Genome editing

EU-IN Horizon Scanning Report

15 February 2021
EMA/319248/2020

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1. Introduction

Genome editing is perhaps the best example of a new biomedical technology and treatment paradigm progressing at speed. It has the potential to treat an increasing range of diseases including some with no available therapies. Given its ability to permanently alter the target human genome, it can have long-lasting or curative disease effects, instead of the multi-drug treatment or chronic dosing regimens often seen with other therapies. This potential is first being realised in monogenetic diseases, but research in other, prevalent disorders is emerging such as the introduction of protective mutations to treat cardiovascular diseases, HIV, Alzheimer's disease and haemoglobinopathies, or removal of mutations associated with cancer, obesity, hyperlipidaemia, diabetes and atherosclerosis. An accelerator of this innovation is the exploration of genome editing in several industries such as agriculture and medicine.

Such innovative products come with new challenges to develop, manufacture, evaluate and ultimately make them available to patients. These have been detailed in academic overview publications,[1,2,3,4,5] and during the EMA expert meeting in 2017,[6] and are discussed below.

This horizon scanning report will explore the challenges and opportunities of genome editing from a regulatory perspective. It will focus on *ex* and *in vivo* genome editing as a medicinal product for treating human patients, and how it may change over the coming 10 years. It does not cover other uses of genome editing that play an increasing role in discovery and translation e.g., to investigate genomic steps in ontogeny and pathophysiology, to identify potential molecular targets for medicinal products, for diagnosis, in epigenome editing or microbial gene engineering,[7] for veterinary use or in agriculture.[8,9] Established technologies such as viral transfection and transduction are not included in this horizon scanning report.

2. Current status and key emerging trends

There is a growing pipeline of products and technologies fuelled by the advancements in genome editing methods and associated technologies, such as the exponential advances in sequencing technology to uncover many of underlying genetic basis of disease. This has moved a bottleneck in medicines development from basic research and target finding to choosing how and which target to develop.

Despite this recent growth in the pipeline, much of the basic science it is built upon has been accruing for decades, with restriction enzymes to cut DNA discovered in the 1960's. Over the last 20 years, however, the development of new approaches, from homologous recombination onto the use of meganucleases, has made editing of the genome less expensive, more precise and efficient compared to previous tools. Recent and promising tools include zinc finger nucleases (ZFN), transcription

[1] https://www.nature.com/articles/d41573-020-00096-y (May 2020) (Gene-editing pipeline takes off)
[2] https://www.nature.com/articles/s41392-019-0089-y (Jan 2020) (Applications of genome editing technology in the targeted therapy of human diseases: mechanisms, advances and prospects)
[3] https://www.nature.com/articles/s41587-020-0561-9 (June 2020) (Genome editing with CRISPR–Cas nucleases, base editors, transposases and prime editors)
[4] https://www.spandidos-publications.com/10.3892/ijmm.2020.4609 (Advance genome editing technologies in the treatment of human diseases: CRISPR therapy)
[5] For publications giving an overview on genome editing in applied medicine see, for example: https://www.nuffieldbioethics.org/publications/genome-editing-an-ethical-review, https://www.nuffieldbioethics.org/blog/a-genome-editing-month
[6] https://www.ema.europa.eu/en/events/expert-meeting-genome-editing-technologies-used-medicine-development
[7] https://www.sciencedirect.com/science/article/abs/pii/S0167779920301748
[8] https://www.frontiersin.org/articles/10.3389/fpls.2019.00525/full, https://bmcplantbiol.biomedcentral.com/articles/10.1186/s12870-020-02385-5
[9] E.g. https://www.digitaltrends.com/cool-tech/8-example-crispr-projects-changing-world/

activator-like effector nucleases (TALENs), clustered regularly interspaced short palindromic repeats (CRISPR) and CRISPR associated proteins (Cas), prime editing and peptide nucleic acids. The clinical applications of these genome editing tools are intended to repair, modulate, replace or add gene(s) to achieve a desired phenotype. These tools compete for some applications since each have their pros and cons and they are constantly being modified and improved. To date, these genome editing tools and the resulting products have mainly originated in academic spin-offs and SMEs; however, big pharma has become increasingly engaged.

With the growth in this novel and promising technology, it is important to foster early dialogue to address its challenges upfront. This dialogue needs to happen between developers, such as academic hubs and pharmaceutical companies; patients and consumers; healthcare professionals; and regulatory authorities in the EU network, including GMP supervisory authorities. This will facilitate its progress from clinical development to marketing authorisation assessment and onto patient access at an EU and international level.

