ABPI Response to Nuffield Council on Bioethics Call for Evidence: Genome Editing

Summary

- The Association of the British Pharmaceutical Industry (ABPI) represents innovative research-based biopharmaceutical companies, large, medium and small, leading an exciting new era of biosciences in the UK. Our industry, a major contributor to the economy of the UK, brings life-saving and life-enhancing medicines to patients. Our members supply 90 per cent of all medicines used by the NHS, and are researching and developing over two-thirds of the current medicines pipeline, ensuring that the UK remains at the forefront of helping patients prevent and overcome diseases.

- Our industry is committed to engaging with patients and broader society as they develop medicines for the benefit of patients. We welcome the Nuffield Council's work on genome editing technologies, and value the opportunity to contribute to this important discussion.

- Genome editing has the potential to bring significant health benefits to patients, particularly where there is current unmet medical need.

- In the biopharmaceutical industry, genome editing may be used either as a research tool or applied directly in a clinical setting. It is important to delineate between these applications as they have distinct considerations and implications.

- For use as a research tool, genome editing techniques do not differ significantly from previous genome modification tools, other than in speed and accuracy. They should be considered and evaluated within the robust UK research governance and legislative landscape.

- Where genome editing technologies may be applied clinically (in the context of somatic cells), the risk: benefit ratio should be evaluated on a case by case basis by medicines regulators, as for all new medicines.

- Our industry is committed to engaging with patients and society to explain and discuss the benefits and limitations of the medicines they develop.

Response

1.1 The Association of the British Pharmaceutical Industry (ABPI) represents innovative research-based biopharmaceutical companies, large, medium and small, leading an exciting new era of biosciences in the UK. Our industry, a major contributor to the economy of the UK, brings life-saving and life-enhancing medicines to patients. Our members supply 90 per cent of all medicines used by

the NHS, and are researching and developing over two-thirds of the current medicines pipeline, ensuring that the UK remains at the forefront of helping patients prevent and overcome diseases.

Perspectives on genome modification

Is there anything special about the genome that makes intervening in it different from other ways of manipulating nature (e.g. selective breeding of plants or animals)? To what extent can the development of genome editing techniques be regarded as distinct from or continuous with existing techniques? In what way are the differences significant?

2.1 Genome editing has the potential to be used in the biopharmaceutical industry to bring significant health benefits to patients, particularly where there is current unmet medical need.

2.2 It is important to distinguish clearly the context in which genome editing may be used. Particularly in the biopharmaceutical industry, it may be used either as a research tool, to improve and accelerate our understanding of disease and the development of novel medicines, or applied directly in a clinical setting. It is important to delineate between these applications as they have distinct considerations and implications.

2.3 Research use: The biopharmaceutical industry has used genetic modification techniques for many years in the research and development of new medicines, primarily to generate genetically modified cell lines and animal models, either for basic research e.g. into disease models and underlying pathology, or to evaluate potential new medicines. Recently, genome editing techniques have been taken up by a number of biopharmaceutical companies to facilitate this research. When used in this context, genome editing techniques may not be significantly distinct from existing genetic modification techniques other than in cost, speed, and accuracy, although their use has often necessitated the acquisition of new skills, and sometimes the development of new research groups, for many companies.

2.4 Clinical use: Some members of the biopharmaceutical industry are interested in using genome editing techniques in a clinical context. In recent years, the potential for advanced therapies, including gene and cell therapies, has begun to be realised, with four advanced therapy medicinal products (ATMPs) currently approved in the EU, and many more in development. To date no approved products use genome editing techniques, but there is potential for them to be used in many contexts including in somatic gene therapy, or to modify cell therapy products *ex vivo* such as CAR-T cells. Such products are already under development in the biopharmaceutical sector and there are examples of such techniques being used in a clinical setting for the individual treatment of patients[1]. Many of the considerations of clinical uses of genome editing, including of safety, regulation, and ethics, can build upon and be informed by the considerations applied to previous gene therapy strategies. In some ways though the use of genome editing techniques in a clinical context may be a step change for several reasons. Firstly, it is likely to facilitate the development of ATMPs, leading to a rapid increase in these therapies, which currently represent a very small proportion of total available therapies. This will have associated challenges, including the need for development of regulatory expertise, training and education of clinical staff, and development of appropriate clinical pathways. Additionally, genome editing techniques open the possibility of

[1] For example the use of gene edited T-cells to treat a paediatric patient at Great Ormond Street Hospital last year, http://www.gosh.nhs.uk/news/press-releases/2015-press-release-archive/world-first-use-gene-edited-immune-cells-treat-incurable-leukaemia

germline editing for heritable diseases, which is a significant step change from currently available therapy options, and has a number of unique safety and ethical challenges.

