and biosafety. The first focuses mainly on intended effects in target animals, the second on unintended effects on ecosystems; the fields often represent conflicting perspectives. Central to the territorial battle are the regulatory definitions of 'medicinal product', 'genetic modification' and, as a result of exemptions already laid down in European regulations, the issue of what constitutes an 'organism.'

Definitions

People intuitively understand the term 'medicinal product' to mean preventing, diagnosing or treating disease. The definition is in fact broader, in that a substance that may be administered to animals with a view to modifying physiological functions is likewise considered a veterinary medicinal product, as stated in the European Union (EU; Brussels) Directive 2001/82/EC. Illustrative examples are CSL Animal Health's (Parkville, Victoria, Australia) gonadotropin-releasing factor vaccine (Improvac) developed for male pigs to

eliminate the boar taint from pork—a process called 'immunocastration'—and the vaccines being developed to reduce the fertility of pest animals like the wild Australian rabbit.

Similarly, genetic modification is not limited to the addition of heritable properties. The definition of genetic modification of organisms is based on the technology used and not on the intention. In the EU directive 2001/18/EC on deliberate release of GMOs, the term GMO is defined as '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.' In the Cartagena Protocol on Biosafety to the Convention on Biological Diversity, the focus is likewise on the technology used and not on the properties added. Here, the equivalent of a GMO, a 'living modified organism' (LMO), is defined as 'any living organism that possesses a novel combination of genetic material obtained through the use of modern biotechnology.' Medication using an integrative gene therapy construct could, for instance, be seen to lead to a 'novel combination of genetic material.'

When is medication also modification?

The definition of genetic modification in the EU directive 2001/18/EC is made deliberately vague to cover new methods developed: "genetic modification occurs at least through the use of techniques listed in Annex I A, part 1." Injection of genetic material into testes is now being explored as a new method for genetically modifying animals¹. In the annex list, this method is covered under "techniques involving the direct introduction into an organism of heritable material prepared outside the organism including micro-injection, macro-injection or micro-encapsulation." Therefore, genetic modification can occur by injecting genes into whole animals, rather than manipulating cells in the laboratory. It is also genetic modification if, instead of direct injection, the foreign nucleic acid molecules are inserted 'into any virus, bacterial plasmid or other vector system' and incorporated 'into a host organism in which they do not occur naturally but in which they are capable of continued propagation.' Thus, gene medication applying heritable material or recombinant nucleic acid

molecules capable of continued propagation could be seen as genetic modification.

According to the Cartagena Protocol as well, methods of gene medication can be covered under the LMO definition in the protocol. Here 'modern biotechnology' means "the application of a) *in vitro* nucleic acid techniques, including recombinant 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."

When the fate of the added DNA is uncertain, it is not clear how the definitions will be interpreted. Is testing of the offspring needed to decide whether the added gene was indeed 'heritable material'?

Different interpretations

Regulatory bodies can interpret the definition of genetic modification differently. In a report last year, The British Agriculture and Environment Biotechnology Commission (London) took a stand on DNA-vaccinated animals²: "Importantly, the foreign DNA is not expected to integrate into the host's genome and so the vaccinated animal is not genetically modified." A more precautionary view is held by the Norwegian Directorate for Nature Management (Trondheim, Norway). In response to specific enquiries regarding gene medication of farmed salmon, they stated that a DNA-vaccinated fish is to be considered genetically modified for as long as the added DNA is present in the fish.

Interestingly, in the United States, where there is no specific regulation of GMOs, genetic modification of animals is to be regulated as medication. The US Food and Drug Administration (FDA; Rockville, MD, USA) has asserted that the genetic constructs used to create transgenic fish (and other animals) fall under the legal definition of a drug as a substance "...intended to affect the structure or function of the body of man or other animals." In a report issued in January and prepared for the Pew Initiative on Food and Biotechnology (Cambridge, MA, USA)³, concern is expressed over the FDA's legal authority and its limited ability to consider the ecological risks of

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GMOs. No federal agency seems to have clear-cut legal authority to regulate or ban transgenic fish on environmental grounds. The report also points to the lack of transparency and public participation associated with the assessments.

Unintended risks and product authorization

The risk of an event is defined as the probability of the event times its consequences. Therefore, one could argue that where the consequences are particularly adverse, the risk could still be high, despite a low probability of the event. To address the risk of unintended as well as intended consequences, a thorough risk assessment is required when applying for deliberate release of GMOs into the environment. The assessment is evaluated by the relevant national GMO authority. In the case of gene medication, unintended spreading, uptake and integration of the foreign DNA are likely to happen at a certain low frequency. The questions then are, how adverse are the possible consequences, which institution(s) should evaluate these potential GMOs, and with whom should the responsibility of assessing the risks lie?