The current genome editing technologies available include:

- Meganucleases, which are a class of genome editing tools that are highly specific to their target and that recognise comparatively large sections of DNA and cut a double stranded break. However, each nuclease has to be custom designed to cut each target, which is costly, and so their uptake has been limited.
- In contrast to meganucleases, other nucleases such as zinc finger nucleases (ZFN) and TALENs (transcription activator-like effector nuclease) use a non-specific DNA cutting catalytic domain, in combination with a customised targeting domain. For ZFN, when both fingers co-locate to the targeted sequence, they cause a double stranded cut which can be repaired via error-prone non-homologous end joining (NHEJ), or via homologous recombination with a repair template: homology-directed repair (HDR). However, this targeting is not perfect and off-target double stranded breaks in other regions of chromosomes are often introduced. With TALENs, this approach is made more efficient with a more specific targeting mechanism and therefore fewer off-target effects.
- Another nuclease, CRISPR-Cas9 has enjoyed global recognition due to the ease with which it can be produced; its recognition of specific sections of DNA requires a custom guide RNA, rather than the more complicated custom protein required of ZFN and TALEN. It then cuts a double stranded break using a Cas protein. CRISPR/Cas is being investigated for use across several disease areas: AIDS, neurodegenerative disorders, hereditary eye diseases, DMD, haemophilia, ASD, ALS and SCD, amongst others.
- Prime editing consists of a prime editing guide RNA (gRNA, which includes a reverse transcriptase template) and a prime editor (Cas9n, a mutant that only nicks and cuts a single strand of DNA, thus does not induce double-strand breaks). After multiple steps via an intermediate heteroduplex DNA this results in the desired edits in both DNA strands. Prime editing is useful for inducing single base changes (base-editing), small insertions and deletions. Since prime editing uses the CRISPR/Cas in addition to reverse transcriptase, it promises greater specificity, reducing on and off-target effects through the requirement of two additional nucleic acid matching steps. It also promises greater targeting flexibility due to its ability to edit further away from the CAS9 nicking site. However, it is limited in the size of the base pairs it can edit, and the error rate of reverse transcriptase is currently unclear.[10] Like other genome

[10] https://www.nature.com/articles/d41586-019-03164-5

editing tools, it also shows cell-line and cell-state dependent efficiency, likely due to differing expression of DNA repair proteins and prime editing components.

- Peptide nucleic acids (PNAs) are synthetic DNA analogues, one of several alternative nucleic acid structures that can adopt diverse three-dimensional formations. PNAs invade the double helix to form high-affinity base-pairs with DNA and this recruits endogenous DNA repair mechanisms which reads desired edits from a ssDNA template.

2.1. New products/methods under development

Further details on products, developments and regulatory interactions are in the Annexes.

As of mid-2020, no medicinal product is authorised (in the EU or in the U.S.) that employs genome editing *ex vivo* or *in vivo*. World-wide, there are currently 65+ companies developing therapies using genome editing technologies, including 15+ with clinical stage compounds, and 32 ongoing genome editing clinical trials.[11] These are intended to treat cancers, endocrine and metabolic disorders, bleeding disorders, HIV, and certain forms of inherited blindness. Many of these trials use TALEN or ZFN technology, but there are an increasing number using CRISPR technology. The volume of products and indications is expected to increase as developers cycle through new genome editing methods.

Human *in vivo* genome editing[12] was first reported in 2017, when in the U.S. a man received an AAV delivered ZFN to treat an inborn error of metabolism (Hunter syndrome).[13] In 2020, *in vivo* CRISPR (AGN-151587) delivered by AAV injected into the eyes was used to treat blindness (Leber congenital amaurosis) in a clinical trial in the U.S.[14] This trial is ongoing.

As of March 2021, no clinical trials of *in vivo* genome editing are known to be underway in the EU but a few trials[15] using *ex vivo* genome editing, to modify autologous cells, are reported in the EU Clinical Trials Register (information on phase 1 clinical trials in adults is not publicly available in this register).

A small number of paediatric (investigation) development plans were received by the EMA and discussed mostly for clinical development issues, including a product manufactured from several genome editing events or including a self-destruct switch.[16]

Orphan designations have been granted for genome editing products such as for treatment of mucopolysaccharidosis (Hunter's Syndrome), beta-thalassaemia intermedia and major, and sickle cell disease[17].

The EMA's Innovation Task Force has seen some early-stage products using genome editing;

Since 2019, EMA scientific advice have worked on several requests for ATMPs involving gene editing, including CRISPR/Cas9 products for *in vivo* use. An *ex vivo* genome editing product has recently received PRIME designation for treatment of severe sickle cell disease (CTX001).[18] This edits the erythroid enhancer region of the BCL11A gene in autologous CD34+ haematopoietic stem cells with CRISPR-Cas9.

[11] Alliance for Regenerative Medicine, in https://www.mednous.com/gene-edited-therapies-produce-first-clinical-data
[12] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6163904/
[13] https://www.nature.com/articles/s41392-019-0089-y#Sec28
[14] https://clinicaltrials.gov/ct2/show/NCT03872479
[15] E.g., https://www.clinicaltrialsregister.eu/ctr-search/trial/2018-003916-38/DE, https://www.clinicaltrialsregister.eu/ctr-search/trial/2018-001320-19/BE
[16] https://www.ema.europa.eu/en/medicines/human/paediatric-investigation-plans/emea-001869-pip01-15-m02
[17] https://ec.europa.eu/health/documents/community-register/html/reg_od_act.htm?sort=a
[18] https://www.ema.europa.eu/en/human-regulatory/research-development/prime-priority-medicines

The EMA's Business Pipeline, which receives information on anticipated product marketing applications through to 2022, has no products using gene editing *ex* or *in vivo* (but some products are expected that use gene addition).

