REGULATORY HORIZONS COUNCIL

Regulatory Horizons Council

Report on Genetic Technologies

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Note on report versions

The report was originally published on 1st September 2021. It was updated in July 2022 to take account of recent developments in regulatory adaptation in the UK, and in response to comments on the previous version.

Contents

Foreword

Dr Peter Kearns, Special Adviser, Re-Imagine Europa

I am pleased to write a foreword to this report, which is thorough, thoughtful and timely. At the time of its publication, the UK retains EU law in respect of GMOs and related biotechnologies, despite Brexit. The UK now has both the opportunity and the challenge to consider how to put in place a system of governance in the post-Brexit era which best suits the UK in this new situation. This is one of the main premises behind the report but of equal importance is the knowledge that the UK's scientific profile in genetic technologies is of global excellence, including in agricultural research, and this should be strengthened in the future. Against this background, I would like to empathise three key features of the report which I believe to be of importance.

First, the methodology by which the report was drafted is to be commended. For example, the preparations involved a series of workshops in which various groups of stakeholders were consulted. This was followed up by in-depth interviews with additional stakeholders as well as officials from five other jurisdictions which have recently undergone regulatory reform. There is a long history of polarisation in assessing the use of genetic technologies in agriculture and the engagement of stakeholders is a prerequisite for making progress. Recommendation 1 extends the notion of stakeholder engagement in a more systematic way to future governance arrangements.

Second, I fully endorse the recommendations in the report. They involve several principles which are worth emphasizing. For example, the need to balance a sensible precautionary approach with a more 'innovation-friendly' approach, given that innovation can itself improve safety. They stress the need to take a more proportionate approach to applications based on the potential risks. It is clear that 'one-size' does not fit all. One of the clearest examples given is the special case of simple genome editing, which can lead to new plant varieties that could have arisen in nature or during conventional plant breeding, as compared with GMOs which involve transgenic material. There is also the principle of a flexible regulatory approach, which is able to take into account future innovations. Nevertheless, it is important to ensure that the governance of all genetic technologies is based on the same set of principles. This concept is emphasised in the report.

Third, it is important that the report has considered the international dimensions of genetic technologies in several different ways. The UK agricultural and food production sector operates in a global environment and the UK needs to innovate without being out of step with major trading partners. It is of value, therefore, that the report takes into account international developments such as the definition of Living Modified Organism associated with the Cartagena Biosafety Protocol and OECD's regulatory principles.

Finally, I encourage the Department for Business, Energy & Industrial Strategy as well as other UK government departments to consider the Recommendations in the report and I look forward to following the next steps.

Executive summary

Background

1. The Regulatory Horizons Council was asked by the UK Government to devise ways to regulate genetic technologies in agriculture in future so as to encourage safe and beneficial innovation.

2. Following the UK's departure from the European Union, the Government is considering immediate reform of rules for simple genome editing, followed by the adoption of an improved governance system for all genetic technologies.

3. The aim is to make the UK an international leader in regulatory adaptation to support the development of plant and animal varieties that can benefit consumers while enhancing the environment.

Scope and methodology

4. This report covers the use of genetic technologies in all plants, animals and micro-organisms contributing to agriculture and food production.

5. We conducted four workshops with different sets of stakeholders, followed by in-depth interviews with businesses, scientists, advocacy groups, public officials and regulators from the UK. We held meetings with officials from five countries that had recently undertaken regulatory reform in this area.

The impact of genetic technologies

6. Genetic modification (GM) of crops has produced significant gains in both productivity and environmental impacts, with higher yields, lower chemical use and an excellent safety record, including fewer insecticide poisonings.

7. The first generation of GM technologies had a limited range of applications and was dominated by multinational companies. Deployment within the EU and the UK was largely prevented by a complex, expensive and unpredictable regulatory system.

8. Second-generation genetic technologies (genome editing, synthetic biology and engineering biology) create opportunities to transform agri-food systems through nutritionally healthier crop varieties, disease resistance, reduced insecticide and fungicide use, reduced greenhouse gas emissions, improved climate resilience, and contributions to sustainability and biodiversity conservation.

9. At a time of growing public opposition to the use of chemicals in agriculture, but low take-up of organic farming, genetic technologies promise to allow the protection of crops and animals with significantly less use of synthetic chemicals.

Stakeholder involvement

10. We are proposing a new, more integrated approach to interactions with stakeholders, to enable novel genetic technologies to be developed safely and equitably in this sometimes controversial area.

11. We envisage two types of engagement: stakeholder surveys involving members of the public; and a long-term Stakeholder Advisory Panel, potentially sponsored by the Department for Business, Energy and the Industrial Strategy (BEIS) and complementing the National Quality Infrastructure (NQI), representing key relevant stakeholders, including public/lay representation, to comment on and guide decision-making on market approval for new classes of product **(recommendation 1)**.

A new regulatory approach for all genetic technologies

12. We propose that the underlying principles of good regulation are: ensuring safety; balancing precaution about future hazards with ambition to gain future benefits; taking decisions in a timely, proportionate and predictable manner; being adaptable to future innovations; ensuring improvements in the quality of animal welfare **(recommendation 2)**.

13. Regulatory data requirements should be proportionate to the nature and scale of potential risks; should include information on potential benefits; and should not require the collection of data that do not relate to a clearly specified policy **(recommendation 3)**.

14. Standards and guidelines (instead of ‘hard law’ like legislation) should facilitate regulatory adaptation where possible. This includes labelling to indicate a product’s origins and the potential societal and environmental benefits of using genetic technologies where appropriate **(recommendation 4)**.

Regulatory triggers

15. The regulatory system proposed here focuses on the properties of the end products rather than the methods used to develop them. It would apply to any product (plant, animal or micro-organism) obtained using genetic technologies (including gene editing, synthetic biology and engineering biology), to be used in agriculture, food production and other uncontained conditions **(recommendation 5)**.

16. A guiding assumption should be that *similar* products (phenotypically and genetically) arising from *different* genetic techniques would not be expected to have different risks and so should be subject to similar regulatory scrutiny **(recommendation 6)**.

Revised regulatory pathway for new products of genetic technologies

17. We propose that the Advisory Committee on Releases to the Environment (ACRE) should become a different type of organisation (ACRE-2), led and staffed by permanently employed risk assessors and regulators, potentially following the model of the Medicines and Healthcare products Regulatory Agency (MHRA). It should be the central organising node for the regulation of new products of genetic technologies and have sufficient expert staff for this enlarged role **(recommendation 7)**.

18. If there are no expected risks or other concerns arising from the genetic changes to the product, the specific genetic technique involved in its production being irrelevant, it would proceed to the normal regulatory process for similar types of product, administered through sectoral regulators[1] such as the Animal and Plant Health Agency (APHA) / Plant Variety Rights and Seeds Office (PVS) or the Food Standards Agency (FSA) / Advisory Committee on Novel Foods and Processes (ACNFP), and ACRE-2 would have no further regulatory involvement.

19. Where ACRE-2 decides that there are special and novel concerns related to the use of a genetic technology, beyond what is normally required, for example, for the products of conventional plant or animal breeding, then ACRE-2 would be responsible for overseeing the regulatory process and for the final decision on market authorisation.

20. ACRE-2 would request sectoral regulators to plan a pathway to provisional regulatory approval on the basis of their requirements for the product, taking into account expected use, including relevant standards and tests and an indication of the expected timescale and costs involved for the applicant.

21. A flow diagram of the new pathway can be seen in Figure 2 in section 6.

22. We propose undertaking a regulatory sandbox to test and refine the proposed regulatory approach (**recommendation 8).**

[1] By this term we mean those regulators that have responsibility for products used in specific sectors, for example, the Food Standards Agency having regulatory oversight for any novel food, regardless of the origin of the product.

Special case of simple genome editing

23. We propose the use of the approach described above for simple genome editing as a trial for the next-stage consideration of a new regulatory approach for all genetic technologies **(recommendation 9)**.

24. We accept the policy case for giving immediate attention to products of simple genome editing, on the grounds that it generates varieties that could be produced by conventional breeding, but not the rationale for the distinction.

25. Natural products and conventional techniques can be hazardous; conversely, techniques such as genetic modification can be safe. In addition, it is inaccurate to say that genetic technologies that use transgenesis do not have a natural equivalent: cross-species gene transfer does happen naturally.

26. Given the scale and extent of the potential benefits from all genetic technologies, it is important to ensure that the UK regulatory approach adopted for products of simple genome editing does not create regulatory precedents that would restrict our freedom to act in the near future on the regulation of all genetic technologies **(recommendation 10)**.

1. Introduction and background

1.1 Remit

The Regulatory Horizons Council (RHC) is an independent expert committee, supported by a team of civil servants, established by the Department for Business, Energy and Industrial Strategy (BEIS). A commitment from the White Paper on Regulation for the Fourth Industrial Revolution, it provides the Government with impartial, expert advice on regulatory reform to support the rapid and safe introduction of technological innovations with high potential benefit for the UK economy and society.

The RHC was commissioned by a cross-Government working group on genetic engineering to examine how genetic technologies would benefit from regulatory reform. Following horizon scanning and prioritisation exercises to get to a shortlist of priority areas, the RHC accepted this commission and chose genetic technologies as one of its four initial areas to focus on alongside fusion energy, unmanned aircraft and medical devices. The RHC has been conducting a 'deep dive' into this topic since September 2020, engaging with relevant stakeholders and looking into the options available within our regulatory reform remit with an end output of recommendations to Government, as contained in this report.

In response to this commission, we focused our attention on crop, animal and microbial products of genetic technologies, intended for *deliberate release* to the environment, as used in agri-food and environmental sectors. Regulatory regimes for these products, particularly in the EU, have been the subject of continual debate, and sometimes dispute, since the 1980s, and have been brought into sharper focus by recent developments in genetic technologies. This area of regulatory adaptation is the focus for this report.

The use of genetic technologies in microbial adaptation for use in industrial biotechnology applications is also important but this area is not included in this report. It is subject to a different regulatory regime, for *contained use* applications, led by the Health and Safety Executive, reporting to the Department for Health and Social Care (DHSC).

As described in the following sections, we are distinguishing between the first-generation genetic technologies that are the basis of today's widely used genetically modified (GM) crops, and second-generation technologies: genome editing, synthetic biology and engineering biology (see glossary for further explanation). These second-generation technologies have been the subject of intensive research programmes and have transformed our capabilities to modify and adapt genomes, more rapidly and with much greater precision than before. They can be translated to a much broader range of applications with more varied and significant benefits for society, the environment and the

economy. The countries with expertise in this area are all aware of the need to adapt their regulatory regimes to be compatible with the properties of the new product ranges and to be adaptive in the face of future transformative research breakthroughs. Benefits will accrue to the nations that can re-design their regulatory regimes to enable the timely translation of innovative products to a diverse array of markets, while continuing to ensure safety for people and the environment.

Our recommendations have been based on an extensive programme of stakeholder engagement and evidence gathering. Over the last 8 months, we have organised a series of workshops with over 100 representatives from industry, academia, policy makers and advocacy groups, run interviews with a range of regulatory and legal experts and conducted international outreach with several countries that have recent experience of regulatory adaptation in this area[2]. These activities have provided a broad range of innovative ideas on the regulation and governance of genetic technologies, which we summarise in our issues paper (see Annex A) and which have been invaluable in the production of this report.

In our consultation for this project, there were concerns among many stakeholders about intellectual property regimes having an inhibitory impact on innovation, and about the related control of innovation opportunities by multinational companies. Although this is an important issue and should be noted for further investigation, it is beyond the remit of this report.

Where our proposals relate to an area of devolved competence, it would be for the devolved administration to decide whether to take forward proposals in those areas.

This report represents views from across the RHC and was led by Professor Joyce Tait with significant support from Dr Andy Greenfield and Matt Ridley[3].

1.2 First-generation GM crops – potential benefits for agriculture, the environment and society

GM crops, first introduced in the 1990s, have seen faster uptake by farmers internationally than any other modern agricultural technology, from 1.7 million hectares in 1996 to 179.7 in 2015 (over 10% of the world's arable land). The main crops involved, in order of scale, are soybean, maize, cotton and oilseed rape, and the most important producer countries

[2] Our international engagement has involved multiple meetings with regulators of genetic technologies in the US (including the Environmental Protection Agency, Animal and Plant Health Inspection Service and Food and Drug Administration), Canada (including Health Canada and Agriculture and Agri-Food Canada), Argentina (Ministerio de Agricultura), Brazil (CTNBio), and Norway (including the Norwegian Environment Agency and Norwegian Biotechnology Advisory Board).

[3] RHC membership details are here: https://www.gov.uk/government/groups/regulatory-horizons-council-rhc#membership

are the USA, Brazil, Argentina, India and Canada[4]. There has been no evidence of any adverse effects on human or animal health from the consumption of food or feed from GM crops, and benefits from these uses of GM crops internationally[5] include:

- Economic outcomes for producers have been generally favourable, depending on the scale of pest infestations (including better outcomes where infestations are higher);
- Insect pest-resistant crops saw smaller yield losses from insect pests and where the GM variety was widely adopted, all farmers in the region benefitted from a reduction in pest incidence;
- The adoption of insect-resistant crops resulted in increased insect biodiversity on farms;
- No-till agriculture has resulted in savings in CO_2 emissions and soil improvement, including significant increases in carbon capture in the soil; and
- Yield/productivity gains resulting in potential land-saving outcomes (productivity increases imply producing more outputs with lower inputs).

Along with a reduction in pesticide use on insect-resistant crops, there have been significant reductions in cases of pesticide poisoning among farm workers, particularly for small-scale farmers. In India, on insect-resistant cotton, pesticide applications have been reduced by 50-70% and it has been estimated that this GM crop helps to avoid several million cases of pesticide poisoning per year[6]. There have also been significant economic and health benefits for small farmers growing cotton in South Africa[7].

[4] The Royal Society (2016) What GM crops are currently being grown and where? https://royalsociety.org/topics-policy/projects/gm-plants/what-gm-crops-are-currently-being-grown-and-where/#:~:text=The%20farming%20of%20GM%20crops,of%20the%20world's%20arable%20land.

[5] National Academies of Sciences, Engineering, and Medicine 2016. Genetically Engineered Crops: Experiences and Prospects. Washington, DC: The National Academies Press. https://doi.org/10.17226/23395

Burachik, M. (2010) Experience from use of GMOs in Argentinian agriculture, economy and environment. *New Biotechnology,* 27(5), 588-592.

Mahaffey, H., Taheripour, F. and Tyner, W.E. (2016) Evaluating the Economic and Environmental Impacts of a Global GMO Ban. Journal of Environmental Protection, 7, 1522-1546. http://dx.doi.org/10.4236/jep.2016.711127

Kristiina Ala-Kokko, Lawton Lanier Nalley, Aaron M. Shew, Jesse B. Tack, Petronella Chaminuka, Marty D. Matlock, Marijke D'Haese, Economic and ecosystem impacts of GM maize in South Africa, Global Food Security, Volume 29, 2021. https://doi.org/10.1016/j.gfs.2021.100544.