What obligations do scientists involved in developing and using genome editing technologies owe to society and what freedoms should society allow to these scientists? Do genome scientists have any special obligations to society that are distinct from those of other scientists?

3.1 Clinical use: The pharmaceutical industry is committed to developing and delivering new medicines for the benefit of patients. The industry therefore has responsibilities to ensure that patients can access information on the possible effects of their medicines and therapies, both positive and negative. The need for involvement of patients in the whole of the R&D process has also been increasingly recognised and this is important for a number of reasons including that of ensuring industry develops medicines which meet their needs. Such patient engagement will be particularly important in the development of genome editing technologies for clinical use, where patients may have particular concerns, questions, or distinct perspectives that sit apart from scientific considerations.

3.2 Research use: Whilst the protection of commercially sensitive and confidential information is key, the pharmaceutical industry is committed to greater transparency on the processes of research and development of new medicines where possible, and to engaging with the public on controversial research issues. This is demonstrated for example in the industry's commitment to the Concordat on the Openness on Animal Research[2], where ABPI and a number of our member companies have committed to greater public engagement on the use of animals in research, a controversial research issue. If genome editing were to similarly become an issue of public interest, it would be important for the industry to engage with the public to explain how and why these techniques are being used for the development of new medicines, and the benefits as well as limitations of this science.

To what extent is the development of genome editing valuable as a pure research tool, and to what extent is its value dependent on envisaged practical applications?

4.1 As outlined above, genome editing technology is envisaged in the pharmaceutical industry to play a role both as a research tool and in future clinical applications. Many companies are already, or are looking to begin, using genome editing technologies as a research tool to generate cell or animal models for the research and development of new. However, some companies are also interested in using genome editing technologies in a clinical context, for example in gene therapy or genome edited cell therapies.

What obligations do governments have towards society to ensure 'safe' science or otherwise to shape the scientific research and development?

5.1 It is important that the governance of scientific research is robust and transparent, but also flexible and agile to respond to developing scientific fields. The UK has a robust regulatory system governing many aspects of scientific research, and we are confident the UK will be able to lead on the effective governance of genome editing technologies.

5.2 Where genome editing techniques are developed for use in a clinical context, medicines regulators (the Medicines & Healthcare products Regulatory Agency (MHRA) for the UK, or European Medicines Agency (EMA) for the EU) will play a key role in assessing the benefit: risk balance of new

[2] Concordat on Openness on Animal Research 2014, http://www.understandinganimalresearch.org.uk/policy/concordat-openness-animal-research/

therapies for patients, including evaluating safety, as for all new medicines. All ATMPs (where genome editing technologies are most likely to be used) are assessed centrally in the EU by the EMA's Committee for Advanced Therapies. This is a specialist committee which ensures that members have the expertise necessary to evaluate these specialist therapies. The MHRA will also play an important role locally in ensuring therapies are developed and manufactured under conditions meeting appropriate standards; for example Good Laboratory and Manufacturing Practice must be applied to the development and production of all medicines, including ATMPs.

Genome Editing in Animals

Current research
What is the current state of the art in the field? What are the current technical limitations and constraints/ bottlenecks? What are the main directions of travel? What are the envisaged endpoints/ applications? What is the rate of travel? What are the expected timescales for realising the envisaged endpoints? Are gene drives an area of particular interest or concern and, if so, why?

6.1 Some members of the pharmaceutical industry may use genome editing technologies to generate genetically modified animal lines, particularly to create novel disease models. These animal lines would be used primarily for basic research into disease pathology, and to test potential new medicines. These techniques are already being developed and used for such applications in some biopharmaceutical companies.

Conditions of research and innovation
What are the main 'drivers' and 'obstacles' for genome editing in relation to envisaged endpoints? What is (and what should be) the current level and focus of public debate?

Impacts
What overall impact might genome editing have on animal lives? Can genome editing be expected to contribute to or inhibit the replacement, reduction or refinement (the '3Rs') of the use of animals in research? Does genome editing give rise to special moral considerations about generating artificially modified animals for research (including disease models in large or highly sentient animals) or for trivial/ commercial reasons (e.g. 'toy' pigs)?

7.1 We anticipate genome editing technologies contributing to the reduction and refinement of the use of animals in research. The use of such technologies can reduce the number of animals required to generate novel animal models, and may have less potential to cause pain, suffering, distress, or lasting harm than traditional genetic modification techniques. There is the potential that the technical developments which have made genome editing significantly easier and cheaper may lead to an increase in the number of new animal lines developed. However, traditional genetic modification techniques are already widely applied throughout the bioscience sector, including the pharmaceutical industry, so we do not think this increase will be significant.

