

BENCHMARK GENE EDITING POSITION STATEMENT

Introduction

Benchmark is a global leader in the genetic development of aquaculture species making them more fit for the farming environment. We value our position to act as guardians of the animals under our care, developing genetics and strains capable of high performance in modern production systems, under management systems which deliver high standards of health and welfare, with nutrition which meets the requirements of all stages of the reproduction and production process.

Background information

Conventional animal breeding carried out over many centuries in crops and terrestrial livestock, and over the last few decades in aquaculture, has involved choosing the most desirable individuals as parents of the next generation, resulting in the broad range of breeds and strains of plants and animals used in agriculture and aquaculture. In the 1990's it became possible to move genes between species using various techniques to create new genotypes, a process known as transgenesis, creating plants and animals generally described as Genetically Modified Organisms (GMO's). GMO's became the subject of moral and regulatory debate with regulatory acceptance of particular GMO crops in some regions, but very limited acceptance of GMO's in animal production. Transgenesis in microorganisms has resulted in novel products used extensively in food, drug and other manufacturing processes.

Over the past two decades, bacterial enzyme complexes were identified which were capable of targeted modification of DNA sequences. In a process known as Gene Editing (or Genome Editing), these enzyme complexes can make precise, targeted changes in the genomes of microorganisms, plants and animals, introducing desired alterations (or mutations) to change genotype and performance. This process is fundamentally different to the transgenic approach used for GMO's where foreign genetic material is introduced. Gene Editing makes precise, targeted changes in the DNA sequence of the organism itself. Such mutations would occur naturally in populations of plants and animals, but at a very low level.

Benchmark recognises that Gene Editing is a novel technology which involves making new genotypes which may result in improved performance of the organism. The company believes that this technology should be evaluated by regulators and the Industry in a constructive manner considering the opportunities to produce new products and develop new genotypes which show better adaption to the farming environment, an improved health and welfare.



Benchmark Gene Editing Position statement

Benchmark's mission is to be a global leader in driving sustainable solutions in the food chain and proposes a clear, principled approach to gene editing, ensuring that the Company remains at the cutting edge of this technology whilst establishing a position to improve health, welfare and economics of aquaculture and agriculture. Our position statement will be reviewed as the science and regulation develops.

- Benchmark considers gene editing of crops and animals to be a separate technology to transgenesis (moving genes between species), which should be considered as different from those methods included in the original GMO regulations. Editing of genes with naturally occurring genetic variation represents a much lower risk to animal welfare and environment.
- Benchmark considers gene editing of microorganisms and cell lines as a valuable tool for production of novel biotechnology products, and for understanding the how genes work at a fundamental level and in producing a phenotype.
- Benchmark recognises gene editing as a potential tool for breeding livestock with improved health, animal welfare and performance, and will research and investigate possible applications that do not constitute a risk to the genetic integrity of the individual, population or to the environment, or involve transfer of genetic material between species boundaries.
- Benchmark will consider possible applications of gene editing on a case by case basis under the 3E framework. Benchmark will take into consideration the potential ethical, economic and environmental impacts associated with the application of gene editing for the animal itself, the production system, the producer, potential consequences on agricultural practices, food systems and downstream effects on the environment.
- Benchmark recognises that gene editing may be one of many useful tools for improving health and welfare of farmed animals along with conventional breeding, nutrition, vaccination, health management and husbandry.
- Benchmark will implement this technology where it proves to be socially and legally acceptable and when it can be shown to improve the efficiency, health and welfare of our animals.

Supporting Information

Methods and techniques

Gene editing (or genome editing) is the insertion, deletion or replacement of DNA at a specific site in the genome of an organism. This can be achieved using enzyme complexes such as TALENS, CRISPR -Cas9 and Zinc Finger Nucleases which cut and repair DNA. These enzyme complexes can be modified to make specific changes to the DNA code. Gene editing DNA modifications fit into one of two categories:

- Loss of function - Where the cell repairs the break in the cleaved DNA effectively silencing or 'knocking out' the targeted gene.
- Gain of function - Where a faulty gene is 'corrected' by inserting a new segment of DNA or a new gene altogether is introduced, sometimes termed 'knocking in' (REF; Royal Society of Biology).

(see more: <https://www.gene-editing.org/genome-editing>).

The technology behind gene editing is now well described in-depth on the internet and elsewhere (eg Genetic Literacy Project, <https://geneticliteracyproject.org/#> , https://royalsociety.org/topics-position_statement/projects/genetic-technologies/what-are-genetic-technologies/)

The main systems used in gene editing are:

Zinc Finger Nucleases – described in 1990s, used mainly in research to promote mutagenesis and repair. (see more: <https://www.sciencedirect.com/topics/neuroscience/zinc-finger-nuclease>);

Transcription Activator-like Effector Nucleases (TALENs) – described in 2012. A DNA cutting enzyme combined with a target sequence to accurately cut and repair DNA at an identified point. Used to gene edit rice for disease resistance and cattle for polled, hornless genotype. (see more: <https://www.sciencedirect.com/topics/neuroscience/transcription-activator-like-effector-nuclease>);

Clustered Regulatory Interspaced Short Palindromic Repeats (CRISPR CAS-9)– Described in 2010-2012, CRISPR CAS-9 is an enzyme complex used to control bacteriophage infection by bacteria. The enzyme complex and template can be modified to target specific sequences for cutting and repair resulting in editing of the gene sequence. (see more: <https://www.gene-editing.org/genome-editing>);

Regulations – Major Groups

EU

GMO's are defined by the EU as a non- human organism in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination and therefore includes gene edited plants and animals. Despite proposals that gene editing should be excluded from current regulation as a form of mutagenesis, and the results are indistinguishable from natural mutation, the European Court of Justice has ruled that gene editing is a form of GM and the gene edited plants should be regulated in the same way as conventional GMO's. Gene edited animals have not yet be considered by the European authorities but are likely to be classified in the same way as gene edited plants.