[6] Kouser, S., and Qaim, M. (2011) Impact of Bt cotton on pesticide poisoning in smallholder agriculture: a panel data analysis. *Ecological economics*, 70, 2105-2113.

[7] Richard Bennett , Stephen Morse & Yousouf Ismael (2006) The economic impact of genetically modified cotton on South African smallholders: Yield, profit and health effects, The Journal of Development Studies, 42:4, 662-677, DOI: 10.1080/00220380600682215

1.3 Regulation of first-generation GM products – 'product vs process'

In the 1980s, when regulators began to consider how they would regulate GM crops, a split emerged between the USA and EU over the primary trigger, the property used to capture a new entity under the surveillance of a specific regulatory regime[8]. In discussions at the time, the USA favoured an approach that focusedon the properties of the final crop product, its benefits and risks. By contrast, the EU favoured an approach that focused on the process of genetic modification itself and captured all products, regardless of their properties, within a common regulatory regime, developed specifically for this purpose[9]. This division persists today and the current EU regulatory system for GM organisms has been accused of deliberately setting up a technical barrier to trade, leading to several successful legal actions against the EU by the World Trade Organisation[10].

The EU regulatory system, along with the very precautionary and politicised approach to its implementation, has resulted in the absence of any significant adoption of GM crops in the EU and the departure of European companies working on GM technologies to the USA and other countries. Some other countries have adopted an approach similar to that of the EU, for trade-related reasons (a desire to export agricultural products to the EU particularly African nations) or because of internal political opposition to the adoption and use of GM crops.

Where the regulatory trigger is based on the properties of the product, regulators need to decide on the properties that would locate potentially hazardous products within a specific regulatory regime and exempt others that present low or no risks. Triggers adopted so far for GM crops and animals have been based on regulatory regimes already in place for non-GM products and in some cases this has had problematic outcomes, for example:

- in the USA, GM crops were themselves regulated as potential plant pests because of their development using genes from *Agrobacterium tumefaciens*, a recognised pest;

[8] McHughen, A. (2016) A critical assessment of regulatory triggers for products of biotechnology: Product vs. process. *GM Crops and Food,* 7.125-158. DOI: 10.1080/21645698.2016.1228516

[9] Tait, J. and Levidow, L. (1992) Proactive and Reactive Approaches to Risk Regulation: the Case of Biotechnology, Futures, April, 1992, pp 219-231

[10] King & Spalding LLP (2015) Do the new EU BMO rules comply with its WTO obligations? https://www.lexology.com/library/detail.aspx?g=db9d9679-c98c-4eeb-9789-b6e8dfb2fd28

- a decision was taken to regulate GM animals such as salmon or cattle using the drug development regulatory system, entailing lengthy delays in the market authorisation process[11] [12];

- Canadian regulators chose 'novelty to Canada' as being more clearly product-based and science-based than other regulatory regimes, but in doing so it also captured products of conventional plant breeding, leading to opposition from the organisations concerned.

None of these triggers has yet been seen as setting a precedent for other nations to follow and lengthy arguments about the relative merits of different regulatory approaches have been described as stalling progress[13].

Overall, regulatory systems in existence for the products of genetic technologies today could be described as a 'systemic mess', a complex system of interacting problems[14], at least from the point of view of evidence-based risk management. However, as noted in Section 1.2, the GM crops available so far have succeeded in safely delivering major benefits to farmers, the environment and societies in many countries, based on a variety of regulatory approaches, none of which could be regarded as ideal or a template for regulation of the products of second-generation genetic technologies. There is now an opportunity for creative adaptation of current regulatory regimes, to learn from experience of safe use of GM technologies, and to allow opening up of innovation opportunities beyond large multinational companies and today's limited range of commodity crops[15].

Many influential organisations have written in support of moving to product- or trait-based regulatory approaches, for example: the European Academies Science Advisory Council (EASAC), European Plant Science Organization (EPSO), European Seed Association (ESA), the Royal Swedish Academy of Agriculture and Forestry (KSLA), the National Academy of Sciences (NAS) in the US, and the Biotechnology and Biological Sciences Research Council (BBSRC) and the Advisory Committee on Releases to the Environment (ACRE) in the UK. The RHC is aligned with such organisations in supporting the position that the regulatory focus should be on the properties of the product rather than the genetic technology used to produce it. However, in practice, the nature of the genetic changes made to the product will need to be considered at the beginning of the regulatory process in order to understand the kinds of risks that it might pose. Beyond this point, as discussed in detail in sections 5 and 6, the RHC is proposing that adaptation of regulatory assessment can succeed in delivering a more proportionate regulatory system that

[11] Van EEnannaam, A L, Wells, K D and Murray, J.D. Proposed US regulation of rene-edited food animals is not fit for purpose (2019). *Science of Food*, 3(3) https://doi.org/10.1038/s41538-019-0035-y

[12] Cohrssen, J J, and Miller, H I (2017) *Nature Biotechnology*, (35(7), 620-622

[13] Kuzma, J. (2016) *Nature,* 531, 165-167

[14] Ackoff, R.A., (1981) The art and science of mess management. *Interfaces*, 11(1), 20-26

[15] http://www.tsl.ac.uk/tsl-statement-gene-editing/

discriminates among products on the basis of the risks they are likely to present rather than the technology used to develop them.

1.4 Second-generation genetic technologies

The technical terms introduced in this section are defined in the Glossary.

The first-generation genetic technologies that formed the basis for today's GM crops (section 1.2) have been transformed by research on genome editing, synthetic biology and engineering biology to be more rapid, precise and targeted, with more predictable consequences for the final product.

Both synthetic biology and engineering biology cover a broad range of genetic technologies, including those that do and do not involve the transfer of genetic material across species boundaries. They aim to make biology easier to engineer. They involve the convergence of advances in chemistry, biology, computer science, and engineering that enable transitioning from idea to product faster, cheaper, and with greater precision than before. They can be thought of as a biology-based "toolkit" that uses abstraction, standardization, and automated construction to change how we build biological systems and expand the range of possible products. A community of experts across many disciplines has come together to create these new foundations for many industries developing products relevant to agriculture/food production, medicine, manufacturing, energy and the environment[16].

Genome editing[17] (GE) is a major technical improvement on first-generation GM-based approaches, given its scope to deliver a range of different genetic variants with speed and with an unprecedented degree of precision. It could transform our capacity to modify plants, animals and micro-organisms in ways that will deliver significant societal benefits. Also, in its simplest forms (SDN1 and SDN2) that do not involve cross-species genetic transfer, its products could potentially be developed without triggering current GMO regulations (see Section 5.2). A number of genome editing methodologies exist, including zinc finger nucleases and TALENs[18], and the most powerful, CRISPR-Cas9[19], as part of an adaptable and constantly expanding toolkit.

In discussions about appropriate regulatory regimes, definitions of these technologies are often hotly debated with the aim of either ensuring, or preventing, their triggering capture

[16] https://www.nature.com/subjects/synthetic-biology

[17] Also referred to as gene editing. Here, we use 'genome editing' to capture not just changes to DNA sequence but also modifications that alter gene expression, such as CRISPR interference/activation and targeted changes to the epigenome.

[18] Carroll D. Genome Editing: Past, Present, and Future. Yale J Biol Med. 2017 Dec 19;90(4):653-659. PMID: 29259529; PMCID: PMC5733845.

[19] Knott GJ, Doudna JA. CRISPR-Cas guides the future of genetic engineering. Science. 2018 Aug 31;361(6405):866-869. doi: 10.1126/science.aat5011. PMID: 30166482; PMCID: PMC6455913.

under specific regulatory regimes. The approach we are proposing in this report aims to avoid debates of this nature by focusing on the properties of the end products and how they are used.

1.5 Opportunities from second-generation genetic technologies

The benefits from first-generation GM crops are impressive (Section 1.2), and could have been greater given wider uptake of these technologies. However, today's technologies are more powerful, could be developed to market by small companies (changing the dynamics of existing industry sectors and delivering benefits to niche markets not served by today's multinationals) and would contribute to the UK's major policy initiatives, particularly in the context of climate change. Many products of genome editing that are in development, in plants, animals and micro-organisms, are designed to deliver specific environmental benefits. Where they fail to deliver benefits for any reason, they are unlikely to be developed commercially.

The following is just a sample of the benefits that could be delivered on a timescale that will depend both on further scientific and technological progress and on the nature and application of future regulatory regimes.

Crop-related

- **Reduced insecticide use**. Insect-resistant varieties of crops such as sugar beet already exist, but breeding this trait into high-yielding varieties is slow and laborious. Genome editing, targeting the genomes of viruses that are spread by insects, or naturally occurring resistance genes,[20] would potentially speed this process up by several years[21], with benefits to growers and the economy and to soil organisms, pollinators and aquatic ecosystems from reduced insecticide use. Tomato yellow leaf curl virus (TYLCV) is one of the most devastating viral pathogens affecting tomato crop yield. It is transmitted by whiteflies and insecticides are used to control the disease. CRISPR has been employed in elite tomato cultivar BN-86 to introduce pathogen resistance, leading to suppression of accumulation of TYLCV and the potential for future reduced insecticide use[22]. Researchers are working on many similar potential

[20] Cao Yongsen, Zhou Huanbin, Zhou Xueping, Li Fangfang. Control of Plant Viruses by CRISPR/Cas System-Mediated Adaptive Immunity. Frontiers in Microbiology. 2020. Vol (11) https://www.frontiersin.org/articles/10.3389/fmicb.2020.593700/full

[21] Lyzenga WJ, Pozniak CJ, Kagale S. Advanced domestication: harnessing the precision of gene editing in crop breeding. Plant Biotechnol J. 2021 Apr;19(4):660-670. doi: 10.1111/pbi.13576. Epub 2021 Mar 25. PMID: 33657682; PMCID: PMC8051614 and https://geneticliteracyproject.org/2021/02/25/gene-editing-could-boost-uks-virus-plagued-sugar-beet-industry-countrys-agriculture-minister-says/.

[22] Pramanik, D.; Shelake, R.M.; Park, J.; Kim, M.J.; Hwang, I.; Park, Y.; Kim, J.-Y. CRISPR/Cas9-Mediated Generation of Pathogen-Resistant Tomato against *Tomato Yellow Leaf Curl Virus* and Powdery Mildew. *Int. J. Mol. Sci.* **2021**, *22*, 1878. https://doi.org/10.3390/ijms22041878

benefits that would be in addition to the already significant reductions in insecticide use from first-generation genetic technologies (Section 1.2). These innovations would also support the pesticide reduction policies that are part of many Governments' long-term plans for their agricultural systems.

- **Reduced fungicide use**. Fungus infections are responsible for major crop failures or reductions in yield, and genetic technologies could enable most crops to resist attack from a broad range of fungi. For example, powdery mildew-resistant land-races of wheat exist and genome editing could quickly introduce fungal resistance into high yielding varieties[23]. Potatoes require up to 15 sprays per season to defeat blight and fungus-resistant crops have already been demonstrated to reduce the number of sprays required to two or three, benefiting soil biodiversity and structure and wild ecosystems in general[24]. Powdery mildew resistant tomatoes have also been generated by genome editing[25]. Rice blast, caused by *Magnaporthe*, is one of the most devastating diseases affecting rice production worldwide and fungal resistance has also been generated using genome editing[26]. Some fungus infections of crops create serious threats to human health; for example, *Aspergillus flavus* and *A. parasiticus* cause high levels of the carcinogen aflatoxin in peanuts with significant impacts on human health.

- **Reduced greenhouse gas emissions from farming**. Genome editing could reduce pesticide and fertiliser use, increase no-till agriculture, (potentially) improve plants' ability to fix nitrogen[27], reduce emissions from manufacture and application of these products, and increase carbon capture in soils.

[23] Xie J, Guo G, Wang Y, Hu T, Wang L, Li J, Qiu D, Li Y, Wu Q, Lu P, Chen Y, Dong L, Li M, Zhang H, Zhang P, Zhu K, Li B, Deal KR, Huo N, Zhang Y, Luo MC, Liu S, Gu YQ, Li H, Liu Z. A rare single nucleotide variant in Pm5e confers powdery mildew resistance in common wheat. New Phytol. 2020 Nov;228(3):1011-1026. doi: 10.1111/nph.16762. Epub 2020 Jul 26. PMID: 32569398.
Wang Y, Cheng X, Shan Q, Zhang Y, Liu J, Gao C, Qiu JL. 2014 Simultaneous editing of three homoeoalleles in hexaploid bread wheat confers heritable resistance to powdery mildew. Nat. Biotechnol. 32, 947–951. (doi:10.1038/nbt.2969)
Zhang Y, Bai Y, Wu G, Zou S, Chen Y, Gao C, Tang D. 2017 Simultaneous modification of three homoeologs of TaEDR1 by genome editing enhances powdery mildew resistance in wheat. Plant J. 91, 714–724. (doi:10.1111/tpj.13599)

[24] Jones JD, Witek K, Verweij W, Jupe F, Cooke D, Dorling S, Tomlinson L, Smoker M, Perkins S, Foster S. Elevating crop disease resistance with cloned genes. Philos Trans R Soc Lond B Biol Sci. 2014 Feb 17;369(1639):20130087. doi: 10.1098/rstb.2013.0087. PMID: 24535396; PMCID: PMC3928893 and https://www.bbc.co.uk/news/science-environment-26189722

[25] Nekrasov V, Wang C, Win J, Lanz C, Weigel D, Kamoun S. 2017 Rapid generation of a transgene-free powdery mildew resistant tomato by genome deletion. Sci. Rep. 7, 482. (doi:10.1038/s41598-017-00578-x)

[26] Wang F, Wang C, Liu P, Lei C, Hao W, Gao Y, Liu YG, Zhao K. 2016 Enhanced rice blast resistance by CRISPR/Cas9-targeted mutagenesis of the ERF transcription factor gene OsERF922. PLoS One 11, e0154027. (doi:10.1371/journal.pone.0154027)

[27] Sheoran, S., Kumar, S., Kumar, P. *et al.* Nitrogen fixation in maize: breeding opportunities. *Theor Appl Genet* **134,** 1263–1280 (2021). https://doi.org/10.1007/s00122-021-03791-5

- **Enabling agriculture in the face of climate change**. Scientists are already using genetic technologies to engineer plants with improved flood tolerance[28],[29],[30],[31]. These plants could, given further development and the right supporting policies, lead to less pressure to convert areas of high biodiversity (forests and wetlands) into arable land.

- **Enabling organic farming**. Organic farming's share of UK farmed land decreased from 668,000 hectares in 2010 to 457,000 in 2019 (2% of land farmed organically)[32]. Given the ability of genetic technologies to reduce the use of insecticides and fungicides and (potentially) to substitute for conventional fertilisers, organic farming could benefit significantly from the products of these technologies. One organic farmer, previously an anti-GM campaigner, has recommended that organic farmers should be open to considering the use of genome-edited crops that could contribute to tackling climate change[33].

