GENE EDITING REGULATIONS:

A POSITION PAPER FROM THE EUROPEAN FEDERATION OF BIOTECHNOLOGY

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Table of Contents

Summary 3

REASONS WHY THE RULING BY THE COURT OF JUSTICE SHOULD BE REVERSED ... 4

Differences between gene editing and genetic engineering. 4

Why some gene editing should not be considered to be equivalent to genetic engineering. 5

Why the 2001 / 18 Directive is irrelevant to traditional mutagenesis techniques. 6

The response of the European Federation of Biotechnology to Directive 2001 / 18 6

Safety: why the precautionary principle of Directive 2001 / 18 is inappropriate to gene editing 7

Consequences of the Directive for the Bioeconomy 8

Consequences of the Directive for the food security. 9

Consequences of the Directive for the Environment 9

Summary

On 25th of July 2018, the Court of Justice of the European Union ruled that the regulatory framework for genetic engineering should be extended to recently developed methods of gene editing. The judgement is based on the precautionary principle and a strict interpretation of directive 2001/18. The European Federation of Biotechnology regrets this ruling because it ignores scientific arguments that the interpretations of the technologies are scientifically inaccurate. The consequences will be the failure to encourage exploitation of gene editing within the EU, which will impact Society in the following ways:

- Failure to exploit the full potential of gene editing to improve human and animal health.
- Higher costs of food and other products because they will be imported rather than produced locally.
- Less security (safety and supply) due to dependence on products from outside the EU.
- Less ability to control safety standards or animal welfare.
- A negative impact on the environment.
- Failure to optimise the generation of new jobs in Europe.

"This ruling ignores scientific arguments that the interpretations of the technologies are scientifically inaccurate"

REASONS WHY THE RULING BY THE COURT OF JUSTICE SHOULD BE REVERSED

Differences between gene editing and genetic engineering.

Gene editing covers a range of different technologies and formats. In its simplest form an enzyme is directly targeted towards a certain DNA sequence and thereby introduces a double stranded cut in the DNA molecule. The cell responds to this by repairing the DNA and thereby small mutations are introduced. This is a process very similar to natural processes in which DNA strand breaks that occur naturally are repaired by the cell leading to mutations.

"Gene editing is very similar to natural processes in which DNA is repaired by cell leading to mutations"

Such events happen all the time in every cell and constitute a fundamental mechanism not only for evolution of species, but also for breeding of plants and animals by human selection. The most basic form of this type of gene editing format is termed Site Directed Nuclease 1 (abbreviated SDN1) mutagenesis and avoids the introduction heterologous DNA molecules. In other gene editing formats either small single stranded DNA molecules or large heterologous DNA molecules are inserted into the DNA strands at the breakpoint (the so called SDN2 and SDN3 formats, respectively).

Why some gene editing should not be considered to be equivalent to genetic engineering.

The term Genetic Engineering is defined in directive 2001 / 18 as

> *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 the 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.*

For the following reasons, gene editing using the SDN1 format is fundamentally distinct from genetic engineering.

1. No vectors are used to transfer the mutation to the target gene.
2. No foreign DNA is introduced into the target.
3. It is almost identical to, but potentially safer than, traditional random mutagenesis because there is no foreign DNA to be passed on to subsequent generations.
4. It simulates the natural evolution events that happen continuously to every single living cell.

The conclusion is that these gene editing formats should not be regulated more strictly than traditional breeding or conventional mutagenesis techniques that have been used safely in agriculture and industry for thousands of years and decades, respectively.

"SDN1 format is distinct from genetic engineering and should not be regulated more strictly than traditional breeding and conventional mutagenesis techniques"

Why the 2001 / 18 Directive is irrelevant to traditional mutagenesis techniques.

The second clause of the recent ruling by the Court of Justice ignores long-term established experience of science, industry and society and opens the door to fragmented legislation in EU states. It reads:

> *The Member States can regulate and subject to obligations the organisms obtained by methods of mutagenesis and which are exempted from Directive 2001/18.*

In essence this means that individual EU states are now free to legislate that strains improved by traditional "trial and error" or chemical mutagenesis approaches can be brought under the genetic engineering framework even if no safety issues have been identified. Examples that this might include are improved yeast for baking, brewing and wine making and all food crops used in modern agriculture. This ignores the fact that every organism in the environment has evolved under selective pressures and has potentially been exposed to horizontal gene transfer.

The response of the European Federation of Biotechnology to Directive 2001 / 18

The European Federation of Biotechnology (the EFB) regrets the decision that the regulatory framework for genetic engineering should be extended to recently developed methods of gene editing for the following reasons that will be amplified in subsequent sections.

1. The judgement is based on the precautionary principle and a strict interpretation of directive 2001/18. It ignores scientific arguments that the interpretations of the technologies are scientifically inaccurate.
2. Simplest format of gene editing (SDN1) poses no safety risk that cannot easily be resolved by safety checks already applicable to all products sold in the European Union.
3. The EU regulatory system in practical terms prevents approval of GMO plants and microorganisms to be used, for example to improve human or animal health, in fields as improved crop varieties, or to promote plant growth.