2.2. Key emerging trends

Over the next 3-10 years, genome editing (GE) tools will continue in their rapid evolution, as seen with the multiple modifications to the CRISPR/Cas approach. The tools should become more accurate, efficient and therefore safer, and this should lead to a larger and more viable pipeline, as the commercial barriers to the market reduce.

Equally, genome editing therapies to date have focussed on gene deletion or reactivation, in the future there will be more precise tools that allow for more complex applications such as multiple edits, whole gene introduction/deletion, and safety features such as suicide genes and reporter genes to track treated-cell fate. Another safety feature is self-inactivating GE tools, which limit the amount of time genome editing products are editing and thus reduce the number of off-target effects.[19,20] This is particularly promising for *in vivo* applications. These may evolve from fusion genome editors constructed from different natural systems. Increasing genomic knowledge could see the editing of non-coding regions of the human genome, RNA editing or epigenome modifications. Technological advance is also allowing treatments to move to human *in vivo* application, at least in self-contained sites and those which pose lower systemic risks such as the eye, certain solid tumours or the liver.[21]

These advances may also permit genome editing for very rare diseases, where there are hundreds of mutations underlying a phenotype. Validated *in vitro* testing and diagnostics could be used to approve expanded indications of well characterised genome editing medicines across a range of mutations, which could not all be tested in clinical trials. This would be possible if the disease and medicine is well understood, and the benefit/risk (B/R) well established, as illustrated by the case of CTFR mutations.[22] It could also be possible that genome editing becomes patient specific, and multiple genome edits are made, possibly using different genome editors within one medicinal product. Corrective *in vivo* somatic gene editing of predispositions have been discussed in the literature ("prophylactic gene editing") and piloted in non-clinical studies, e.g. for cancers related to BRCA mutations;[23] if feasible, this approach might reduce the burden of disease and of conventional measures such as prophylactic mastectomy, ovarectomy and life-long imaging / endoscopy of other cancer predisposed tissues.

It is unclear if the speed of evolution in genome editing will outpace its inclusion in products themselves, since product development takes longer than improving GE tools. This may generate expectations from patients, clinicians, developers or regulators for pathways to exchange or update GE tools during development and/or to shorten development activities that normally take a long time. This dilemma is not limited to GE but during this phase of rapid innovation, it may be more prominent.

As genome editing technologies continue to innovate, it is important that regulators not only stay abreast of these developments, but steer research to better understand the underlying biology and towards applications which are acceptable to regulators and public health. This will involve better understanding of off/on-target effects and therefore advancing unbiased batteries and the use of in silico tools, as well as the risk of integration of the vector and also of the gene editor (e.g. Cas9, ZFN) into the genome.

[19] https://doi.org/10.1038/ncomms15334
[20] https://doi.org/10.1016/j.ymthe.2019.09.006
[21] https://doi.org/10.1042/BSR20200127
[22] https://www.fda.gov/media/130482/download#page=23
[23] https://doi.org/10.1073/pnas.1904697116

Regulators will also require better understanding of how novel methods will affect immunogenicity, dosing, long-term clinical efficacy and safety and whether repeat administration is beneficial.

Regulators should also keep an eye on any unregulated sale of such therapies due to high prices and patient demand, as has happened with stem cells.

High asking prices for genome editing-based therapies should incentivise developers to seek early collaboration with HTA bodies and payers to define reimbursement models, and regulators should flag such products to HTA bodies and payers at an early stage.

Moreover, since novel genome editing tools and techniques may first be explored in other sectors such as agriculture, it will be helpful to consider interactions across sectors.

Ethical issues will also need addressing, in particular for human heritable/germline editing, any potential use for functional enhancement of people and unconventional trial designs acceptable for different stakeholders and the equipoise principle.

3. Challenges, opportunities and considerations from a regulatory perspective

Quality / CMC issues

Genome editing is a comparatively new field and currently, guidance and quality requirements published by regulators for gene therapy and gene editing medicinal products follow a risk-based approach, at a sufficiently high level to allow for flexibility while maintaining stringent manufacture and control standards.[24]

Furthermore, as manufacturing and genome editing technologies will be evolving, demonstration of comparability will require careful consideration. In certain scenarios, it may not be appropriate to rely solely on the results of quality comparability studies and additional non-clinical/clinical data may also be required. Additionally, due to the personalised nature of certain genome editing therapies, regulatory batch testing and release requirements can consume a significant proportion of the batch which has implications for release testing strategies. Batch release testing requirements have been raised as an area of high regulatory burden for products with small batch sizes. In response, efforts towards international harmonisation on batch testing are being explored. Finally, the generation of on- and off-target modifications should be considered as part of process development and characterisation.

Delivery systems

The delivery systems of genome editing are varied, from electroporation, plasmids and viral vectors to nano vesicles such as exosomes. These vary in their efficacy in different *in vitro/ex vivo* settings and in their ability to target cells *in vivo*.[25] The biodistribution of their application *in vivo* will also require studying.