- **Food-related benefits**. Genetic technologies can be used to reinstate the original quality and strength of flavour into crop varieties that have been bred to be high-yielding and pest/disease-resistant with no concern given to flavour[34]. They can also be used to create varieties that will deliver health benefits more easily and cheaply to consumers, for example, the anthocyanin-rich purple tomato developed by the John Innes Centre[35].

[28] Reynoso MA, Kajala K, Bajic M, West DA, Pauluzzi G, Yao AI, Hatch K, Zumstein K, Woodhouse M, Rodriguez-Medina J, Sinha N, Brady SM, Deal RB, Bailey-Serres J. Evolutionary flexibility in flooding response circuitry in angiosperms. Science. 2019 Sep 20;365(6459):1291-1295. doi: 10.1126/science.aax8862. PMID: 31604238; PMCID: PMC7710369 and https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/flooding-tolerance.

[29] Chen, JH., Chen, ST., He, NY. *et al.* Nuclear-encoded synthesis of the D1 subunit of photosystem II increases photosynthetic efficiency and crop yield. *Nat. Plants* **6,** 570–580 (2020). https://doi.org/10.1038/s41477-020-0629-z

[30] Rida Fatima Ahmed, Muhammad Irfan, Hafiz Abdullah Shakir, Muhammad Khan & Lijing Chen (2020) Engineering drought tolerance in plants by modification of transcription and signalling factors, Biotechnology & Biotechnological Equipment, 34:1, 781-789, DOI: 10.1080/13102818.2020.1805359.

[31] Nguyen, Q.H., Vu, L.T.K., Nguyen, L.T.N. *et al.* Overexpression of the *GmDREB6* gene enhances proline accumulation and salt tolerance in genetically modified soybean plants. *Sci Rep* **9,** 19663 (2019). https://doi.org/10.1038/s41598-019-55895-0

[32] https://www.statista.com/statistics/298986/organic-land-used-in-the-united-kingdom-uk/

[33] https://www.thegrocer.co.uk/food-safety/why-the-organic-sector-shouldnt-oppose-gene-editing-/652456.article

[34] Tieman D, Zhu G, Resende MF Jr, Lin T, Nguyen C, Bies D, Rambla JL, Beltran KS, Taylor M, Zhang B, Ikeda H, Liu Z, Fisher J, Zemach I, Monforte A, Zamir D, Granell A, Kirst M, Huang S, Klee H. A chemical genetic roadmap to improved tomato flavor. Science. 2017 Jan 27;355(6323):391-394. doi: 10.1126/science.aal1556. PMID: 28126817

[35] https://www.jic.ac.uk/purple-tomatoes/

Use of genetic technologies in animals

There are applications of new genetic technologies that are expected to have positive impacts on animal welfare and/or to contribute to reduced environmental impact and efficiency of production. Members of the Farm Animal Breeding & Reproduction Technology Platform (FABRE TP), representing animal breeders in Europe, have commented that GE could be one way of helping animal breeders to improve animal health and welfare[36]. Examples include:

- Resistance to porcine reproductive and respiratory syndrome virus (PRRSV) in pigs should improve animal welfare and productivity, and reduce food waste[37].

- The POLLED variant in cattle causes hornlessness, resulting in fewer injuries to animals and their handlers, and avoids the suffering and distress associated with dehorning and disbudding[38].

- A genetic technology has been used to develop a test to identify salmon for breeding that are resistant to infectious pancreatic necrosis, improving animal welfare and saving the UK economy £26.4M. Genome editing could be used to introduce disease resistance into a wide range of breeds[39].

- CRISPR also has the potential to contribute to the sustainability of aquaculture, for example, targeting disease resistance in commercially important species and inducing sterility to prevent wild introgression in Atlantic salmon. The reproductive biology of aquatic species makes them particularly amenable to the application of genetics and breeding technologies[40] [41].

- Genetic technologies also have the potential to improve animal productivity. However, most public consultations have pointed to general public unease about using genetic technologies to improve productivity because of animal welfare concerns.

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[36] https://www.effab.info/uploads/2/3/1/3/23133976/short_webinar_report.pdf

[37] Proudfoot, C. et al. (2019) Genome editing for disease resistance in pigs and chickens. *Animal Frontiers, 9(3),* 6-12. (https://doi.org/10.1093/af/vfz013)

[38] Mueller ML, Cole JB, Sonstegard TS, Van Eenennaam AL. Comparison of gene editing versus conventional breeding to introgress the POLLED allele into the US dairy cattle population. J Dairy Sci. 2019 May;102(5):4215-4226. doi: 10.3168/jds.2018-15892. Epub 2019 Mar 7. PMID: 30852022

[39] Gratacap, R.L. et al. (2019) Potential of Genome Editing to Improve Aquaculture Breeding and Production. *Trends in Genetics*, 36(9), 672-684

[40] Gratacap, R.L. et al. (2019) Potential of genome editing to improve aquaculture breeding and production. *Trends in Genetics*, September 2019, Vol. 35, No. 9

[41] Güralp H, Skaftnesmo KO, Kjærner-Semb E, Straume AH, Kleppe L, Schulz RW, Edvardsen RB, Wargelius A. Rescue of germ cells in dnd crispant embryos opens the possibility to produce inherited sterility in Atlantic salmon. Sci Rep. 2020 Oct 22;10(1):18042. doi: 10.1038/s41598-020-74876-2. Erratum in: Sci Rep. 2021 Mar 22;11(1):6981. PMID: 33093479; PMCID: PMC7581530

2. The UK opportunity

As noted in Section 1, there is agreement among scientists, companies and policy makers in the UK and the EU that the European regulatory system for genetic technologies is inhibiting useful innovation, disadvantaging farmers, and depriving us of useful future products that could help to meet societal needs, including mitigating climate change, delivering healthier diets, enabling the circular economy in food and feed products, and contributing to the UN Sustainable Development Goals. At the same time, it is necessary to ensure that these products are safe, effective and of high quality. Given the knowledge gained from years of experience of regulating and using genetically modified products we are now in a good position to apply this knowledge to creating more proportionate and adaptive regulatory systems for the products of new genetic technologies.

Since the UK is no longer a member of the EU, the Government has an opportunity to take a leading role in demonstrating how current regulatory systems can be adapted, or new regulatory systems developed, to enable innovative, safe and beneficial products of genetic technologies to reach their intended markets, at home and abroad.

The question that must be addressed is, *"How can UK regulators respond creatively to this opportunity, deliver the expected benefits to consumers, companies and the environment, and at the same time support future trading relationships with a much broader range of nations than has been the case to date?"*

The UK bioeconomy strategy, published in 2018[42], aims to capitalise on our world-class research, development and innovation base to grow the bioeconomy by: maximising productivity and potential from existing UK bioeconomy assets; delivering real, measurable benefits for the UK economy; and creating the right societal and market conditions to allow innovative bio-based products and services to thrive. The strategy also recognises that "to create, operate and deliver new technologies and products into the marketplace, we need to have the right regulatory landscape in place" and that that landscape must include public trust.

An important part of this opportunity to adapt our regulatory systems is the impact this could have on the nature and scale of innovative activity around genetic technologies. For any industry sector, the more onerous, expensive and lengthy its regulatory system, the more that sector will be dominated by the incremental innovation that fits the business models of very large companies and the more difficult it will be for a competing disruptive

[42] HM Government (2018) *Growing the Bioeconomy. Improving lives and strengthening our economy: a national bioeconomy strategy to 2030.* (https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/761856/181205_BEIS_Growing_the_Bioeconomy__Web_SP_.pdf)

innovation to succeed in displacing incumbent company business models. The sectoral regulatory regime will determine, not just which products and processes are developed but also what scale of company can participate in their development and ultimately the competitive advantage of nations and regions. The countries that make the most proportionate and adaptive regulatory decisions will therefore be expected to see the greatest economic, societal and environmental benefits from genetic technologies[43].

There is already evidence of this effect from Argentina, which significantly adapted its regulatory regime for new breeding techniques, as applied to crops, animals and micro-organisms, in 2015. These regulatory changes have already led to[44]:

- A shift in the landscape of technology developers/providers applying for product registration, from a system that was dominated by foreign multinational companies to one where a significantly higher proportion of applications are from local companies and public research organisations and foreign SMEs (seen by some as a process of 'democratisation' that could have an influence on public attitudes to new genetic technologies);

- The diversification of product traits submitted for registration, particularly in new market areas such as consumer health and preference, improved animal welfare, heat and drought tolerance, fungus and virus resistance; and

- The expectation that potential impacts will be greater for market niches that have not yet been targeted by first-generation genetic technologies.

Argentina's experience has been that a more dynamic set of innovation opportunities expands the supply of local technologies and strengthens the agricultural innovation system. Even though it has only been applied to a subset of today's genetic technologies, this has made it easier for SMEs and public R&D laboratories to develop new products on their own, expanding the market, in terms of both participants and products. In addition, the reduction in the scale of production necessary to reach profits can favour the development of local economies. Several other South American countries have now followed Argentina's example[45].

Given the UK's strengths in research and innovation in second-generation genetic technologies, we could expect regulatory adaptation as proposed in Section 6 to have a very significant impact on our future innovation capabilities. Following this route will have

[43] Tait, J., Banda, G. and Watkins, A. (2018) Proportionate and Adaptive Governance of Innovative Technologies (PAGIT): Case Study: Responsible Governance of Innovative Technologies, Final Report. Innogen Institute Report to the British Standards Institution. https://www.innogen.ac.uk/reports/1302

[44] Whelan AI, Gutti P and Lema MA (2020) Gene Editing Regulation and Innovation Economics. Front. Bioeng. Biotechnol. 8:303. doi: 10.3389/fbioe.2020.00303

[45] Officials in both Argentina and Brazil mentioned that Argentina's regulatory adaptation and approach has been broadly copied by several other countries in South America.

trade-related implications. For example, there may be negative impacts on trade with the EU, although the EU is under considerable pressure to revise its regulatory systems to be better aligned with other countries[46]. However, trading opportunities with most of the rest of the world beyond the EU will be opened up and, given the current lack of EU trade in products of genetic technologies, the balance for the UK is likely to be positive.

This is also an area where there is still space for the UK to take an international lead and to devise a regulatory approach that will allow greater trade-related flexibility, trading opportunities beyond the EU, and also opening up UK agri-food and industrial biotechnology sectors to innovation opportunities across a much broader range of companies, particularly smaller companies. When it comes to the regulation of products involving transgenesis, where the benefits could dwarf those based on simple genome editing, **there is an opportunity for the UK to take on a path-finder role to define a dynamic regulatory regime that can readily evolve to cope with current and future technological changes**.

[46] European Commission (2021), *Study on the status of new genomic techniques under Union law and in light of the Court of Justice ruling in Case C-528/16.* SWD(2021) 92

3. Regulatory Principles for UK Governance of Genetic Technologies

As noted above, genetic technologies are important to:

- the future of the UK economy,
- the delivery of societal, health and environmental benefits, and
- meeting UK national and international policy commitments.

Second-generation genetic technologies have much greater potential to deliver these benefits than the GM technologies developed in the last century. However, they also face a legacy from these GM technologies in the form of complex, time-consuming and costly regulatory systems that may no longer be relevant to the products of the new genetic technologies, and changing but still divergent interests and values among stakeholders related to the desirability of their use (Section 4).

We therefore propose a set of regulatory principles to guide decision makers on the future governance and regulation of products from genetic technologies[47]. These principles, in addition to other benefits outlined below, will support systemic integration across Government departments, including those that have not previously had decision-making roles in this area but, we argue, should now have responsibilities related to the governance of genetic technologies, given the importance of regulatory decisions for innovation and trade potential and for a broad range of national policies (the Department for Environment, Food and Rural Affairs (DEFRA), BEIS, the Department for International Trade (DIT), the Treasury).

3.1 Balance Principle

Balance is understood here as "*Weighting the relative importance or salience of differently-held perspectives, making clear the reasoning behind the resulting decision*", the aim being to achieve, wherever possible, an acceptable balance across the perspectives of Government, industry and civil society. We propose it here as an underlying regulatory principle to be employed where there is vagueness, conflict or disagreement among other principles, interests and/or values, or among other regulatory or governance criteria. To give just two examples: it will be relevant to the resolution of differently-held stakeholder

[47] The RHC has taken a similar approach in other reports, such as the key criteria that were developed on the fusion energy regulation report. Different considerations for other areas led to focusing on different aspects.

perspectives or to balancing the attention given to expected risks and benefits of products arising from genetic technologies.

3.2 Precautionary Principle (PP)

The precautionary principle requires decision-makers to adopt precautionary measures when scientific evidence about an environmental or human health hazard is uncertain and the stakes are high. However, the European Parliament has noted that there is no universally accepted definition and there are multiple interpretations of the principle[48]. The principle underlies the current European regulatory system for genetic technologies and also the UN Convention on Biological Diversity (CBD), which is the basis of EU and many other national regulatory regimes, so it will remain part of the overall picture for the UK, since it is a signatory to the CBD. The EU has developed guidelines for its use in the context of GM organism regulation, with the intention of ensuring proportionality in its use[49], but the application of the principle in the EU is still subject to criticism for being disproportionate and unnecessarily inhibiting of innovation[50].

3.3 Innovation Principle

The innovation principle notes that the encouragement of progress and innovation is itself a social good (like sustainability) that should not be unfairly prevented, implying that Governments should have regard to the need for beneficial innovation. Its role in regulatory reform is complemented by the associated principles of adaptation and proportionality[51] [52]. The *adaptation principle* refers to achieving a balance between predictability of the regulatory environment, fostering confidence of investors to support innovation, and adaptation to technological and scientific progress. The *proportionality principle* refers here to the need for policy and regulatory initiatives to be proportionate to the scale of the potential harms and benefits, implying balancing of the principles of precaution and innovation.

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[48] European Parliament (2015). The Precautionary Principle: Definitions, application and governance. In Depth Analysis. PE537.876 https://www.europarl.europa.eu/RegData/etudes/IDAN/2015/573876/EPRS_IDA(2015)573876_EN.pdf)

[49] Commission of the European Communities (2000). *Communication from the Commission on the Precautionary Principle*. Brussels, 2.2.2000 COM(2000) 1 final.

[50] ALLEA (2020) lead authors: Dima, O.; Bocken H.; Custers, R.; Inze, D.; Puigdomenech, P.; *Genome Editing for Crop Improvement*. Symposium summary. Berlin. DOI: 10.26356/gen-editing-crop and Urnov, F., Ronald, P. & Carroll, D. A call for science-based review of the European court's decision on gene-edited crops. *Nat Biotechnol* **36,** 800–802 (2018). https://doi.org/10.1038/nbt.4252.