In Europe, pharmaceuticals based on biotechnology are authorized through a centralized procedure by the European Agency for the Evaluation of Medicinal Products (EMA; London). For medicinal products containing or consisting of GMOs, a compromise has been reached; they are exempted from the EU directive on deliberate release of GMOs when placed on the market, provided that the authorization procedure includes an environmental risk assessment equivalent to that provided for by the directive. As part of the procedure, the national GMO authorities are involved in evaluating the environmental risks of the medicinal products and the animals receiving them.

Noticeably, the applications concerning GMO medicinal products lack the public openness central to other GMO applications and the GMO authorities do not have access to all the information needed for a cost-benefit analysis of the GMO. Moreover, the decision on market authorization is taken by the medicinal agency and not by the GMO authority as it is for other GMOs.

The Cartagena Protocol, which entered into force on September 11 this year, does not have a similar exemption for veterinary medicinal products, only for products for human use. Therefore, countries that have ratified the protocol, including the EU, have to disclose detailed information about these products if a receiving country wishes to do a cost-benefit

analysis before importation.

To date, few veterinary gene medication products have been granted market authorization. The first application of an experimental veterinary DNA vaccine was seen in the US in January this year. Californian condors in zoos and in the wild were vaccinated in an attempt to protect this endangered species from the West Nile virus⁴.

Labeling issues in the EU

When administering gene medication, food producers may risk having their living animals termed 'GMO' for a shorter or longer period. What may have more influence, however, is the fear of having to label the products of the animals as 'GM food.' Interestingly, the new EU regulation on GM food and feed (2001/0173(COD)) specifies that products of animals treated with GM medicinal products are not to be labeled as GM food. Considering the overlap between gene medication and genetic modification, does this exemption pave the way for the use of gene medication as a means of genetic modification through the backdoor?

Gene medication products that are not GMOs in themselves are neither evaluated by the GMO authority as part of the authorization procedure, nor covered by the Cartagena Protocol. The philosophical question of what constitutes an 'organism' becomes a highly practical one the moment these regulatory differences influence the choice of vector used for gene medication.

In the EU directive on deliberate release of GMOs, 'organism' means any biological entity capable of replication or of transferring genetic material. Similarly, in the Cartagena Protocol, 'living organism' means "any biological entity capable of transferring or replicating genetic material, including sterile organisms, viruses and viroids." Plasmids are not seen as organisms in themselves.

Although standard viral and plasmid vectors are easily categorized, the difference between genetically engineered viral genomes and plasmid-based viral genes packed into viral particles can be far from obvious. To a large extent, vectors can be engineered to suit the category preferred.

It is not obvious whether the labeling exemption is limited to the medicinal products authorized as GMOs, or whether it also covers medicinal products based on naked recombinant DNA. Should the exemption cover GMOs only, organisms might be favored over non-organisms as vectors for gene medication, regardless of the fact that plasmids might represent a lower risk both for the animal and the environment compared with viral vectors.

A possible compromise?

The Norwegian Biotechnology Advisory Board (Oslo) has made suggestions for how to regulate the overlap between gene medication and genetic modification. In theory, gene-medicated animals could have the same kind of adverse effects as transgenic animals, although generally with a substantially lower probability. The Board therefore recommends that all gene transfer to animals outside the laboratory, whether the intent is medicinal or not, should be assessed on a case-by-case basis by the authority assessing deliberate releases of GMOs and evaluated according to the same principles. However, the Board sees it as important not to dilute the concept of GMO and recommends that animals treated with gene medication products in general should not be termed GMO. To avoid creating a new category of 'gene-medicated organisms' that has no foundation in international regulations, the risk evaluation should be part of a process of considering whether the animal ought to be termed genetically modified or not.

The Norwegian Biotechnology Advisory Board suggests that the gene-medicated animal could be termed GMO if any of the following scenarios can be shown probable: first, that the added genetic material will be inherited by the offspring; second, that the genetic material will pose a risk to health or the environment if it is inherited; third, that the genetic material, through recombination, can result in organisms with new, unwanted properties; or fourth, that the genetic material will give the organism properties that will lead to a public outcry. Detailed guidelines need to be worked out for this system to become functional.

In the present overlap between the fields of gene medication and genetic modification, the devil is in the details, both in the biological and regulatory sense. To avoid bizarre interpretations, creative loopholes and unforeseen environmental effects, a more subtle system is needed. We have presented a possible compromise where the GMO authority is formally involved in assessing the environmental risk of all gene transfers to animals outside the laboratory. This allows better regulation where less depends on the definitions, the most appropriate vector can be chosen and the development of low-risk medicinal products is encouraged.

1. Sato, M. *et al.* *Mol. Reprod. Dev.* **61**, 49–56 (2002).
2. The British Agriculture and Environment Biotechnology Commission. *Animals and Biotechnology* (BAEBC, London, September 2002).
3. The Pew Initiative on Food and Biotechnology. *Future Fish, Issues in Science and Regulation of Transgenic Fish* (Pew Initiative, Cambridge, MA, January 2003).
4. Bouchie, A. *Nat. Biotechnol.* **21**, 11 (2003).