Non-clinical

Efficacy

Particular challenges exist with non-clinical efficacy models to predict clinical effects in humans of genome editing treatments, due to the importance of the *in vivo* cellular environment on genome

[24] https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-quality-non-clinical-clinical-aspects-medicinal-products-containing-genetically-modified_en-0.pdf
[25] https://doi.org/10.1039/C8NR07321J, https://dx.doi.org/10.1042%2FBSR20200127, https://doi.org/10.1038/s41565-019-0539-2, https://doi.org/10.1039/c7nr07999k

editing efficiency, for example. While there is a notion that genome editing treatments may not require or may not have relevant non-clinical efficacy models, this would be a premature conclusion and in regulatory interactions, thorough investigation and attempts to develop such relevant non-clinical efficacy models should be discussed in any case and requested on a case by case basis.

Resistance

Genome editing faces biological resistance, either immunological or through selection of cells which have a resistant target region. Some suggest that genome editing treatments should target multiple, conserved and functionally important sites on genomes[26] and use multiple genome editing events[27] to prevent the development of resistance. This would come at the cost of multiplying genome editing effects and associated risks but new technologies and further GE improvements, could eventually overcome these hurdles.

On-/Off-target effects

With respect to safety and toxicity, the non-clinical challenge is to comprehensively identify on and off target toxicities following genome editing. Off-target effects depend on the quality of the genome editing tool, its delivery system, the DNA target, the cell type and differentiation stage, the chromatin structure and duration of the nuclease exposure, as well as the route of administration e.g. *in vivo* or *ex vivo*. The effects of editing off-target include errors resulting in single nucleotide point mutations, insertions, deletions and chromosomal translocations, which can have a varying degree of pathogenic significance.

Even when the genome editing occurs on-target, it can lead to single nucleotide errors, adding surplus DNA or "scarring" of the genome.[28] In addition to the on-target mistakes of the DNA repair systems, particularly through error prone Non-homologous end joining (NHEJ), CRISPR-CAS9 has caused deletions and genetic alterations near the cut site, posing risks of near-target pathogenic effects.[29] These can be substantial rearrangements or deletions stretching for thousands of base pairs.[30]

Sensitive and unbiased methods to understand on/off-target effects are available and were discussed to some extent during the 2017 workshop. These include *in vivo*, *in vitro* and *in silico* methods. These can be biased approaches, which take what is known about the genome editing product to assess on/off-target effects, and independent or 'unbiased' approaches, which are agnostic to the genome editing product and comprehensively cover the DNA (or other molecular targets). Amongst these unbiased methods, GUIDE-seq and CIRCLE-seq have emerged as two complementary and sensitive methods for defining engineered nuclease activity.[31,32] *In silico* models, on the other hand, predict the effects of a genome editing tool using by inputting a variety of factors.

Future *in silico* models will need to be built that integrate the current heterogeneous *in vivo*/*in vitro* genome editing data to reduce bias.[33] Each of the above measurement approaches has its limitations in terms of sensitivity, specificity and efficiency. Therefore, methods to detect off-target effects should report their sensitivity, specificity, stability, analysis, and clinical significance of the results. It is also recommended that genome editing products conduct a range of methods to map on/off-target effects, and the extent of this mapping should scale with the risk of the product.

[26] https://pubs.acs.org/doi/10.1021/acsinfecdis.7b00273
[27] https://www.sciencedirect.com/science/article/pii/S0952791518300815
[28] https://febs.onlinelibrary.wiley.com/doi/10.1111/febs.14626
[29] https://doi.org/10.1038/nbt.4192
[30] https://www.nature.com/articles/d41586-020-01906-4
[31] https://doi.org/10.3390/cells9071608
[32] https://doi.org/10.1016/j.jgg.2019.11.002
[33] https://doi.org/10.1016/j.tibtech.2016.06.008

These empirical methods can guide the choice of genome editing target, nuclease, and formulation. Assessing the unintended on and off-target genome modifications is crucial to minimize the risks associated with therapeutic genome editing. However, no general conclusion can be drawn about the specificity of engineered nucleases: each therapeutic candidate has to be evaluated individually by an appropriate range of validated safety assays. Despite a variety of these methods being available, we remain far from comprehensively measuring and understanding off-target effects, especially in genetic regions whose functions are unknown.

The comprehensive measurement and modelling of off-target effects should go further and include measurement of the heterogeneity of off-target effects between cells, their secondary impact on intracellular and inter-cell functioning, such as DNA structural change, RNA expression and cell signalling. It should also evaluate the possibility of editing non-target cells, particularly germ-line cells. Even if it is not possible to characterise the impact of all off-target effects, knowing their quantity and distribution helps estimate their importance.

There is room for regulators to do more to foster the standardisation of off-target (and on-target) effect measurement, including appropriate method and method batteries, sample handling, procedures, quality control, data analysis, and clinical interpretation.[34] Currently, the EU guidelines on quality, non-clinical and clinical requirements for genetically modified cells do not specify methodologies for measuring on/off-target effects, as these are rapidly evolving[35]. Similarly, guidance issued by the FDA (see section 4.2.) does not specify methods for long-term follow-up of off-target effects noted in pre-clinical studies.

There is important potential for progress in non-clinical methods to mitigate risks associated with use in patients, such as by modelling the most suitable gene editor and its delivery method, and optimising the time during which a genome editor is active.