[51] European Political Strategy Centre, (2016) *Opportunity Now: Europe's Mission to Innovate.* EPSC Strategic Notes, Issue 15, 5 July, 2016. (https://ec.europa.eu/epsc/sites/epsc/files/strategic_note_issue_15.pdf

[52] European Political Strategy Centre, (2016) *Towards an Innovation Principle Endorsed by Better Regulation.* EPSC Strategic Notes, Issue 14, 30 June 2016. (https://ec.europa.eu/epsc/sites/epsc/files/strategic_note_issue_14.pdf

Responsible Innovation

The innovation principle is not unconditional. Entrepreneurs are increasingly expected to ensure that they innovate in a responsible manner, involving "*… careful consideration of, and action to address, the potential impact of introducing a new product, service, process or business model*". They should "*consider the benefits that are derived from an innovation and seek to eliminate, minimize or mitigate any potential downsides from the perspectives of the company, its employees, suppliers and customers, and stakeholders who might be impacted, directly or indirectly, by the innovation. It is an attempt to improve our collective futures by taking responsibility for, and improving, today's innovation practices*"[53]. The defining requirement of responsible innovation is to engage widely about product development with *all* stakeholders, particularly members of the public, and UK-based and other companies should adopt such a standard.

Section 4 describes how we envisage responsible innovation functioning in the development and approval of the products of new genetic technologies.

3.4 Organisation for Economic Cooperation and Development (OECD) Regulatory Principles

The OECD has been involved in developing regulatory principles and approaches relevant to genetic technologies since 1986 when it published the first legal instrument on the governance of recombinant DNA technologies[54]. Kearns et al. (2021)[55] suggest that regulatory systems internationally would benefit from consolidation and revision of the OECD's work on regulation of genetic technologies since the 1980s to develop a new recommendation on 'Safety Considerations for Products of Modern Biotechnology: Applications in the Environment, Agriculture and Food/Feed Production', an initiative to which the UK would be well-placed to contribute. A recently announced public consultation from the OECD on "Recommendations on Agile Regulatory Governance to Harness Innovation"[56] is very compatible with the proposals described in Sections 5 and 6.

[53] British Standards Institution (2020) *Responsible Innovation – Guide.* British Standards Institution, PAS 440. https://pages.bsigroup.com/l/35972/2020-03-17/2cgcnc1?utm_source=pardot&utm_medium=email&utm_campaign=SM-STAN-LAU-PAS-PAS440-2003

[54] OECD (1986) *Recommendation of the Council Concerning Safety Considerations for Applications of Recombinant DNA Organisms in Industry, Agriculture and the Environment.* (OECD/LEGAL/0225) (http://www.oecd.org/sti/emerging-tech/40986855.pdf)

[55] Kearns, P.W.E., et al., (2021). Biotechnology and Biosafety Policy at OECD: Future trends. *Trends in Biotechnology*. (doi: 10.1016/j.tibtech.2021.03.001).

[56] https://www.oecd.org/gov/regulatory-policy/Draft-Recommendation-Agile-Regulatory-Governance-to-Harness-Innovation.pdf

4. Stakeholder roles in regulatory processes

In its report 'Science, Technology and Innovation Outlook 2021: Times of Crisis and Opportunity', the OECD acknowledges the importance of inclusion of stakeholders early in the innovation process: '*Engaging stakeholders and citizens in these efforts will expose policymakers to diverse knowledge and values, which should contribute to policy resilience'* [57]*.* The *regulatory* engagement process envisaged here would, among other things, act as a mutual information exchange, potentially helping to improve understanding of current and future regulatory systems.

Two complementary approaches are proposed here for the involvement of stakeholders, including public voices, in regulatory processes:

1. Involvement in an advisory committee (Stakeholder Advisory Panel) that brings the full range of stakeholder perspectives into the regulatory decision-making process (Section 4.1); and

2. Larger-scale opinion surveys that focus on the operation of the regulatory system to deliver safe products with societal as well as commercial benefits (Section 4.2).

Stakeholder engagement, including public engagement and dialogue, in regulatory decision-making should be guided by the principles of responsible innovation and balance (Section 3).

4.1 Involvement of stakeholders in a Stakeholder Advisory Panel

Examples of involvement of a broad range of stakeholders in regulatory decision making include the following:

The Board of the Human Fertilisation and Embryology Authority (HFEA)[58], the independent statutory regulator of *in vitro* fertilisation and human embryo research, has a lay majority, a lay chair and has a track-record of decision-making in a sometimes-controversial sector. In reaching its decisions, consensus is not always possible, and this requires agreement that there was a transparent *process* that was adhered to, which was

[57] OECD Science, Technology and Innovation Outlook 2021: Times of Crisis and Opportunity, (2021). https://www.oecd-ilibrary.org/sites/75f79015-en/index.html?itemId=/content/publication/75f79015-en

[58] https://www.hfea.gov.uk

reasonable, and during which individual stakeholder views were heard and diverse strands of evidence were taken on board[59].

The US approach to *'negotiated rule making'*[60], has a role in making decisions on future regulatory instruments, defined as:

> *"[A] consensus-based process through which an agency develops a proposed rule by using a neutral facilitator and a balanced negotiating committee composed of representatives of all interests that the rule will affect, including the rulemaking agency itself. This process gives everyone with a stake a chance to try to reach agreement about the main features of a rule before the agency proposes it in final form."*

Negotiated rule making requires a role for members of the public and its goal is to reach consensus, understood to mean that each represented interest concurs in the result, unless all members of the committee agree at the outset to a different meaning.

The British Standards Institution has involved members of a consumer representative panel in the development of its standards[61] for 70 years and is setting up a sustainability standards network to have a similar function[62].

Building on these examples, we propose that UK regulators should establish a Stakeholder Advisory Panel, involving representatives of all relevant stakeholders, including public/lay representatives, with a role in contributing to the adaptation and operation of the UK regulatory regime and to the outcomes of its decisions. Its role could include enabling regulators to experiment and to learn from the experience of others. Further detail of our proposals for this body can be found in section 6.3.

4.2 Understanding public perspectives on innovative technologies and their regulation

In addition to the above decision-making role for citizens, there will also be a need to explore public perspectives on the varied products emerging from new genetic technologies, and on their future regulation. This would benefit from a different engagement focus when compared to previous public attitude surveys in this area.

The following guidelines could be used as a basis for public engagement and dialogue initiatives relevant to regulatory decision making. They build on previous experience of

[59] RHC Communication, Peter Thompson, CEO, HFEA.
[60] Anon (1996) *What is negotiated rule making?* https://www.ams.usda.gov/sites/default/files/media/Feb82011IntrotoNR.pdf
[61] https://www.bsigroup.com/globalassets/localfiles/en-gb/about-bsi/nsb/consumer/bsi_consumers_standards.pdf
[62] Scott Steedman, 2021, Speech to the BSI Annual General Meeting, 18 May, 2021.

stakeholder engagement about genetic technologies and also advice from other stakeholders involved with a broader range of technologies[63] [64].

Guidelines for stakeholder engagement about products and their regulation

1. There should be equitable treatment across all stakeholders:

- discussions should be open and accommodate the full range of relevant opinions;
- agendas should be flexible and allow stakeholder input; and
- no single perspective should dominate other opinions or dictate the terms of engagement.

2. The engagement should be tailored to the relevant product and its development stage to consider:

- who should be involved;
- which topics are relevant to be addressed; and
- whether and how the outcomes should be implemented.

3. Engagement should be carefully timed:

- too early and its value will be undermined by uncertainty about the nature of future technology-related developments;
- too late and it may be too expensive to change the design of a product or the proposed regulatory approach, or stakeholder opinions and political positions may have become entrenched so that accommodation or consensus will be more difficult to achieve.

4. Participants should accept that consensus may not be attainable and expectations should be managed accordingly.

5. The engagement process should ensure that stakeholders are well-informed about the nature of innovation and regulatory processes and how they work.

6. The process should ensure a balanced consideration of benefits and risks associated with the innovation, and where its impacts will accrue.

[63] Lyall, C. and Tait, J. (2019) Beyond the Limits to Governance: new rules of engagement for the tentative governance of the life sciences. *Research Policy, 48(5),*1128-1137. doi.org/10.1016/j.respol.2019.01.009

[64] BSI (2020) *Responsible Innovation – Guide.* British Standards Institution, PAS 440. https://pages.bsigroup.com/l/35972/2020-03-17/2cgcnc1?utm_source=pardot&utm_medium=email&utm_campaign=SM-STAN-LAU-PAS-PAS440-2003

7. Standards should be included for the quality and breadth of evidence that is considered as a basis for discussion and decision making.

8. Where there is conflicting evidence, the expertise of those promoting the evidence, including both scientific and practical, should be taken into account.

The improved understanding of public perspectives and attitudes will be an important source of evidence to be taken on board in decision making and future communication about regulation of genetic technologies. Based on the above guidelines, such surveys should be undertaken as independent Government-sponsored initiatives, carried out, for example, by independent professional bodies or national academies, as has been the case in the past. It is not envisaged that they would be an integral part of the proposed regulatory system.

4.3 Stakeholder concerns about genetic technologies

Public and other stakeholder concerns about genetic technologies, based on information from stakeholder engagement, news media and websites, are varied but include some that are based on misunderstanding of the nature of current regulatory requirements for all products placed on the market and can be at least partly addressed by better information. Others will need to be addressed by further consultation and/or adaptation, either to regulatory systems or to products themselves.

Where a concern relates to a broader societal issue, such as the nature of farming systems or animal welfare, these may be better addressed through other areas of public policy and regulation. There are no benefits, and potentially considerable losses, if a useful product is rejected because it might have an impact on a broader issue, particularly where that is already addressed by other policy or regulatory regimes. Examples include concerns about the complete absence of regulatory oversight if products are no longer regulated as GM organisms, or about disease resistance in animals enabling reduction in welfare standards. Section 6.6 describes how such issues are or could be addressed.

4.4 Making stakeholder engagement work as part of regulatory adaptation

As noted in Sections 5 and 6, there are good reasons to consider taking early action on regulatory adaptation for simple genome editing, but there are flaws in the way the case for such action is being presented to public audiences[65]. Most important are claims that some outcomes of genome editing could occur ’naturally’ through conventional plant

[65] McHughen, A. (2016) A critical assessment of regulatory triggers for products of biotechnology: Product vs. process. *GM Crops and Food,* 7.125-158. DOI: 10.1080/21645698.2016.1228516

breeding and should therefore not be regulated as GM organisms. In addition to ignoring the actual role of biotechnology in generating genome-edited products, the implications of this statement are that:

- what occurs naturally is safe,
- transgenesis does not occur in nature (now known to be inaccurate[66]); and
- not being natural, transgenic technology is potentially more hazardous.

These assumptions have little rational foundation. Conventional forms of selective breeding and their deployment can, on occasions, have hazardous as well as beneficial outcomes and existing processes/systems have an excellent record of ensuring safety, quality and efficacy of such new products. In brief, genetic variants can have beneficial or detrimental impacts *however they are generated*. In addition, the '*could have occurred through traditional plant breeding*' formulation is *vague* over the status of multiple genome edits, which may be very important for producing particular traits: each single edit might have occurred '*naturally*', but each additional edit makes the combination more improbable by chance, although not impossible. Such vagueness could result in many decisions being challenged.

Innovators and regulators are aware of the insubstantial basis for claims about naturalness, but they are pushed in that direction by regulatory convenience. Where a regulatory system is based on the technique used to develop the product a legal case could be made that certain genome-edited products are not captured under the definition of a GM organism. Pragmatic approaches like this will probably be needed in some cases to enable regulatory adaptation and they should not necessarily be ruled out. However, it is important that the case is made in a way that does not reinforce existing prejudices about products that *do* involve transgenesis, and that the benefits of this regulatory adaptation are not achieved at the expense of trust in the regulatory system as a whole and a path to more substantial future benefits.

Sections 4.1 and 4.2 recommend the setting up of a Stakeholder Advisory Panel with the aim of instigating novel approaches to stakeholder engagement about products of genetic technologies, taking on board a broader range of stakeholder perspectives and a broader range of regulatory issues and concerns. Section 6.3 provides detail on how this could be operationalised. Sections 5 and 6 describe an alternative approach to regulatory adaptation that could enable a more collaborative basis for prioritising regulatory adaptation for all genetic technologies. As part of this process, future stakeholder engagement about regulation of genetic technologies should acknowledge the inconsistencies concerning how the technologies have been regulated and represented

[66] Xia, J. (2021) Whitefly hijacks a plant detoxification gene that neutralises plant toxins. *Cell,* 184(7), 1693-1705. https://doi.org/10.1016/j.cell.2021.02.014

publicly so far. They should emphasise that genetic technologies themselves are not the central regulatory issue and move to a more pragmatic footing based on the properties of individual products and their intended use as a basis for decision making.

5. Regulating the products of second-generation genetic technologies

5.1 The regulatory trigger

As noted in Section 1.3, regulating the use of products developed using genetic technologies has been nationally and internationally divisive to the point where "*So great are the political divisions that jurisdictions cannot even agree on the appropriate triggers for regulatory capture, whether product or process*"[67]. Although the safety record of such products has been excellent over the past 25 years, across all countries and regulatory systems, only large multinational companies have had the financial and other resources needed to develop products based on genetic technologies. This is largely as a result of time-scales and financial costs associated with regulation (Section 2). The result is that we have not yet seen much of the predicted disruptive innovation that could move the agri-food sectors onto a new, more sustainable innovation trajectory, with the participation of numerous independent SMEs[68].

Until recently, in many countries, emphasis on the precautionary principle has not been balanced by consideration of the innovation principle. The prevailing regulatory ethos for new technologies has been that innovators must tailor their products to fit the requirements of the existing regulatory systems, however inadequate, leading to additional costs and delays and sometimes sub-optimal product design. Partly under the influence of the innovation principle, most regulators have now accepted a more proactive role in enabling new developments that are safe for people and the environment and deliver societal benefits, if necessary tailoring the requirements of the regulatory system to fit the nature of the technology. However, this is new territory, lacking a history of past experience to draw on, and today's national and international dialogues among regulators with responsibility for genetic technologies are paving the way for new ways of thinking about regulatory systems.

The UK is currently regulated under retained EU law, which covers products of both first- and second-generation genetic technologies, on the basis of precise definitions of the techniques used to develop them (Sections 1.2-1.4 and 2). The UK's departure from the EU opens up an opportunity to adapt its regulatory regime to be more closely aligned with those of other countries, in compliance with the regulatory principles outlined in Section 3.

[67] McHughen (2016) op cit

[68] Laurenz Klerkz and David Rose (2020) Dealing with the game changing technologies of Agriculture 4.0. *Global Food Security*, 24. https://doi.org/10.1016/j.gfs.2019.100347

Within the EU system, a request from the French Government to the Court of Justice of the European Union (ECJ)[69] [70] could have resulted in a reinterpretation of the definition of a GM organism to exclude simple genome-edited products from the GM regulatory system. However, in 2018 the ECJ ruled that genome-edited products must be treated in the same way as transgenic GM organisms. The UK argued against this position and in July 2020, following the UK's exit from the EU and in response to amendments to the Agriculture Bill, the Government stated that it would consult on amending the definition of a GM organism to clarify that it did not include organisms (produced by precision breeding) that could have been produced by traditional breeding[71]. It stated that its position "*was, and is still, that if the products of genome editing could have been produced naturally or by using traditional breeding methods, they should not be regulated as GM organisms*"[72]. The ECJ decision is also not going unchallenged within the EU (see Section 2).