The Norwegian Biotechnology Advisory Board has proposed a 4 level system of regulation for gene technology which is currently under public consultation and review. This 4 level system may set a precedent in Europe.

USA

The United States does not have any federal legislation that is specific to genetically modified organisms. Rather, GMOs are regulated pursuant to health, safety, and environmental legislation governing conventional products. The US approach to regulating GMOs is premised on the assumption that regulation should focus on the nature of the products, rather than the process in which they were produced. Gene editing currently falls outside the United States regulatory process under the Coordinated Framework for Regulation of Biotechnology.

The regulatory situation in USA is complex, with GM and gene edited animals falling under the jurisdiction of the FDA, whereas crops are regulated by USDA. There is current debate in USA about which authority is most appropriately placed to oversee new breeding techniques in agriculture and aquaculture, and how to ensure effective and efficient regulation and development of new products.

Plants

Over 8 species of crop plants are licenced for production in the USA. The main species are maize and soy beans. Genes for herbicide resistance, insect resistance, higher oil or sugar levels amongst others have been incorporated.

Animals

Only one species of animal has been licenced for production – the AquAdvantage salmon produced by Aquabounty has been licenced after over 20 years consideration by FDA, although legal debate continues regarding labelling of GMO salmon for sale to the public. The AquAdvantage salmon contains the growth hormone gene from Chinook salmon linked to a promotor from ocean pout. Production is carried out under highly restrictive conditions ie closed containment systems, sterile (triploid) females.

Other Animals

Several species are being prepared for commercial production. Pigs with gene edits to make them resistant to PRRS have been described in USA and UK. Cattle with a gene edit to the polled gene (ie hornless) have been developed. It is anticipated applications may be made to the USA authorities to produce animals containing these gene edits in the next few years.

Other Countries

Although many countries will follow the approach taken by the USA or EU, there are indications that some countries will take a relaxed approach to gene edited agriculture and aquaculture products, examining each product on a case by case basis. This is already established in USA, Canada and some Latin American countries for crops (Argentina, Brazil and Chile).

In October 2018 a coalition of thirteen countries led by Argentina announced through WTO that they would “support policies that enable agricultural innovation, including genome editing.” The countries include Argentina, Australia, Brazil, Canada, Colombia, the Dominican Republic, Guatemala, Honduras, Jordan, Paraguay, the United States, Uruguay and Vietnam. The statement is also endorsed by the Secretariat of the Economic Community of West African States.

China is taking a relaxed approach, regarding gene editing as a tool to advance crop breeding and production, and likely to take similar approach in animals.

The Norwegian Biotechnology Board argue that organisms can be divided into different levels based on the genetic change that has been made, according to general principles. For example, relevant criteria can be whether or not the change is permanent and heritable, whether or not the change can also be made using conventional breeding techniques, and whether or not the change crosses species boundaries. At the lowest level, a notification to the authorities (receipt required

before the organism can be released) may be sufficient. At higher levels, organisms would require approval before release is authorised, but may be subject to different risk assessment and approval requirements.

Definitions

Scientific

Genetic Engineering – the deliberate alteration of the genetic constitution of a living organism or cell by artificial means (i.e. not by conventional breeding), such as the introduction of a gene from another species or the introduction of a mutation into a specific gene. Bacteria, cultured cells, plants and some animals can be altered in this way (Henderson’s Dictionary of Biology 14th Edition).

Transgenic organisms – animals or plants into which genes from another species, or mutated versions of their own genes, have been deliberately introduced by genetic engineering (Henderson’s Dictionary of Biology 14th Edition).

(See also <https://www.britannica.com/science/genetically-modified-organism>)

EU

Legal definition: Genetically Modified Organisms (Contained use) European Regulations, 2000:

“**genetic modification**” in relation to an organism means the altering of the genetic material in that organism in a way that does not occur naturally by mating or natural recombination or both. Genetic modification occurs at least through the use of the techniques listed in Part I of Schedule 2;

SCHEDULE 2

PART I - EXAMPLES OF TECHNIQUES CONSTITUTING GENETIC MODIFICATION

1. Examples of the techniques which constitute genetic modification which are referred to in sub-paragraph (a) of the definition of “genetic modification” in regulation 2(1) are—

(a) 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;

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

(c) cell fusion or hybridization techniques where live cells with new combinations of heritable genetic material are formed through the fusion of two or more cells by means of methods that do not occur naturally.

USDA:

(<https://www.usda.gov/topics/biotechnology/biotechnology-glossary>)

Genetic modification: The production of heritable improvements in plants or animals for specific uses, via either genetic engineering or other more traditional methods.

Genetically modified organism (GMO): An organism produced through genetic modification.