Clinical

The clinical opportunities for genome editing products are manifold and substantial. However, there are important safety considerations. These include those from the effects of the genome editing itself and from the delivery system for the genome editing tool.[36] Some risks may be mitigated in a variety of ways (see preceding section), but still require systematic long-term clinical safety assessment, as well as provisions for molecular interrogation of any unexpected adverse events.[36] The documentation of these products' safety typically continues from trials through registries that track patients; however, the implementation of such registries can still improve with further investment and collaborative approaches that involve stakeholders.

Regulatory issues

Regarding regulatory classification and handling of genome editing products, there are some areas of uncertainty.

Some genome editing products are subject to GMO regulation and requirements (Directive 2001/18/EC on the deliberate release into the environment of GMOs; Directive 2009/41/EC on the contained use of genetically modified micro-organisms). In most EU member states, different competent authorities evaluate an ATMP GMO submission and a Clinical Trial Application (CTA) submission. This leads to potential submission mismatch in terms of timings and content/requirements. For GMO designation and Environmental Risk Assessment, there are ongoing efforts by EU member states and

[34] https://doi.org/10.1007/s10565-019-09475-7, https://doi.org/10.1016/j.tibtech.2014.12.001
[35] https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-quality-non-clinical-clinical-aspects-medicinal-products-containing-genetically-modified_en-0.pdf
[36] https://doi.org/10.1016/j.ymthe.2020.03.015

the European Commission for GMO harmonisation and to better clarify and harmonise requirements, including common application forms and good practice documents (Advanced therapies – GMO requirements for investigational products).[37] However, there is concern that these are not yet used systematically at the member state level and thus more efforts should be undertaken across member states and directives.

The majority of *ex vivo* genome editing medicinal products will fulfil the ATMP definition as GTMP or cell therapies; all *in vivo* approaches will be medicinal products, including some being GTMPs, some being biologicals and some that could be considered as small molecules.[38] The situation in the US is slightly more straightforward: all genome editing products (*in vivo* and *ex vivo*) are considered by FDA as gene therapy products.

In view of their long-lasting or potentially curative effects, genome editing products may also present challenges with respect to maintaining orphan designation and demonstrating significant benefit: clinical efficacy data to show superiority may not be obtainable for scientific reasons, with clinical safety or even only non-clinical data as primary support of a significant benefit claim.

Ethical issues

Genome editing is only in the foothills of its ethical implications, having mainly been used *ex vivo* on somatic cells with a clear human disease phenotype. Future applications will require novel trial designs with ethical implications for different stakeholders and the equipoise principle, for example the type of treatment that would be acceptable in a trial as a comparator for a genome editing product.

Since the birth of twins genetically altered using CRISPR/Cas9 was revealed in 2019 in China, the international community has sought a moratorium on heritable genome editing (HGE) whilst a series of expert groups are convened to develop international governance frameworks. However, best practices of inclusive multi-stakeholder decision-making are established[39] and should be followed. Therefore, regulators should ensure stakeholder consultation informs any substantial advancement in the use of genome editing. This will help ensure legitimacy of decisions and of regulators themselves.

The European Group on Ethics in Science and New Technologies (EGE) is currently (mid 2020) developing an Opinion on the Ethical implications of Gene Editing, at the request of the European Commission. This follows an initial opinion dating from 2016.[40] In 2019, the EGE convened an Open round table on the topic, which covered somatic and germline editing as well as genome editing in plants and animals (where for non-human primates, international guidelines and standards are lacking). From their round table, a distinction was drawn between conditions described as 'devastating' and other conditions, where for devastating conditions a genome editing product should be used as soon as possible, and this may include germline (that is, heritable) genome editing.

Prior to this, the Council of Europe's Committee on Bioethics (DH-BIO) had issued a first Statement on Genome Editing Technologies in 2015, reflecting on the importance of article 13 of the Oviedo convention.[41] This position was reaffirmed in a press release in 2018, while DH-BIO currently works on germline editing, and there have been suggestions to amend article 13.[42]

[37] https://ec.europa.eu/health/human-use/advanced-therapies_en#1
[38] https://doi.org/10.1038/s41431-020-0607-y
[39] https://doi.org/10.1001/amajethics.2019.1065
[40] https://ec.europa.eu/info/sites/info/files/research_and_innovation/ege/gene_editing_ege_statement.pdf
[41] "An intervention seeking to modify the human genome may only be undertaken for preventive, diagnostic or therapeutic purposes and only if its aim is not to introduce any modification in the genome of any descendants." https://www.coe.int/en/web/conventions/full-list/-/conventions/rms/090000168007cf98
[42] https://www.coe.int/en/web/bioethics/-/ethics-and-human-rights-must-guide-any-use-of-genome-editing-technologies-in-human-beings

The discussions on editing germline cells will have to address when it is appropriate, how it can be conducted safely and what evidence would allow an intergenerational benefit/risk evaluation to be conducted.[43] The evidence will need to go beyond benefit/risk for regulators and into wider societal effects, such as inequalities, intergenerational protection and non-discrimination. Whilst this may be beyond the role of regulators, they can inform the debate.