As part of the RHC's remit, we spoke to regulators in a number of other countries who have been working on similar questions to those addressed here (Argentina, Brazil, Canada, Norway, USA). It is clear that there is no regulatory solution that will be universally applicable, since each country has different pre-existing legislative foundations and future policy ambitions; but these conversations and the reports provided by the regulators we spoke to contributed to our analysis in Sections 5.2 and 5.3 and our proposals in Section 6. Our proposed regulatory approach is designed to ensure our ability to trade and engage productively with a broader range of countries internationally.

5.2 Genome editing as a candidate for special treatment

A majority of countries have accepted the arguments for early adaptation of regulatory systems for second-generation genetic technologies, specifically for the simplest forms of genome editing, SDN1 and SDN2[73] (Section 1.4). The arguments being made for treating SDN1 and SDN2 genome editing as special cases include some that are related to benefits foregone under current regulatory regimes and some that are related to the adaptation of current regulatory regimes:

1. Because some products of this powerful technique do not involve cross-species genetic transfer (transgenesis), they have been identified as potentially not falling

[69] https://curia.europa.eu/jcms/upload/docs/application/pdf/2018-07/cp180111en.pdf

[70] Callaway, E. (2018) CRISPR plants now subject to tough GM laws in European Union. *Nature,* 560, 6.

[71] https://www.euractiv.com/section/agriculture-food/news/uk-gene-editing-amendment-withdrawn-but-government-commits-to-consultation/

[72] Lord Gardiner quote, House of Lords debate, 28/07/2020. https://hansard.parliament.uk/lords/2020-07-28/debates/47D6DD2A-6DB4-440A-A881-51AAA8FEC4F4/AgricultureBill

[73] Friedrichs S, Takasu Y, Kearns P, Dagallier B, Oshima R, Schofield J, Moreddu C. Policy Considerations Regarding Genome Editing. Trends Biotechnol. 2019 Oct;37(10):1029-1032. doi: 10.1016/j.tibtech.2019.05.005. Epub 2019 Jun 19. PMID: 31229272.

under the definition of a GM organism for regulatory purposes and therefore not being captured under that regulatory regime (Section 4.4).

2. Restrictive regulation of GM organisms is seen by many as counterproductive (Section 1.3). It has constrained consumer choice on the range of foodstuffs available to EU citizens; it has led innovative companies to move elsewhere, to the detriment of the European economy[74]; and it has disadvantaged European farmers in comparison to the rest of the world[75].

3. The process by which a new variety is produced is relevant to assessing its potential risks and benefits, but risk assessment should be based on the properties of the product itself, which will be determined by a wide range of other considerations. It makes little sense to regulate two identical (or nearly identical) genetic varieties differently depending on how they were developed, rather than on their relevant characteristics.

4. Restrictive, lengthy and expensive regulatory approval procedures for GM organisms resulted in applications for marketing approval coming almost solely for global commodity crops from large firms with extensive financial resources. There has been an almost complete absence of innovation in smaller scale niche markets by small/medium-sized firms and publicly-funded organisations. This form of regulatory adaptation for genome-edited crops in both Argentina and the United States has already resulted in many more applications from smaller research teams and more local SMEs, related to different characteristics such as nutritional enhancement, easier handling and different taste or colour (Section 2).

5. With the exception of the European Union, other countries are moving to relax rules surrounding genome-edited crops or to treat them in the same way as conventional varieties. If products of genome editing are widely approved in the rest of the world, but not the UK, then British consumers will have less access to diverse new products, farmers will be at an increasing competitive disadvantage, and opportunities for environmental improvement may be missed.

Basing regulatory decision making for a product on the criterion whether it could have been produced by traditional breeding methods has a number of examples internationally, but also raises questions about the rational basis for the argument (Section 4.4). In its 2020 regulations, the US Department for Agriculture (USDA) exempted single-edit GE products from regulatory oversight on the basis that these are '*genetic changes that could practically be achieved by conventional breeding methods in any plant'*.[73] For this reason, the USDA limits the exemption to additions to known DNA sequences that currently have

[74] https://www.politico.eu/article/what-future-for-gm-crops-in-europe/

[75] Hundleby, PAC and Harwood. W.A. (2018) Impacts of the EU GMO regulatory framework for plant genome editing. *Food and Energy Security, 8.* https://doi.org/10.1002/fes3.161

been observed to exist in the plant's gene pool. The USDA also does not automatically exempt multiple-edit GE products, based on its conclusion that multiple edits may not be possible through conventional breeding methods in all plant species and for all types of edits.[74] Indeed, the USDA's criterion of '*could practically be achieved by conventional breeding methods*' would be restrictive for most current, and especially future, applications of genome editing.

An alternative to tying the regulatory trigger to traditional breeding methods, with similar practical consequences, is Argentina's trigger of whether the final genome-edited product contains a '*novel combination of genetic material*' and is '*free from transgenes*'. Satisfaction of these conditions leads it to be classed as a product of a '*New Breeding Technique*' (NBT) and subject to a more proportionate, non-GM regulatory framework.

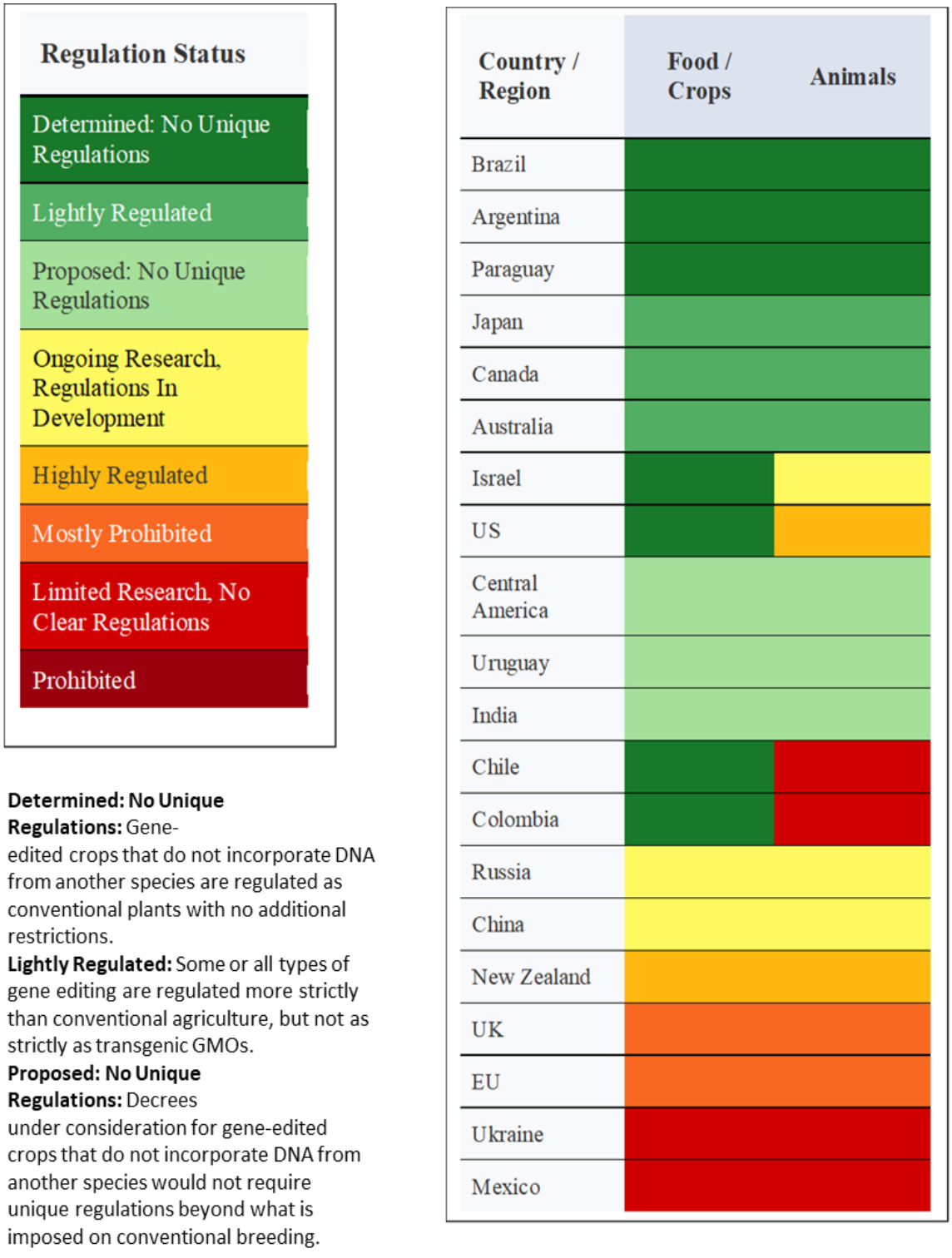
Figure 1[76] summarises how different countries are progressing regulatory adaptation for the products of simple genome editing, with most having embarked on a path to more proportionate regulation of these products or having no unique regulations. The EU so far is committed to ensuring that all products of genetic technologies, including genome editing, continue to be regulated as GM organisms, reinforcing the *status quo,* although this is now being reconsidered[77]. However, for many EU stakeholders[78], the avoidance of a GM-based regulatory system for products of simple genome editing is perceived as a low-hanging fruit with the potential to open up the EU to future benefits from the further development of crops and animals (Section 1.5).

[76] Global Gene Editing Regulation Tracker (2019). *Human and Agriculture Gene Editing: Regulations and Index*. Genetic Literacy Project. https://crispr-gene-editing-regs-tracker.geneticliteracyproject.org/

[77] https://ec.europa.eu/food/sites/food/files/plant/docs/gmo_mod-bio_ngt_eu-study.pdf

[78] Van der Meer, P. *et al.* (2021) The status under EU law of organisms developed through novel genomic techniques. *European Journal of Risk Regulation,* pp 1-20. (DOI: https://doi.org/10.1017/err.2020.105)

***Figure 1: Global genome editing regulatory landscape (2019).*[79]**



[79] Global Gene Editing Regulation Tracker (2019). *Human and Agriculture Gene Editing: Regulations and Index*. Genetic Literacy Project. https://crispr-gene-editing-regs-tracker.geneticliteracyproject.org/

The Global Gene Editing Regulation Tracker notes[80] that two factors are expected to be relevant to future decisions on adaptation of regulations for genome-edited crops and animals: the UN CBD Cartagena Protocol on Biosafety[81] (Section 1.3), and pressure from many scientists and companies. The USA, Canada, Chile, Argentina and the Russian Federation are either not signatories to the Cartagena Protocol or have not ratified it into their national law, and would be expected to have more freedom of action to move to a product-based, more permissive regulatory approach. Countries with a regulatory trigger based on production methods rather than properties of the product include Brazil, India, China, Australia, the EU and New Zealand. From the information in Figure 1, the nature of the regulatory trigger does not seem to have a deciding influence on a country's ability to adapt its regulatory regime so that genome-edited crops or animals are not covered by existing GM regulations. Also, Japan, which has no commercialised GM organisms and is a signatory to the Cartagena Protocol, is emerging as a leader in the introduction of genome-edited crops with an approach based on the production process[82]. A majority of the countries included in Figure 1 are well advanced in regulatory adaptation for simple genome editing (SDN1 and, in some cases, SDN2) and many have already decided that there should be no unique regulation, or at least lighter regulation, of genome-edited crops and animals.

5.3 Regulatory adaptation across all genetic technologies

All the above points have been made mainly in relation to regulatory adaptation for products of simple genome editing and few countries are yet actively reviewing regulatory regimes for products of all genetic technologies, including those involving transgenesis.

As noted in Section 1.5, the scope and potential benefits from products of second-generation genetic technologies involving complex genome editing, synthetic biology and engineering biology could greatly out-weigh those of simple genome editing. A case can be made that products of all genetic technologies, including those involving transgenesis should be equally urgent candidates for regulatory adaptation. Factors supporting this course of action include:

- The track record of safety of GM organisms is excellent, after 25 years of increasing use in many countries and no significant adverse impacts on either health or the environment (Section 1.3).

- Public acceptance of the products of genetic technologies remains an important factor in their chances of successful commercialisation and is context-dependent and

[80] Global Gene Editing Regulation Tracker, op cit.

[81] https://bch.cbd.int/protocol/

[82] https://www.biodic.go.jp/bch/download/genome/genome_chirashi_english.pdf
http://www.biodic.go.jp/bch/english/cartagena/images/e_cartagena.pdf

complex[83]; but there is some evidence that public acceptance of the use of such technologies in plants has increased[84] and several campaigning organisations are focusing more on other issues such as climate change, where such products could have significant benefits (Section 4).

- Opportunities to combine genome editing with transgenesis promise products with even greater benefits than genome editing alone, for example, in the development of self-fertilising crops that fix their own nitrogen from the air (Section 1.5).

- These technologies are not mature. Innovations as powerful as CRISPR will undoubtedly occur in the coming years and a wide spectrum of different techniques are now used in developing plant, animal or microbial varieties with very blurred divisions between them, including marker-assisted breeding, chemical mutagenesis, wide crossing, embryo rescue, protoplast fusion, speed breeding, genome editing, and genetic modification. The recent announcement of synthetic bacteria with non-canonical amino acids[85] is a reminder of how fast genetic technologies are developing and how unpredictable future possibilities will be. Future regulatory systems will need to be adaptive enough to cope with this rapidly shifting foundation.

The RHC is proposing (Section 6) that, while noting, and acting on, the current opportunity to make special arrangements for simple genome-edited products, the UK should begin now to consider how it will regulate all products of genetic technologies in future. For this reason, in Section 6 we first outline our proposals for all genetic technologies, treating simple genome editing as a special case of that more general process. Most of the rest of the world has already moved quite a long way towards regulatory adaptation for the products of simple genome editing but, for products building on all the other genetic technologies, the UK could take on a path-finder role to define a dynamic regulatory regime that is designed to be able to evolve to cope with future technological change.

[83] Shew, Aaron & Nalley, Lawton & Snell, Heather & Nayga, Rodolfo & Dixon, Bruce. (2018). CRISPR versus GMOs: Public acceptance and valuation. Global Food Security. 19. 71-80. 10.1016/j.gfs.2018.10.005.

[84] Mihael Cristin Ichim (2021) The more favorable attitude of the citizens toward GMOs supports a new regulatory framework in the European Union, GM Crops & Food, 12:1, 18-24, DOI: 10.1080/21645698.2020.1795525

[85] https://www.eurekalert.org/pub_releases/2021-06/urai-fcr052821.php

6. Recommendations for the future regulation of genetic technologies in the UK

6.1 Overview

We noted above the scale of the potential contribution of second-generation genetic technology products to UK environment and climate change policy goals, to the viability and sustainability of UK farming systems, and to the UK economy, including domestic and export markets (Section 1.5). There is an important opportunity now to adapt the regulatory system to enable competition on an even footing with other nations and also to contribute intellectually to the ongoing international dialogue on the regulatory framework for innovative genetic technologies. Most of the policy discussion has focused on crop-related developments for the agri-food sector but it is equally important to include developments involving animals and micro-organisms, including those designed for the aquaculture sector (Section 6.6).