7.2 Similarly, since traditional genetic modification techniques are already widely applied to generate animal models of disease in a range of species, we do not feel that genome editing should raise special moral considerations outside those addressed by the current harm: benefit assessments applied by the Home Office in their regulation of the use of animals in research.

Genome Editing in Microorganisms

Current research
What is the current state of the art in the field? What are the current technical limitations and constraints/ bottlenecks? What are the main directions of travel? What are the envisaged endpoints/

applications? What is the rate of travel? What are the expected timescales for realising the envisaged endpoints?

8.1 There is the potential for the industry to apply genome editing techniques to microorganisms with a therapeutic application, for example to target drug resistant infections, or other bacterial or viral infections.

Conditions of research and innovation
What are the main commercial applications of genome editing in microorganisms and what are the main economic drivers of development?

8.2 For the potential application outlined above, applying genome editing techniques to prevent or treat bacterial or viral infections, commercial drivers could exist for the pharmaceutical industry as for other therapeutic modalities.

Biomedical research and human applications

Current research
What is the current state of the art in the field? What are the current technical limitations and constraints/ bottlenecks? What are the main directions of travel? What are the envisaged endpoints/ applications? What is the rate of travel? What are the expected timescales for realising the envisaged endpoints?

9.1 As outlined above, many members of the biopharmaceutical industry will apply genome editing techniques to develop novel cell lines, and animal models, for research into disease pathology and to evaluate potential new medicines. Some companies may also look to apply genome editing technologies for clinical use, primarily as somatic gene therapy, or to edit somatic cells for cell therapy.

Conditions of research and innovation
What are the main 'drivers' and 'obstacles' in relation to envisaged endpoints? What bearing do international ethical debates and agreements (e.g. high level statements or calls for moratoria) have on the pace or organisation of research?

Who should lead and who should be involved in setting policy for research and human applications of genome editing? Is this significantly different from other kinds of experimental or reproductive medicine?

10.1 As outlined above, where genome editing technologies may be applied in a clinical context, medicines regulators will play a key role in evaluating the benefit: risk ratio of new therapies. All ATMPs (where genome editing technologies are most likely to be applied) are assessed centrally in the EU by the EMA's Committee for Advanced Therapies. This is a specialist committee which already has experience evaluating gene therapies, and we envisage they would regulate the clinical use of gene editing technologies in a similar way. The MHRA will also play an important role locally in ensuring therapies are developed and manufactured to appropriate standards.

10.2 Other government departments have important roles for specialised policy and research areas, including Department for Environment Food & Rural Affairs (Defra), Home Office, Human Fertilisation and Embryology Authority (HFEA) and Human Tissue Authority (HTA). This robust UK governance framework has successfully facilitated the advancement of science and medicine for the benefits of patients within an appropriate regulatory framework, in many areas of scientific

research, and is well placed to build on previous work to oversee the development and use of genome editing technologies.

10.3 However, understanding and navigating the complex regulatory landscape can be a challenge for pharmaceutical companies. The MHRA Innovation Office one-stop shop for regenerative medicine, which brings together the MHRA, HTA, HFEA, and (Health Research Authority) HRA to provide advice and clarification, is a useful approach. As genome editing techniques develop further, a similar approach to bring together different agencies to lead the development of policy on this topic may be useful.

Impacts

Have advances in genome editing affected what research is funded, what research strategies are used (e.g. derivation of stem cells) or the comparative development of therapeutic strategies?

What are the significant decisions that need to be taken before therapeutic use of genome editing may be contemplated (for non-heritable and heritable genetic changes) and who should have the responsibility for those decisions?

Are the benefits and costs of treatments that involve genome editing likely to be distributed equitably (or any more or less equitably than existing or alternative treatments)? In what way might genome editing differentially affect the interests of people in vulnerable or marginalised groups?

11.1 If patients are to eventually access genome editing technologies, as for many other types of ATMP or regenerative medicines, it will be important to ensure that mechanisms are developed to establish appropriate commercial arrangements, assess value for money and ultimately commission and prescribe in a way that is fit for purpose. Genome editing, for example, may require the NHS to expand the use of multi-year contracts or other commercial arrangements that take account of the fact that cost of the (one shot) treatment may need to be spread over time. HTA methods and processes need to be adapted to cope with such new technologies and NICE is currently conducting mock technology appraisals for ATMPs, which may inform this process going forward.

11.2 If applied clinically, the specialised nature of genomic editing technologies, and associated gene or cell therapies, means that such therapies are likely to be available only at highly specialised centres. This will necessarily increase travel for patients to treatment centres, which may differentially affect certain groups of patients.