Furthermore, regulators should stay wary of motivations beyond treating disease, such as individual enhancement. Here, learned medical societies have started to articulate their responsibility as a profession, stating that "genetic manipulation of nondisease traits or the eugenic development of offspring may never be justifiable".[44] A review of national and international laws and safeguards concerning non-medicinal product genome editing is beyond the scope of this report. To mitigate against misuse of genome editing tools, regulators should also consider the need to support anti-editing tools such as anti-CRISPR which can inhibit or reverse unwanted genome editing.[45]

4. Regulatory preparedness

4.1. EU regulatory initiatives

The EMA's Regulatory Science Strategy to 2025[46] and the European Medicines Regulatory Network (EMRN) Strategy to 2025[47] have set out a number of relevant recommendations to be delivered over the next five years and these are set out in the Annex.

The EU has funded research projects across genome editing technologies, in particular in the biomedical sector, but also others:

- There are about 200 EU projects in the CORDIS database containing "gene editing" in their description. These are diverse in size and scope, including in the medical therapeutic areas oncology, healthy aging, haematology, neurodevelopmental disorders (e.g., Down syndrome, project GenEdiDS) heritable diseases (muscular dystrophy, skin diseases, immunodeficiencies, ADA deficiency), cardiovascular, modelling ontogeny and pathogenesis and a "vaccine" to edit an oncogenic lung cancer mutation. Important technological improvements are also being developed, e.g. in target discovery, *in vivo* genome editing by nanotransducers (UPGRADE), inhibiting BAF to improve gene delivery (IBAF), CRISPR gene-editing enhancement by coiled-coil mediated exonuclease tethering technology, informatics, networking and epigenome editing. A small number of projects are also funded in agriculture, ecosystems and insects.
- IMI: no specific projects found

The EC's Pharmaceutical strategy concerns genome editing through its focus on innovative products that address the highest unmet medical needs such as personalised treatments of serious conditions.

Gene therapy developments within the EU could be an indicator of how far it is a frontrunner in health. Consequently, genome editing products could be seen as a test case for estimating the impact of legislative and non-legislative actions, as well as investments by the EU, and also as a measurement of the competences and capacity of the regulatory system.

[43] https://onlinelibrary.wiley.com/doi/abs/10.1002/hast.924, https://www.sciencedirect.com/science/article/pii/S1472648316305491
[44] https://doi.org/10.1001/amajethics.2019.1056
[45] https://doi.org/10.1042/BSR20200127, https://doi.org/10.20506/rst.36.2.2666
[46] https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/ema-regulatory-science-2025-strategic-reflection_en.pdf
[47] https://www.ema.europa.eu/en/about-us/how-we-work/european-medicines-regulatory-network/european-medicines-agencies-network-strategy

4.2. International regulatory initiatives

International regulators recently discussed these topics related to genome editing in their meetings:

- ATMP cluster (FDA, Health Canada, PMDA/MHLW): Guidelines under development (CAR-T, Human Gene Therapy Products Incorporating Genome Editing) (see below)
- FDA-EMA communication channel on quality aspects for ATMPs: Discussion on genome editing guidance and experience gained through scientific advice
- Orphan cluster: duration of clinical efficacy evaluation

International horizon scanning initiatives are ongoing to capture emerging trends and challenges in areas such as genome editing. Two of the most relevant ones are ICMRA and the EU-IN (this report).

The FDA has issued, since 2019, several guidance documents that concern genome editing including the following:

- Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use
- Long Term Follow-Up After Administration of Human Gene Therapy Products. This includes integration, off-target genome editing activity, prolonged expression, latent virus activation, persistent expression, as well as suggesting a follow-up duration of up to 15 years for clinical trial subjects of genome editing products and 5 years for those delivered through AAV vectors.
- Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)
- No specific genome editing recommendations in: Human Gene Therapy for Hemophilia, Human Gene Therapy for Rare Diseases, Human Gene Therapy for Retinal Disorders, Interpreting Sameness of Gene Therapy Products Under the Orphan Drug Regulations
- Expected soon: Human Gene Therapy Products Incorporating Human Genome Editing

Elsewhere the FDA predicted 10 to 20 cell and gene therapy product approvals per year by 2025, based on an assessment of current pipelines and the clinical success rates of these products.

PMDA has released a Guideline on Ensuring the Quality and Safety of Gene Therapy Products (not specific for genome editing).[48]

4.3. Planned activity and projects

The EMA's Committee for Advanced Therapies (CAT) work plan[49] addresses post-authorisation clinical trials and other clinical data generation and, broadly, facilitating and optimising the development and assessment of ATMPs. The CAT is also expanding the guidelines for genetically modified cells: drafting guidance beyond the *ex vivo*, quality/non-clinical/clinical guidance that is already included. The guideline on gene therapy products covers *in vivo* editing but it was concluded that, at this point, there was insufficient experience for issuing detailed guidance.[50] Developers can seek guidance for their

[48] https://www.pmda.go.jp/files/000235607.pdf
[49] https://www.ema.europa.eu/en/documents/other/cat-work-plan-2020_en.pdf
[50] Requirements for marketing authorisation applications: Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products (EMA/CAT/80183/2014) and Guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells (EMA/CAT/GTWP/671639/2008 Rev. 1); requirements for investigational products: Draft Guideline on quality, non-clinical and clinical requirements for investigational advanced therapy medicinal products in clinical trials (EMA/CAT/852602/2018)

specific product through ITF and Scientific Advice. In addition, the CAT is working on a comprehensive guideline for ATMPs in clinical development.[51]

The European Commission and EMA Action Plan on ATMPs[52] includes the work on guidelines as mentioned above, as well as on the improvement of GMP and GCP inspections, a reflection on hospital exemption which may result in expanding the ATMPs to be regulated by the EMA, and EMA-EUnetHTA interactions.