Our recommendations build on past experience of regulation of GM organisms (Section 1.2 and 1.3) and emerging understanding of the interactions between regulatory regimes and national innovation potential[86]. The UK now has the opportunity to devise a regulatory regime for products of genetic technologies, intended for use in agriculture and food production, that:

1. Is clear, unambiguous and, for each product, triggers the regulatory system that is most appropriate to its properties, including both risks and benefits (Section 5);
2. Satisfies the regulatory principles outlined in Section 3;
3. Learns from the experience of regulating first-generation GM technologies (Section 1.2 and 1.3);
4. Incorporates appropriate timing of regulatory actions and clear pathways and deadlines to enable better, faster decisions by companies and regulators;
5. Incorporates appropriate targeting of regulations and standards to products depending on their properties;

[86] https://www.gov.uk/government/publications/regulation-for-the-fourth-industrial-revolution

6. Where appropriate, enables rapid regulatory adaptation, so that a product can either trigger or avoid triggering a specific component of the regulatory regime as more is learned about its properties during development;

7. Avoids unnecessary costs and time delays, enabling informed investment decisions and the development of new SME-based industry sectors to address new societal challenges.

Trade-related considerations will limit the UK's freedom of action to some extent, since whatever regulatory system we choose to adopt will need to be compatible with the standards of our trading partners, and preferably also with the devolved UK administrations. However, given the number of other countries that are already adapting their regulatory systems (Figure 1), there is an expanding opportunity for trade gains for the UK. While the EU market is highly restricted currently, there are also increasing pressures for regulatory change within the EU[87] that could result in their future alignment with most other countries.

This section covers all products intended for uncontained use in agriculture and food production, developed using second-generation genetic technologies (Section 1.4). There is a case for giving early attention to simple forms of genome editing (SDN1 and certain types of SDN2), given the scale and rate of delivery of the potential benefits and their contributions to meeting important societal goals (Section 1.5). We understand the policy case for this course of action, although there are some flaws with the rationale, as described in Section 4.4.

6.2 The proposed regulatory trigger

We are proposing that the UK regulatory system should apply to novel products (plants, animals or micro-organisms) obtained using genetic technologies (including gene editing, synthetic biology and engineering biology), to be used in agriculture, food production and other uncontained conditions. This description avoids capture of new products that are already well covered by existing regulatory regimes, such as the products of conventional plant breeding. It is intended to apply to products of all genetic technologies, including (i) those that involve cross-species genetic transfer (transgenesis), currently regulated in most countries as genetically modified organisms (GMOs), and (ii) simple genome edited products based on CRISPR and related techniques (site-directed nuclease (SDN) 1 and 2 genome editing), that do not involve permanent cross-species genetic transfer. It will avoid the need to redefine the regulatory focus for each new development in scientific methodology and speed up and simplify regulatory decision making by avoiding over-

[87] European Commission (2021). *Study on the status of new genomic techniques under Union Law and in light of the Court of Justice Ruling in Case C*-528/16. Brussels, 29.4.2021 SWD(2021) 92 final. (https://ec.europa.eu/food/sites/food/files/plant/docs/gmo_mod-bio_ngt_eu-study.pdf)

regulation of safe products and allowing work on different regulatory requirements to proceed in parallel rather than in sequence, as was the case for the rapid regulatory approval of Covid-19 vaccines.[88]

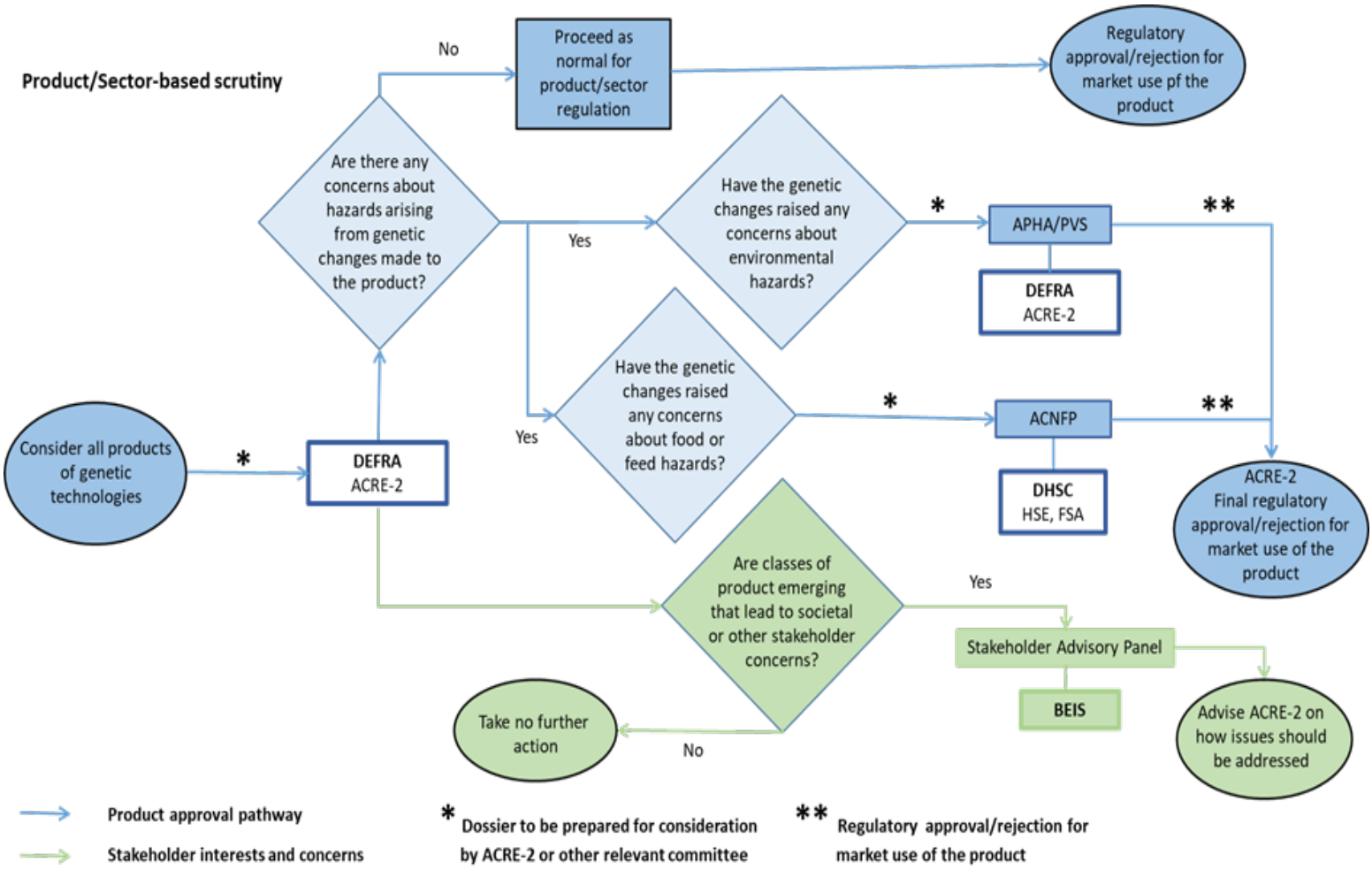
As indicated in Figure 2 (*see below*), products identified in this way would be scrutinised by current sector (market) based regulatory regimes, avoiding discrimination among different products based on the nature of the genetic technology involved in their production and focusing on the properties of the products themselves.

Experience from other countries suggests that successful adaptation of a regulatory regime, and the effectiveness of its day-to-day operation, are highly dependent on the willingness of regulators and innovators to work together to achieve its overall aims. There is general recognition of the need to involve citizens and their representatives in the overall governance process, and this needs to be matched by early and frequent engagement with the companies involved in product development.

Sections 6.3–6.5 outline our proposals for regulation of the products of all genetic technologies that meet the above description and section 6.7 outlines our proposals for a more immediate regulatory decision on simple genome-edited products. Figure 2 below summarises our regulatory proposals.

[88] https://wellcome.org/news/quick-safe-covid-vaccine-development

Figure 2: Proposed regulatory pathway for products of genetic technologies used in agriculture, food production and other uncontained conditions§



§ ACNFP-Advisory Committee on Novel Foods and Processes; ACRE-Advisory Committee on Releases to the Environment; APHA-Animal and Plant Health Agency; BEIS-Department for Business, Energy and Industrial Strategy; DEFRA-Department for Environment, Food and Rural Affairs; DHSC-Department for Health and Social Care; FSA-Food Standards Agency; HSE-Health and Safety Executive; PVS-Plant Variety Rights and Seeds Office.

6.3 Products of all second-generation genetic technologies – starting point of the regulatory process

ACRE-2 and sector-based regulators

We propose that an organisation taking on, and adding to, ACRE's current role (ACRE-2) should be the primary organising node for regulatory scrutiny of new products of genetic technologies and for final approval or rejection for market use (Figure 2). As part of its

submission to ACRE-2, at the beginning of a review of regulatory status, the developer would be expected to include within the dossier all relevant genomic DNA sequence information for the product. The data requirements could be flexible, depending on the nature of the product, based on a recognised approach to risk identification and assessment, decided initially on a case-by-case basis[89]. For example, where elements of vector DNA used in the production process remain in the genome and a pathway to potential harm is identified (with a probability of occurrence that warrants closer investigation), courses of action should be recommended to the developer to mitigate the risk. Such mitigations could include introducing further breeding steps or additional genetic changes, or proceeding with caution and using continuous monitoring to gather evidence of future emergence or non-emergence of a predicted harm.

If there are no expected risks and no other issues arising from the genetic changes that resulted in the product, from that point on it would be treated as a conventional new product to be regulated in the same way as other products in the same sector.

If there are concerns about hazards arising from genetic changes made to the product, for example related to food, feed or environmental hazards, the applicant would be directed to submit a dossier with the relevant information to the appropriate sector-based regulator(s) (e.g. APHA/PVS, ACNFP). Following a sector-based review, the decision(s) of the relevant body or bodies would be passed back to ACRE-2 for a final coordinated opinion.

These sectoral regulators are already involved in the governance of conventional products for similar markets: the Food Standards Agency (FSA) (including the ACNFP), reporting to the DHSC (in addition to food safety its remit also covers environmental concerns and animal welfare); and DEFRA itself (including ACRE and the Plant Variety Rights and Seeds Office (PVS), which is part of the Animal and Plant Health Agency (APHA)). To give an example, registration of a product on the national plant variety list (through APHA) requires evidence that it is a distinct, uniform and stable (DUS) variety and, for agricultural crops, that it delivers value for cultivation and use (VCU). Given that the requirements of DUS are mainly tailored to protection of intellectual property, VCU should have a more important role to play in this process: it has scope to be adapted to incorporate societal and other values (beyond yield, for example) aimed at improving the environment, cultivation or quality of the crop or its products (i.e. evidence of benefit).

Where ACRE-2 identifies additional issues to be addressed for a product, beyond the normal coverage of a sector-based regulator, it should discuss with the sectoral regulator the required testing regimes and the standards to be met.

[89] Devos Y, Craig W, Devlin RH, Ippolito A, Leggatt RA, Romeis J, Shaw R, Svendsen C, Topping CJ. Using problem formulation for fit-for-purpose pre-market environmental risk assessments of regulated stressors. EFSA J. 2019 Jul 8;17(Suppl 1):e170708. doi: 10.2903/j.efsa.2019.e170708. PMID: 32626445; PMCID: PMC7055725.

Applicants for market authorisation should be encouraged to engage with regulators as early as possible to develop guidance on the overall approach, based on a discussion about the expected regulatory regime for the product with the aim of encouraging product adaptation, where necessary, at an early stage of the development process. If ACRE-2, during its initial regulatory status review identifies any plausible pathway to potential harm, this would be immediately communicated to the developer, leading to discussions, wherever possible, on how this could be mitigated to enable the product to be classed as a conventional new product. This is similar to the approach taken by APHIS in the US. Relevant product modifications could include: adaptations to its use (glasshouse, defined zone); or changes to the product genome that would remove or mitigate the cause for concern. For example, a product of genome editing might require screening for potential off-target edits and their elimination by selective breeding, or a non-flowering species for localised use might require a different level of scrutiny and control, compared to a pollinating variety for national use.

There is scope for creative regulatory adaptation based on the product category 'generally recognised as safe' (GRAS)[90], applied in the US to food additives, including micro-organisms. An equivalent category could be brought into use in the UK, for all types of products of genetic technologies, to enable development of registers based on product classes that are deemed to be safe. Based on specified data requirements and previous experience of similar products, GRAS categorisation could become a pathway to a more stream-lined regulatory process.

ACRE-2 and the sectoral regulatory bodies involved in product approval will need more, better and permanent risk assessment expertise if they are to meet the requirements of their additional roles. The Medicines and Healthcare Products Regulatory Agency (MHRA), an executive agency of the DHSC involved in the regulation of medicines, medical devices and blood products, would be a good model for this enlarged role envisaged for ACRE-2. In Canada, the USA, Australia and Argentina, there are non-political regulatory bodies employing risk assessors with decades of experience. Moving to such a system in the UK would ensure a science- and risk-based approach to safety assessment that is proportional to the risks of products. This is an essential foundation for subsequent decisions on whether to approve registration of a product and additional costs would be balanced by the expected increase in innovation capacity, as has been demonstrated in the countries mentioned.

Stakeholder Advisory Panel

We are also proposing a Stakeholder Advisory Panel, to advise ACRE-2 on stakeholder and public perspectives in relation to classes of product that are new, potentially

[90] https://www.fda.gov/food/food-ingredients-packaging/generally-recognized-safe-gras

transformative and/or give rise to societal concerns or, alternatively, raise positive expectations. The Panel would not comment on individual product assessments.

Given the proposed new structure of ACRE-2, it would not be appropriate to include such a body within ACRE-2 itself. However, the MHRA, noted as a relevant model for ACRE-2, has several independent advisory committees that serve such functions, providing the UK Government with information and guidance through the MHRA. It would make sense in this case to locate this panel within the Government department with most previous experience of undertaking the kind of engagement proposed. We therefore propose that it should be sponsored by BEIS, complementing the work of the UK National Quality Infrastructure (NQI)[91](Figure 2), and building on the experience of participating institutions such as the BSI, following the approach and guidelines outlined in Section 4. This could be a pattern for a broader future role for BEIS in promoting responsible innovation in other technology areas.

Final regulatory decision

Once an applicant has demonstrated compliance with the required sectoral regulatory standards, sectoral regulators would inform ACRE-2 of the outcomes and ACRE-2 would be responsible for the final decision on market authorisation (considering, where relevant, any advice on a new product class from the Stakeholder Advisory Panel).

This overall approach should speed up regulatory decision making by avoiding over-regulation of the safest products and allowing work on different regulatory requirements to proceed in parallel rather than in sequence, with benefits that have, for example, been well demonstrated by the rapid regulatory approval of vaccines against Covid-19.

6.4 Product regulation at the sectoral level

The sectoral assessors proposed to be involved in the regulation of products of second-generation genetic technologies and their relationships are outlined in Figure 2. This section discusses how these bodies could address specific questions and issues in ways that would facilitate the regulatory process and support adaptation, while at the same time taking account of public and stakeholder interests, desires and concerns.