4. The regulatory burden will achieve nothing except provide motivation for multinational companies to transfer their research, development and production to countries with equally safe but less restrictive regulations.

Safety: why the precautionary principle of Directive 2001 / 18 is inappropriate to gene editing

The regulations for genetic engineering techniques in Directive 2001/18 were developed long before it was possible to sequence entire genomes rapidly and with high precision. The application of the precautionary principle to products developed by recombinant DNA techniques is justified on two grounds.

1. *Only after their sustained use can we judge whether the introduction of foreign DNA leads to unforeseen negative consequences.*
2. *Mutations introduced by genetic engineering or random mutagenesis might lead to potentially harmful traits.*

Both of these points are irrelevant to simple gene editing. The first point is irrelevant because gene editing using the SDN1 format does not result in the introduction of foreign DNA. The second point can be checked by whole genome sequencing or similar technologies of any newly constructed organism to ensure that there are no unintended secondary mutations in the new strain. This is one of the reasons why whole genome sequencing has been introduced as a requirement in the most recent EFSA guidelines on microorganisms (EFSA Journal 2018;16(3):5206). As with any other product available in the EU, the safety of any new strain must be checked to ensure that the mutation introduced does not result in unforeseen secondary safety issues.

"Gene editing using the SDN1 format does not result in the introduction of foreign DNA"

In summary, far greater safety can be achieved by insisting that any new strain must be fully sequenced and tested for safety before it can be applied for commercial use than by the application of irrelevant regulations designed for strains developed by totally different techniques.

"The introduction of a whole genome sequencing as requirement ensures a greater safety"

Whole genome sequencing of gene edited plants is a much bigger task than for microorganisms, but recent new technologies can support genome sequencing for testing of unintentional changes to the genome (Jupe et al (2019) PLoS Genet 15(1): e1007819. https://doi.org/10.1371/journal.pgen.1007819). The safety guidelines applied to cultivars obtained by traditional radiation or chemical mutagenesis, which represent the majority of crops currently grown in EU and are not regarded as GMO, should be sufficient.

Consequences of the Directive for the Bioeconomy

Gene editing offers great potential for beneficial advances in various areas of the emerging bioeconomy. Reluctance to support it will limit the opportunities for the EU to lead research solutions to many of the current major global challenges that amongst many others include: food security; agricultural production; global warming; environmental pollution; the establishment of a renewable biobased economy; the development of biopharmaceuticals based upon genomic data; and the development of cures for genetically inherited diseases. The EFB regrets that the EU has failed to learn the lessons from our previous failure to encourage exploitation of new strains and processes developed by genetic engineering, which has resulted in the transfer of process development and manufacturing by multinational companies out of the EU into the USA, South America and China.

The ruling will greatly limit technology transfer from academia and research institutes to European industry. Counter-productively, it will stimulate the transfer of intellectual property rights from the EU where they originated to nations with more supportive regulatory frameworks. This will severely limit life science research and inevitably decrease the creation of new employment opportunities in Europe. It will impact the career development of young scientists in Europe and reduce the motivation for a young scientist to stay in Europe and specialize in life science research that cannot be used for any practical purposes. The EU will face unnecessary increased costs resulting from the need to import new products developed in countries outside the EU.

"The EU directive limits the opportunities for the EU to lead research solutions to global challenges"

Consequences of the Directive for the food security.

A high growth rate in food production will be required to avert widespread starvation as the human population increases and the effects of global warming become increasingly severe. Clearly new technologies will be required to meet this world-wide challenge. Gene editing to produce safe but more productive plant strains provides ways to close the gap between supply and demand. The EU is again in danger of forfeiting by default its ability to make an impact on this challenge, with inevitable environmental and economic consequences.

Consequences of the Directive for the Environment

The ruling of the Court of Justice will limit the ability of EU member states to optimise local food production. Inevitable consequences for the environment will include the following.

- Imported foods will be transported longer distances than food produced in sufficient quantities within the EU.

- Less reliance on locally produced food will generate unnecessary extra demand for packaging. This has a double impact on the environment: first, more energy will be required to produce the packaging materials; secondly, the increased need for waste disposal will increase disposal costs and the risk of environmental pollution.
- There will be less incentive to exploit gene editing to develop drought resistant crops or crops that require less water, herbicides, pesticides or industrial fertilizers.

In summary, the adoption of these new regulations for gene editing will have a negative impact on many aspects of the environment, industry, food security, healthcare and innovation in the life science area that otherwise could be exploited for the benefit of European Society and keep Europe competitive. The EFB is pleased to work together with all stakeholders as a voice of science to shape the future of gene editing in a responsible, evidence-based and sustainable way.

Executive Board of the European Federation of Biotechnology. June 2019