No specific workshops are planned at the moment.

The EU Learning management system includes three recorded presentations on ATMPs, which cover genome editing but do not go into detail; a curriculum could be built up along with future activities.

4.4. Existing EMA and Network (EMRN) competences

At present there is some experience and guidance documents in reviewing gene-editing based therapeutics within the regulatory network. Expertise also exists in some NCAs through experience in assessing clinical trial authorisation applications.

It would be helpful to document and share experience to date and identify aspects which may require the development of or access to additional expertise.

5. Recommendations

5.1. Improving knowledge and expertise

- Establish closer exchange and interactions with stakeholders, including basic scientists, to increase the level of understanding of the field and its complexities. This should build on the model of the first genome editing workshop and preferably include other industries and sectors (animals, plants) invested in genome editing.
- Identify the needs and areas of concern from patients, consumers and healthcare professionals. This can also help to identify the expertise gaps for the oversight and implementation of genome editing (e.g. ethical aspects, clinical practice)
- Build an EMRN community for genome editing across NCAs, EMA Committees and experts. Use this to create a sufficiently large pool of European experts in the field, incorporating EMA's external expert database.
- Within the EMRN, collect and share experience with genome editing from regulatory interactions and identify aspects which may require the development of further expertise and / or broader access to expertise.
- Build an EU NTC curriculum in genome editing.

5.2. Changes to the regulatory framework

- Ensure an integrated regulatory approach that looks not only at genome editing but also 'omics and broader physiological and pharmacological effects.

[51] https://www.ema.europa.eu/en/guideline-quality-non-clinical-clinical-requirements-investigational-advanced-therapy-medicinal
[52] https://www.ema.europa.eu/documents/other/european-commission-dg-health-food-safety-european-medicines-agency-action-plan-advanced-therapy_en.pdf

- Develop actions to facilitate, retain and attract genome editing clinical trials in the EU and build up experience with this technology, in particular for *in vivo* uses.
- Clarify the definition and classification of genome editing products. Harmonise this, to the extent possible, with international regulators.
- Consider contributing to a guidance/Q&A for when external controls (concurrent or historic, including RWE and registry data) are acceptable or required.
- Consider clarifying the maintenance of orphan status of potentially curative ATMPs where significant benefit over an authorised ATMP has to be shown but this raises scientific and policy issues.

5.3. Collaboration with stakeholders

- For genome editing products, seek out early interactions with HTA bodies and increase information sharing.
- Consider establishing interaction with other industries or sectors whose genome editing tools, techniques and regulatory science may have relevance for medicine, such as agriculture.
- Continue working with the European Commission to incentivise harmonisation of GMO requirements across MS and across Directives.
- Engage in early dialogue with academia, including academic developers and basic scientists, on scientific topics and developments as well as regulatory support and pathways, where possible leveraging the results and network of the EU-IN STARS project.[53]
- Engage with patients, consumers, academia and healthcare professionals to build understanding in this innovative and complex area.
- Incentivise stakeholders to share data according to principles set out for the European Health Data Space.
- Extend existing international collaboration in genome editing. This should go beyond the technical/regulatory challenges concerning quality and support global alignment through deepening collaboration with other regulators in addition to the FDA:
    - Increase international collaboration in scientific advice procedures and when drafting guidance for genome editing products and maximise the involvement of experts in such procedures and discussions.
    - Work internationally to develop and agree the risk-based principles underpinning the definition and use of on/off-target safety testing batteries. A baseline battery could be agreed which would then be adjusted per product and cell type. To support this, in silico models should be built that integrate the current heterogeneous in vivo/in vitro genome-editing data. These discussions should also explore non-clinical models that measure the heterogeneity of off-target effects between cells, their functional sequelae and impact on intra and inter-cell functioning, such as DNA structural change, RNA expression and cell signalling.
    - Work internationally to develop experience and guidelines for genome editing indications based on *in vitro* data. Advancements in genome editing will likely facilitate

[53] https://www.csa-stars.eu/

its use in very rare diseases, where there are numerous different genotypes / mutations. Validated *in vitro* testing and diagnostics could be used to approve genome editing medicines across a range of mutations, which could not all be tested in clinical trials, or to approve new indications of well characterised genome editing medicines. This would only be possible if the disease and medicine is well understood, and the B/R well established.