Based on the following elements and the above outline for a new approach to regulation, these proposals could be applied to products involving plants, animals or micro-organisms and we recommend that regulatory adaptation should proceed as rapidly as possible for all three.

[91] https://www.gov.uk/guidance/the-uks-national-quality-infrastructure

Assessing potential risks

Where a product has been assessed by ACRE-2 as requiring additional scrutiny beyond that of a conventional new product, depending on the nature of the risk identified, tests will be required by the sectoral regulator to demonstrate that the product meets a specified standard. For example, for an environmental hazard, APHA's inspectorate, with a revised remit, could be the body responsible for overseeing any necessary field trials for a product intended for deliberate release into the environment.

Products involving only incremental changes to well-understood classes of product that have been used safely in the past, should not necessarily be required to repeat all previous safety assessments. If safety has been established, exclusion criteria could be applied; if not, assessment could build on existing evidence. On the other hand, highly innovative products, where there are no previous similar examples, may require additional assessment, proportionate to the level of risk. A guiding assumption here is that *similar* products (phenotypically and genetically) arising from *different* genetic techniques would not be expected to have different risks and so should be subject to similar regulatory scrutiny.

Where additional scrutiny is required, beyond that of a conventional new product, sectoral regulators should plan a pathway to provisional regulatory approval on the basis of their requirements for the product, taking into account expected use, including relevant standards and tests and an indication of the expected timescale and costs involved for the applicant. If standards do not yet exist to cover a specific risk, they should be developed as rapidly as possible, for example using the new BSI Fast Start Innovator Standards system[92]. The absence of such standards should not be used as a reason to hold an application in a state of limbo for an unreasonable length of time. All regulatory bodies involved should have a rolling programme of developing and updating standards and tests so that they are efficient and effective and relevant to the properties of new types of product emerging in their areas. Where applications are received from other countries, the UK could also make effective use of a 'regulatory equivalence' approach (see below) to facilitate trade with other countries.

Where one or more risks are predicted, the relevant sectoral regulator(s) should provide clear guidance and clear end-points for demonstrating safety where possible. If these cannot be met by the developer and no further remedial action is available, the application may be rejected. Regulators should refrain from asking, as has been the case in the EU, for additional data that are not supportive of a hypothesis-driven, science-based risk assessment and would not contribute to decision making.

Some of those we engaged with in our workshops criticised the EU GM regulatory regime for requiring disproportionate amounts of data, and sometimes irrelevant data, for

[92] https://www.bsigroup.com/en-GB/about-bsi/uk-national-standards-body/about-standards/Innovation/fast/

regulatory approval. Testing regimes that have been particularly heavily criticised are the 90-day feeding trials on rats[93] and the requirements for field trials[94]. Where such tests are required, regulators should re-evaluate them with a view to improving efficacy.

Rationalising the data requirements in each sectoral area, and minimising the bureaucratic overload, are important ways in which the UK regulatory approach could be an improvement on the current regime. This will require a balance to be struck between guidelines on data requirements that are broadly specified at a general level and more detailed specifications that can be decided on a more flexible, consultative basis. Problems have arisen in the past where detailed and inflexible data requirements have been technically difficult to deliver, have required often-repeated studies and led to serious delays. The role of consultation in this area would be to improve the design of tests and ensure widespread understanding amongst consultees of their purpose, relevance and technical feasibility.

There should also be provisions to reconsider whether there is a need for additional or less regulatory scrutiny, or to propose different or additional forms of regulatory scrutiny, where new information emerges in the later stages of product development, although this is not expected to be a frequent occurrence.

Regulatory bodies will need to take on additional expertise, in the form of permanent members of staff as proposed above, to cover their new remits. Lack of staff should not be seen as justification for shifting regulatory oversight to another, less appropriate regulatory body, potentially adding unnecessary constraints or delays for product developers. Some relevant expertise will be located in commercial companies and a process should be considered whereby the knowledge and skills within the industry can be accessed without creating conflicts of interest.

Creative use of guidance, standards, policy and technology as aids to regulatory adaptation

Transformational (disruptive) innovations are most likely to require additional regulatory scrutiny and to challenge the capabilities of today's regulatory regimes. The relevant regulatory regime may not be obvious, or may be disputed, as in the case of the arsenic biosensor[95] [96], for which there was a delay of over five years in the EU regulatory system

[93] Devos, Y, et al. (2016) 90-Day rodent feeding studies on whole GM food/feed. EMBO Reports, 17(7), 942-945. DOI 10.15252/embr.201642739.

[94] Gómez-Galera S, Twyman RM, Sparrow PA, Van Droogenbroeck B, Custers R, Capell T, Christou P. Field trials and tribulations--making sense of the regulations for experimental field trials of transgenic crops in Europe. Plant Biotechnol J. 2012 Jun;10(5):511-23. doi: 10.1111/j.1467-7652.2012.00681.x. Epub 2012 Jan 30. PMID: 22284604.

[95] Wan, X., Volpetti, F., Petrova, E. *et al.* Cascaded amplifying circuits enable ultrasensitive cellular sensors for toxic metals. *Nat Chem Biol* **15,** 540–548 (2019). https://doi.org/10.1038/s41589-019-0244-3

[96] https://issuu.com/societyforappliedmicrobiology/docs/sfam_microbiologist_sept_2019_amended_aug23_web

in making a decision on whether to categorise the product as a deliberate release or a contained use of a GM organism. Attempts to commercialise the product in the EU have now ceased.

Genetic technologies are still evolving and the UK's regulatory processes should be able to deal with future unexpected scientific developments. The future UK regulatory system for genetic technologies would benefit from the creative use of guidelines, standards, policies and additional innovative technologies as aids to regulatory decision making that support innovation while continuing to ensure safety to people and the environment.

- Standards and guidelines could be used in the early stages of product development to ensure product safety until there is enough clarity about the nature of the product, its potential properties and markets, to enable well-informed decisions about future regulatory requirements, including whether new legislation will be needed, and if so, which existing regime would be most appropriate[97].

- Using Government policy (through tax incentives or standards) to encourage the development of societally useful products (e.g. those that contribute to the UK's Net Zero commitment or to healthier diets).

- Using secure mechanisms such as blockchain to trace products along a supply chain in order to ensure that the end product in the market place meets relevant standards and regulatory requirements (potentially addressing the challenge that future simple GE products will be difficult to distinguish from the products of conventional plant or animal breeding).

- Partial or phased product approvals could be used with the aim of allowing greater flexibility in risk management and facilitating eventual registration of products deemed safe. Initiatives that would speed up the collection of data required for later stages of the approvals process would be particularly helpful.

6.5 Procedural innovation

Improving efficiency

The commitment to operate their regulatory regimes on a case-by-case basis is written into the regulatory procedures of many countries and it is an important precautionary component of the EU regime. Introducing an element of learning by experience into the regulatory regime would allow adaptation over time so that, where appropriate, products

[97] Tait, J., Banda, G. and Watkins, A. (2017) *Proportionate and Adaptive Governance of Innovative Technologies (PAGIT): a framework to guide policy and regulatory decision making.* Innogen Institute Report to the British Standards Institution. https://www.innogen.ac.uk/reports/1222

with specified properties could be assigned to a specific class with a tailored, simplified regulatory regime.

Mutual recognition of differing rules that reach similar outcomes is a well-established principle in international trade. A regulatory equivalence approach is being proposed for financial services regulation in the UK[98] as part of Brexit-related negotiations, involving assessment by the EU of whether the UK's regulatory/supervisory regime for a particular area is equivalent to that of EU law. While the UK could develop its regulatory regime for the products of genetic technologies with this in mind, prior agreement with any country should not be a pre-condition for regulatory adaptation.

Assessing potential benefits

Assessment of the scale of potential benefits and their probability should proceed in parallel with risk assessment so that the regulator can make a balanced decision about market authorisation. Given that the APHA[99] requirements already involve a form of benefit assessment and that they will be involved in evaluation of all new varieties regardless of risk-related properties, they should be involved in benefit assessment for plants, animals and micro-organisms. However, given the broad range of potential benefits, including contributions to Government policies such as National Food Security, Net Zero, a circular economy and biodiversity enhancement, and the scale of the potential contributions, BEIS, through the proposed Stakeholder Advisory Panel, should also be expected to be involved in such assessments. Work under way in other areas, requiring agri-food systems to demonstrate such contributions to the national economy[100] will facilitate this, for example through the development of life cycle analysis (LCA).

Overall assessment, balancing the relevant benefits and risks, should be done by ACRE-2 as part of its final approval/rejection process. The MHRA, proposed as a model for ACRE-2, already has a role in balancing the benefits and risks of new drugs.

Conducting a regulatory sandbox for new genetic technologies

There is a general lack of understanding of the scale of the benefits to food and feed systems, the environment and the economy, particularly from genetic technologies that involve transgenesis, and also potential disagreement about the value of future adaptation

[98] https://blogs.lse.ac.uk/brexit/2021/03/29/uk-financial-services-should-shift-their-focus-away-from-equivalence/#:~:text=Currently%2C%20the%20UK%20has%20only,for%20central%20counterparties%20(CCPs).

[99] https://www.gov.uk/government/organisations/animal-and-plant-health-agency

[100] Esposito, Benedetta; Sessa, Maria R.; Sica, Daniela; Malandrino, Ornella. 2020. "Towards Circular Economy in the Agri-Food Sector. A Systematic Literature Review" *Sustainability* 12, no. 18: 7401. https://doi.org/10.3390/su12187401

of regulatory systems. We propose a regulatory sandbox[101] to test this report's recommendations and to assess their impact on the ability of companies of different sizes to innovate in these areas.

6.6 Key additional concerns to address

Transparency, labelling and consumer choice

There are concerns that, if products are not labelled as having been produced by a genetic technology, consumers will not have a choice about how their food is produced. Transparency and openness are widely regarded as essential for public acceptance of new genetic technologies and food labelling has been part of this process in many countries, including the UK. On the other hand, labelling has been resisted by some who see it as a warning label that the product is risky, even though it complies with a very rigorous regulatory system. Avoiding this dichotomy, labelling could inform consumers that a product has i) been developed using a genetic technology with regulatory endorsement of its safety, and ii) has potential environmental and societal benefits, providing a better-informed public choice. This approach should also be the subject of stakeholder engagement as part of its implementation.

Taking animal welfare seriously

There are concerns that use of genetic technologies in farmed animals could result in a negative impact on animal welfare. These concerns are addressed for all animals through:

- the Welfare of Farmed Animals Regulations 2007[102], which aim to ensure that high standards of welfare for farmed animals will continue to be a priority, however the animals are bred;
- the Animal Welfare Act 2006 which makes it an offence to cause unnecessary suffering to any animal, or to fail to provide the welfare needs of an animal; and
- the Animal Welfare (Sentience) Act, 2022[103], part of the Action Plan for Animal Welfare[104], which includes plans to improve the welfare of animals, including farmed animals.

[101] BEIS (2021) Report of the Task Force on Innovation, Growth and Regulatory Reform, pp 16-17. (https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/994125/FINAL_TIGRR_REPORT__1_.pdf)

[102] https://www.nature.com/articles/d41586-021-00782-w

[103] https://www.legislation.gov.uk/ukpga/2022/22/enacted

[104] https://www.gov.uk/government/news/uk-to-lead-the-way-on-animal-welfare-through-flagship-new-action-plan

The use of genetic alteration technology in animals for development of new breeds is regulated by the Animals (Scientific Procedures) Act 1986 (ASPA) which brings with it a number of protections, including the requirement to secure a Project Licence, to have appropriately trained personnel and to act in accordance with the principles of the 3Rs (replacement, reduction and refinement)[105], designed to minimise the use of animals in experimentation. Moreover, a licensed establishment must also have an Animal Welfare and Ethical Review Body (AWERB) to review activities and explore scientific and ethical issues arising from ongoing and proposed research. Release of an animal from ASPA regulation, so as to allow a genetically altered animal to be commercially bred, for example, would require the animal to be re-homed, in accordance with ASPA requirements. Consent to re-homing must be given by the Secretary of State. It would also require legal criteria to be met, including an assessment of the animal's state of health and establishing that the re-homing poses no danger to public health, animal health or the environment. Moreover, long-term monitoring of the impacts of genetic technologies on animal health and welfare is strongly recommended.

Beyond immediate impacts on animal welfare from genetic technologies, some have claimed that genome-edited animals, bred to be disease resistant, would permit animal stocking at higher densities, possibly entrenching intensive farming methods, to which many object. However, regardless of the intensity of farming methods, disease outbreaks would still be a significant concern and the reduction in suffering resulting from such edits could lead to a net welfare gain. There is no evidence that such edits in themselves would be harmful to animals or that such animals would be harmful to human health. The role of stakeholder engagement here would be to find ways to deliver the benefits of these genetic technologies in ways that improve the lives of all animals, no matter how they are farmed.

Where issues are identified that cannot be addressed through existing regulations and standards, stakeholder engagement could identify where new standards may need to be developed. For example, genome editing of mammals requires standard assisted reproduction techniques (egg collection, *in vitro* fertilisation, surrogate dams and (possibly) somatic cell nuclear transfer) that can cause suffering or lasting harm, as could altering some productivity traits.

We also recommend that regulatory provisions for assessing the impact of genetic technologies on animals are regularly reviewed, particularly where animals generated by genetic technologies become more common and may come to predominate in certain sectors or areas.

[105] https://www.nc3rs.org.uk

6.7 Regulating products of simple genome editing that do not involve transgenesis (SDN1 and SDN2)

For the regulation of products of simple genome editing, in common with most other nations, DEFRA is adapting the UK regulatory system to develop a more 'fit for purpose' system[106]. As part of this process, DEFRA introduced the Draft Instrument, Genetically Modified Organisms (Deliberate Release) (Amendment) (England) Regulations 2022, to "... enable the bioscience sector to test the benefits and safety of relevant new products" without the burden of unnecessary regulatory processes" "[107]. The legislation removed the requirement in England to submit a risk assessment and seek consent from the Secretary of State before conducting experimental field trials for non-marketing purposes.

This secondary legislation is the first step in a wider reform programme and the next stage in this process was announced in the 2022 Queen's Speech[108], describing plans for a Genetic Technology (Precision Breeding) Bill to create a simpler regulatory regime for plants and animals with genetic changes that could have arisen through traditional breeding and natural processes, along with a commitment not to introduce changes to the regulation of animals until standards of animal welfare are addressed. A Bill to make provision about the release and marketing of, and risk assessments relating to, precision bred plants and animals, and the marketing of food and feed produced from such plants and animals; and for connected purposes received its first reading in the House of Commons on 25th May 2022.

It will be important in the implementation of these plans to ensure that proposals for the regulation of simple genome edited products do not create precedents which then become barriers to the further adaptation of regulatory regimes for products of all genetic technologies. Short-term convenience in regulatory decision-making should not be achieved at the expense of the much greater benefits to be gained from regulatory adaptation applied to products of all genetic technologies.

[106] DEFRA (2021) The Regulation of Genetic Technologies. January 2021 (https://consult.defra.gov.uk/agri-food-chain-directorate/the-regulation-of-genetic-technologies/supporting_documents/20210106%20Gene%20editing%20consultation%20document%20FINAL.pdf)

[107] https://committees.parliament.uk/publications/8865/documents/89203/default/

[108] https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1074113/Lobby_Pack_10_May_2022.pdf

Glossary

Key terms:

Genome: the total complement of DNA found in a species; commonly found in the form of chromosomes (DNA plus proteins) in the nucleus of each cell. Mitochondria have a distinct genome (mtDNA) that forms a part of the genome of a species. Genome sequences will vary from individual to individual in sexually reproducing species. Some viruses have ribonucleic acid (RNA - a molecule with close chemical similarities to DNA) genomes. The genome can be distinguished from the array of chemical modifications to DNA embedded in chromosomes (the epigenome) and the total RNA complement of a cell (the transcriptome).

Genetic modification/genetically modified (GM): this usually refers to older (first-generation) technologies by which plants and animals could be genetically altered. These made use of recombinant DNA (rDNA) as a way of propagating (cloning) genes that could then be introduced into different organisms; sometimes also called genetic engineering. rDNA was developed by the identification of restriction enzymes, which cut DNA; plasmids, which are vectors that allow propagation in bacteria; and methods for recombining bits of DNA (splicing). Introduction of a DNA sequence from one species into another by random insertion into the genome (transgenesis) is perhaps the most familiar example of GM, and is now almost definitional.

Genome Editing (GE; also known as gene editing): refers to a number of techniques that exploit DNA endonucleases (enzymes that cut DNA) that can be targeted to a particular site in a genome (the target); these are also known as site-directed nucleases and include zinc finger nucleases, TALENs and CRISPR/Cas9. The editing is usually effected by cellular DNA repair processes that repair the cut site, with the ability to control these (and introduce desired sequence changes) through the use of a repair template. Edits that appear elsewhere in the genome, perhaps due to similarity to the target DNA sequence, are known as off-target. Different applications of genome editing are typically categorised by the following terms (which are important in understanding regulatory distinctions):

SDN1: In this case, a DNA double-strand break (cut) is introduced by a site-directed nuclease (SDN) and the repair process occurs without the use of a template (donor). This approach is most commonly used to introduce insertions or deletions of DNA that often inactivate a target gene. This approach, which is often very efficient, is widely used in research to study gene function.

SDN2: Here, a repair template (donor) is used to introduce particular sequence changes at the target gene during repair. The donor is usually a short single-stranded DNA sequence. Such changes might range from a single base-pair substitution to several base-pairs. SDN2 is commonly less efficient than SDN1, but outcomes are very much context-dependent.

SDN3: Here, a repair template is used that comprises a longer DNA sequence, perhaps a whole gene(s) or other genetic elements. Efficiency is again lower than SDN1, but also context dependent.

SDN1 and SDN2 do not involve the introduction of any DNA that is not already found in the genome of the organism being edited. This is either because no repair template is used, as with SDN1, or because a small template with a very limited number of sequence variants is used (SDN2). For this reason, SDN1 and SDN2 edits are often described as those that could have arisen naturally or through traditional breeding methods. SDN3 allows the introduction of genes from other species (transgenes or foreign DNA) as well as sequences from sexually compatible species (cisgenes).

Clustered regularly interspaced short palindromic repeats (CRISPR): the most recent and the most impactful GE methodology, comprising a system of RNA-guided (programmable) nucleases (such as Cas9 – hence CRISPR/Cas9). Whilst much genome editing consists of the controlled repair of DNA cuts, CRISPR can be adapted to allow editing in the absence of double-stranded DNA breaks, as with base editing, which permits the direct enzymatic conversion of one DNA base to another. It can also be used to enhance or repress gene expression.

Transgenesis: the deliberate introduction of a DNA sequence (usually a gene sequence) from one species into another. It requires specialist methods, such as embryo injection in mammals. Strictly speaking, the inserted sequence is a **transgene** if it is derived from a sexually incompatible species; if it is from a sexually compatible species, it is called a **cisgene**. Earlier forms of transgenesis that resulted in GM organisms were based on random integration of a transgene into the host genome. Inter-species gene transfer (a form of transgenesis) has also occurred naturally on multiple occasions during evolution.

Genomic safe harbours: regions of a genome that are preferred locations for the insertion of transgenes[109]. They do not encode important sequences, so it is very unlikely that abnormalities will arise following insertion of a transgene at such a locus. They also support active transcription, rather than being generally inhospitable to transgene expression. Without genome editing, it was difficult to exploit such regions, but now

[109] Dong OX, Yu S, Jain R, Zhang N, Duong PQ, Butler C, Li Y, Lipzen A, Martin JA, Barry KW, Schmutz J, Tian L, Ronald PC. Marker-free carotenoid-enriched rice generated through targeted gene insertion using CRISPR-Cas9. Nat Commun. 2020 Mar 4;11(1):1178. doi: 10.1038/s41467-020-14981-y. PMID: 32132530; PMCID: PMC7055238.
Sun Y, Li J, Xia L. Precise Genome Modification via Sequence-Specific Nucleases-Mediated Gene Targeting for Crop Improvement. Front Plant Sci. 2016 Dec 20;7:1928. doi: 10.3389/fpls.2016.01928. PMID: 28066481; PMCID: PMC5167731.
Cantos C, Francisco P, Trijatmiko KR, Slamet-Loedin I, Chadha-Mohanty PK. Identification of "safe harbor" loci in indica rice genome by harnessing the property of zinc-finger nucleases to induce DNA damage and repair. Front Plant Sci. 2014 Jun 26;5:302. doi: 10.3389/fpls.2014.00302. PMID: 25018764; PMCID: PMC4071976.

CRISPR can be used to cut at the safe harbour and a template encoding the desired [110][111].

Traditional breeding methods: refers to a number of interventions that allow breeders to generate and breed novel varieties with desirable traits. In plants, these include ways of enhancing the natural mutation rate, such as chemical mutagenesis, X-ray mutagenesis and protoplast culture. Traits of interest generated by these can be selected for breeding in order to eliminate other, unwanted DNA variants. Even without such enhanced mutagenesis, genomes naturally acquire novel mutations in each generation and these can also be a useful source of variation for breeding novel or improved traits, such as disease resistance. Such naturally occurring variation, allied to natural selection, is the main cause of species evolution.

Synthetic biology/engineering biology: Synthetic biology (SynBio)[112] refers to the design and construction of new biological parts, devices, and systems, and the re-design of existing, biological systems for useful purposes; engineering biology is the application of engineering principles and practice to the design of biological devices and systems for a wide range of applications. Though these terms are sometimes used interchangeably, engineering biology is an overarching term that tends to incorporate ongoing basic research and development – synthetic biology – and its translation into industrial deployment.

[110] Sun Y, Li J, Xia L. Precise Genome Modification via Sequence-Specific Nucleases-Mediated Gene Targeting for Crop Improvement. Front Plant Sci. 2016 Dec 20;7:1928. doi: 10.3389/fpls.2016.01928. PMID: 28066481; PMCID: PMC5167731.

[111] Dong OX, Ronald PC. Targeted DNA insertion in plants. Proc Natl Acad Sci U S A. 2021 Jun 1;118(22):e2004834117. doi: 10.1073/pnas.2004834117. Epub 2021 Apr 30. PMID: 34050013.

[112] https://www.nature.com/subjects/synthetic-biology

Annex

A. Issues paper (collection of evidence from workshops with stakeholders)

RHC issues paper.pdf

B. Acknowledgements (list of stakeholders consulted)

This report would not have been possible without the help of our stakeholders, colleagues, and policy officials internationally. Many thanks to all who offered their expertise (listed below) to participate in workshops, interviews and bilateral meetings during the course of this project.

A special thanks to the GM Team in DEFRA and the BEIS Bioeconomy Team for their ongoing collaboration on the report itself and the FCDO's Science and Innovation Network who were invaluable in facilitating our international engagement on this topic.

Role	Organisation
Chair in Translational Genomics for Plant Breeding	Aberysthwyth University
Member	Advisory Committee on Releases to the Environment
Chair	Agricultural Biotechnology Group
Various	Agriculture and Agri-Food Canada (Canada)
Director	Agri-TechE
Secretariat	All-Party Parliamentary Group on Science and Technology in Agriculture
Chief Technology Officer	Aqua Bounty
Head of Biotechnology	Aviagen
Deputy Director, Global Development	Bill and Melinda Gates Foundation
Chief Executive Officer	The British Society of Plant Breeders
Various	British Standards Institution
Global Head of Bio-innovation	Cambridge Consultants
Research Associate	Centre for the study of Existential Risk, Cambridge University

Director of the Project on Biotechnology	Centre for Science in the Public Interest
Chief Executive Officer	Crop Protection Association
Visiting Fellow	Cornell Alliance for Science
Founder	Compassion in World Farming
Regulatory Affairs Director	Corteva
Various	CTNBio (Brazil)
Principal Microbiologist	Defence Science and Technology Laboratory
Bioeconomy Team	Department for Business, Energy and Industrial Strategy
GM Team	Department for Environment, Food and Rural Affairs
Co-founder	E3G
Council Chair	Engineering Biology Leadership Council
Various	Environmental Protection Agency (US)
Chief Executive Officer	Evonetix
Various	Food and Drug Administration (US)
Various	Food Standards Agency (UK)
Campaigner	Friends of the Earth
Chief Scientific Officer	Genus PLC
Director	GM Freeze
Various	Government Office for Science
Policy Advisor	Green Alliance
Various	Health Canada (Canada)

Microbiology and biotechnology policy team	Health and Safety Executive
Director	Holt Regulatory Solutions Ltd
Various	Home Office
Head of Structural and Synthetic Biology	Imperial College London
Head of Business Development and Strategy	KWS UK Ltd
Various	Ministerio de Agricultura (Argentina)
Various	Ministry of Environment (Japan)
Chief Science and Regulatory Affairs Adviser	National Farmers Union
Chief Executive Officer	National Institute of Agricultural Botany
Various	Norwegian Biotechnology Advisory Board Norway)
Various	Norwegian Environment Agency (Norway)
Assistant Director	Nuffield Council on Bioethics
Various	Office for Life Sciences
Co-founder	Phytoform Labs
Special Advisor	Re-Imagine Europa
Interim Director	Roslin Institute
Various	Rothamsted Research
Senior Policy Advisor	The Royal Society
Senior Science Policy Advisor	Royal Society of Biology
Group Leader	The Sainsbury Laboratory
General Manager	SESVanderHalve
Director	Synthetic Biology Research Centre, University of Nottingham

VP of Technology	Tropic Biosciences
Various	UK Research and Innovation
Accreditation Director	United Kingdom Accreditation Service
Various	United States Department of Agriculture (US)
Reader at Science Policy Research Unit	University of Sussex
Personal Chair in Technology and International Development	Wageningen University

C. RHC Approach to the Genetic Technologies Report

How did the RHC arrive at genetic technologies as a Deep Dive Area?

The RHC conducted a rigorous horizon scanning exercise over a 6-week period and generated a list of 544 distinct innovations. Innovations were then mapped into broader groupings before being prioritised through three primary criteria: economic impact, societal benefits and scope for regulatory change. From this information and refined list, council members then applied their judgement and expertise to select their first tranche of priority areas to conduct deep dive reports into: fusion energy; genetic technologies; unmanned aircraft and medical devices.

The UK Government specifically commissioned the RHC to look into the future governance of genetic technologies and so this was an additional factor in its selection as a priority area.

How did the RHC identify and refine its scope and key question for the report?

The initial commissioning document referred to above, produced by relevant policy teams across Government, provided the initial scope for the RHC looking into this area. The RHC drafted and refined its question for genetic technologies by testing it with key stakeholders. The RHC then arrived at the overarching question of: 'How should the UK's governance of products based on genetic technologies for agriculture and food production, be adapted to support their translation to viable markets, with health, environmental and economic benefits for UK citizens?'.

How did the RHC engage genetic technology stakeholders?

Given that the RHC's genetic technologies deep dive was conducted during the COVID-19 pandemic, all the RHC's engagement was via email, Microsoft Teams, Zoom, or phone call. Whilst this virtual engagement provided certain challenges, it allowed the RHC to reach a wide range of stakeholders more quickly than via traditional in-person engagement.

The RHC's recommendations were based on an extensive programme of stakeholder engagement and evidence gathering. Over 8 months, we organised a series of workshops with over 100 representatives from industry, academia, policy makers and advocacy groups, interviewed a range of regulatory and legal experts and conducted international outreach with several countries that have recent experience of regulatory adaptation in this area. These activities provided a broad understanding of the range of innovative ideas being adopted on the regulation and governance of genetic technologies, which we summarise in our issues paper (see Annex A).

What could the RHC have done differently in retrospect?

As can be expected, more time and more resources would have allowed for increased stakeholder engagement and a more in-depth analysis. However, this approach was balanced against the importance of moving quickly in order to support early decision making about this emerging technology. The RHC's view is that this still allowed for a robust report that identified and provided advice on the crux of the matter in scope.

The compressed timescale of the project meant that invitees to workshops were given relatively short notice, and some were unable to attend. However, we were able to contact some stakeholders for individual interviews and to supplement these personal contacts with information from other publicly available sources.

One group that the RHC would have liked to engage more in retrospect would have been the venture capitalist community for their perspective on the key investment barriers and what reforms are most needed to provide greater regulatory certainty.

With a longer timescale and more resources we would also have to like to have undertaken:

- A more in-depth analysis of the regulatory systems of other countries, how they have operated in the past, and the ways in which they are currently being adapted to deal with genome editing.
- A more thorough background literature review, including particularly experiences to date with GM technologies and expected benefits and risks of new genetic technologies.
- Economic or life cycle analyses of the expected contributions of new genetic technologies to government policies related to climate change and the circular economy.

What Worked Well in the Approach

It was critical to understand quickly what value the RHC could add to the issue of governance of genetic technologies, particularly given the relatively tight time constraints of the work (circa 8 months).

The RHC worked closely with the policy team for genetic technologies which allowed the RHC to consider where it could add value, how it could make its recommendations land, and how they would fit into other reform timelines and considerations.

The RHC's wide engagement with a broad cross-section of relevant stakeholder communities meant we assembled a comprehensive evidence base for our recommendations. Our focus on including SMEs and emerging specialised applications

meant we were able to reflect a more forward-looking view of how regulation should be reformed to enable innovation and the emergence of radically innovative technologies. Our international outreach with regulators from countries with recent adaptation or novel approaches to their governance of genetic technologies added lots of valuable practical lessons for how to design regulatory adaptation in the UK. We were particularly grateful for how open the officials we spoke with were about the strengths and limitations of their respective regulatory frameworks.

Finally, the RHC report was well timed given recent technological advancements in the field and DEFRA's public consultation on the regulation of genetic technologies and the upcoming Government response. Responding to the DEFRA consultation was a key interim output for the RHC and helped formulate our thoughts and findings in more detail in preparation for our final report.