Annexes

Information sources

The draft report used multiple sources of information including but not limited to:

- Innovation office queries or scientific advice requests
- Scientific and regulatory journals, screened the first 100 results and reviewed relevant articles. Search strategy in Embase: ('gene edit*' OR 'genome edit*') AND ('technology'/exp OR technology OR 'method'/exp OR method) AND ('medicine'/exp OR medicine OR 'therapy'/exp OR therapy OR 'drug'/exp OR drug OR 'regulatory challenges'). Years: 2017, 2018, 2019, 2020
- Public consultation summaries to the RSS (responses to questions 3, 5, 6, 7)
- Meetings / conferences with relevant stakeholders
- Information from any relevant funded projects
- Clinical trial registries
- Other horizon scanning services
- Media (commercial, medical and regulatory) EMM scanned since June 2018
- European Commission DG Health and Food Safety and European Medicines Agency Action Plan on ATMPs, EC Pharmaceutical strategy
- Consultation with relevant EMA experts

Overview of genome editing products

Clinical trials

- EudraCT includes several non-public phase 1 trials of genome editing products.
- ClinicalTrials.Gov: more than 550 interventional clinical studies are listed for "Gene therapy" as a standardised intervention name, which is however not specific to genome editing since it can include gene addition, gene transfer and other techniques; no trials were obviously using *in vivo* gene editing. About 30 trials are labelled as phase 3, for indications in haemophilia, thalassaemia, sickle cell disease, muscular dystrophy, muscular atrophy, adrenoleukodystrophy, ischaemia, arthritis etc. https://clinicaltrials.gov/ct2/results?type=Intr&intr=%22Gene+therapy%22

Orphan designations

The following orphan designations have been granted (*ex vivo* and *in vivo* gene editing products):

- Autologous CD34+ haematopoietic stem cells with a CRISPR-edited erythroid enhancer region of the BCL11A gene for beta-thalassaemia intermedia and major (EU/3/19/2210)
- Autologous CD34+ haematopoietic stem cells with a CRISPR-edited erythroid enhancer region of the BCL11A gene for treatment of sickle cell disease (EU/3/19/2242)

- Autologous skin equivalent graft composed of keratinocytes and fibroblasts genetically corrected by CRISPR/Cas9-mediated excision of mutation-carrying COL7A1 exon 80 for the treatment of Epidermolysis bullosa (EU/3/20/2253)
- Adeno-associated viral vector serotype 2/6 encoding zinc-finger nucleases and the human alpha L-iduronidase gene for the treatment of mucopolysaccharidosis type I (EU/3/17/1955)
- Recombinant adeno-associated viral vector serotype 5 encoding Staphylococcus aureus Cas9 endonuclease and two guide RNAs complementary to two regions of intron 26 of the CEP290 gene (also known as EDIT-101) for the treatment of Leber's congenital amaurosis (EU/3/17/1928).

Paediatric investigation plans

Paediatric (investigation) development plan discussions concerned amongst others an *ex vivo* genome editing products such as allogenic anti-CD19 CAR-Ts with a kill switch to treat acute leukaemia.

Innovation Task Force

Summarised in text

Business pipeline

Summarised in text

EU Experts registered in regulatory system

The EMA expert database includes more than 150 experts across the European Union with competences in Quality, Biotechnology products and Gene Therapy.

EMA/EMRN strategic priorities relating to genome editing

The EMA's Regulatory Science Strategy to 2025[54] and the European Medicines Agencies Network (EMRN) Strategy to 2025[55] are grounded in stakeholder consultation and have set out a number of relevant recommendations as listed in the strategy.

Regulatory Science Strategy to 2025:

- Driving collaborative evidence generation for improving the scientific quality of evaluations
- Identify therapies that address unmet medical need (*including through Horizon scanning)*
- Provide assistance with early planning, method development and clinical evaluation *(this is linked to Scientific Advice)*
- Address the challenges of decentralised ATMP manufacturing and delivery locations
- Support evidence generation, pertinent to downstream decision-makers
- Evaluate and improve interactions relevant to ATMPs with European institutions (research, financial and environmental)

[54] https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/ema-regulatory-science-2025-strategic-reflection_en.pdf
[55] https://www.ema.europa.eu/en/about-us/how-we-work/european-medicines-regulatory-network/european-medicines-agencies-network-strategy

- Raise global awareness of ATMPs to maximise knowledge sharing and promote data collection
- Engage with other international regulatory agencies to foster global convergence of requirements for ATMPs
- Clearly inform the public of the scientific underpinning of new veterinary medicines and technologies, such as biological products including DNA vaccines or gene therapies

The EMRN Strategy to 2025[55] includes points that apply to genome editing products, of which the following could be a priority with respect to genome editing:

- Collaborate with HTA bodies, and where appropriate, payers, on pre-planning and generation of post-licensing evidence
- Increasing complexity and diversity of evidence means that further work is needed on how best to document and clearly communicate the regulatory assessment
- Catalyse the integration of science and technology in medicines development and ensure that the network has sufficient competences to support innovators in various phases of medicines development
- Foster collaborative evidence generation - improving the scientific quality of evaluations and ensuring generation of evidence useful to all actors in the lifecycle of medicines, including HTAs, and pricing and reimbursement authorities (with regards to genome editing, academia should be included in this collaborative evidence generation)
- Facilitate the implementation of novel manufacturing technologies
- Develop the regulatory framework for emerging clinical data generation
- Invest in special populations initiatives
- Develop further the collaboration of various groups involved with scientific advice and/or regulatory guidance