Contribution ID: 6a75837d-1094-41f4-ad14-0d82a928438c
Date: 15/05/2020 13:16:55

Stakeholder questionnaire on new genomic techniques to contribute to a Commission study requested by the Council

Fields marked with * are mandatory.

Questionnaire on new genomic techniques to contribute to the study requested by the Council

Discussed and finalised in the Ad-hoc Stakeholder meeting on 10 February 2020

Background

The Council has requested [1] the Commission to submit, by 30 April 2021, "a study in light of the Court of Justice's judgment in Case C-528/16 regarding the status of novel genomic techniques under Union law" (*i.e.* Directive 2001/18/EC, Regulation (EC) 1829/2003, Regulation (EC) 1830/2003 and Directive 2009/41/EC).

To respond to this Council's request, the Commission is collecting contributions from the stakeholders through the questionnaire below. The study covers all new genomic techniques that have been developed after 2001.

Instructions

For the purpose of the study, the following definition for new genomic techniques (NGTs) is used: techniques that are capable of altering the genetic material of an organism and which have emerged or have been developed since 2001 [2].

Unless specified otherwise, the term "NGT-products" used in the questionnaire covers plants, animals, micro-organisms and derived food and feed products obtained by NGTs for agri-food, medicinal and industrial applications and for research.

Please substantiate your replies with explanations, data and source of information as well as with practical examples, whenever possible. If a reply to a specific question only applies to specific NGTs/organisms, please indicate this in the reply.

Please indicate which information should be treated as confidential in order to protect the commercial

interests of a natural or legal person. Personal data, if any, will be protected pursuant to Regulation (EU) 2018/1725 [3].

[1] Council Decision (EU) 2019/1904, OJ L 293 14.11.2019, p. 103-104, https://eur-lex.europa.eu/eli/dec/2019/1904/oj
[2] Examples of techniques include: 1) Genome editing techniques such as CRISPR, TALEN, Zinc-finger nucleases, mega nucleases techniques, prime editing etc. These techniques can lead to mutagenesis and some of them also to cisgenesis, intragenesis or transgenesis. 2) Mutagenesis techniques such as oligonucleotide directed mutagenesis (ODM). 3) Epigenetic techniques such RdDM. Conversely, techniques already in use prior to 2001, such as Agrobacterium mediated techniques or gene gun, are not considered NGTs.
[3] Regulation (EU) 2018/1725 of the European Parliament and of the Council of 23 October 2018 on the protection of natural persons with regard to the processing of personal data by the Union institutions, bodies, offices and agencies and on the free movement of such data, and repealing Regulation (EC) No 45/2001 and Decision No 1247/2002/EC, OJ L 295, 21.11.2018, p. 39–98

Guidelines

Please note that the survey accepts a maximum of 5000 characters (with spaces) per reply field. You might be able to type more than 5000 characters, but then the text will not be accepted when you submit the questionnaire. You will also receive a warning message in red colour below the affected field.

You have the option to upload supporting documentation in the end of each section. You can upload multiple files, up to the size of 1 MB. However, note that any uploaded document cannot substitute your replies, which must still be given in a complete manner within the reply fields allocated for each question.

You can share the link from the invitation email with another colleague if you want to split the filling-out process or contribute from different locations; however, remember that all contributions feed into the same single questionnaire.

You can save the draft questionnaire and edit it before the final submission.

You can find additional information and help here: https://ec.europa.eu/eusurvey/home/helpparticipants

Participants have until 15 May 2020 (close of business) to submit the questionnaire via EUsurvey.

QUESTIONNAIRE

Please provide the full name and acronym of the EU-level association that you are representing, as well as your Transparency Registry number (if you are registered)

If the name of the association is not in English, please provide an English translation in a parenthesis

Alliance for Regenerative Medicine (ARM)
Transparency register number ID: 244710319190-73

Please mention the sectors of activity/fields of interest of your association

The Alliance for Regenerative Medicine (ARM) is the preeminent global advocate for regenerative and advanced therapies. ARM fosters research, development, investment and commercialization of transformational treatments and cures for patients worldwide.
ARM convenes all stakeholders with an interest in regenerative and advanced therapy medicinal products (ATMPs) to provide a unified voice for our 350+ member organizations, including companies – especially small- to medium-sized enterprises (SMEs); academic/research institutions; non-profit organizations; patients, and other members of the advanced therapies community.
To learn more about ARM, visit http://www.alliancerm.org

If applicable, please indicate which member associations (national or EU-level), or individual companies /other entities have contributed to this questionnaire

If applicable, indicate if all the replies refer to a specific technique or a specific organism

Our replies refer exclusively to gene therapies, including gene therapies using genome editing technologies, for human use. Some answers refer specifically to products using genome editing technologies, others refer to gene or gene-modified cell therapies in general. In the large majority of cases, these products fall into the category of medicinal products consisting of or containing GMOs according to European legislation.

A - Implementation and enforcement of the GMO legislation with regard to new genomic techniques (NGTs)

* **1. Are your members developing, using, or planning to use NGTs/NGT-products?**

- (●) Yes
- ( ) No
- ( ) Not applicable

* Please provide details

There are currently 66 companies worldwide developing ATMPs based on genome editing technologies, among which 16 are in clinical stage at the end of 2019. Of those, 13 companies, including 5 clinical-stage companies are headquartered in Europe.
The majority of these companies are members of ARM.

* **2. Have your members taken or planned to take measures to protect themselves from unintentional use of NGT-products?**

- ( ) Yes
- (●) No
- ( ) Not applicable

* Please explain why not

Medicinal products are already highly regulated and already protected for unintentional use including e.g. by complying to traceability requirements, use restricted to some healthcare professionals, supply to expert centres, etc.

* 2 bis. Have you encountered any challenges?

- ○ Yes
- ◉ No

* **3. Are you aware of initiatives in your sector to develop, use, or of plans to use NGTs/NGT-products?**

- ◉ Yes
- ○ No
- ○ Not applicable

* Please provide details

Our data indicate that out of a total of 1066 on-going clinical trials with advanced therapies at the end of 2019, there were globally a total of 804 on-going clinical trials using gene therapies, including gene-modified cell therapies, of which 32 using genome editing technologies. See more in ARM 2019 Annual Report (https://alliancerm.org/publication/2019-annual-report/).
The following EU funded projects and initiatives to support the development of NGTs/NGT-products can also be cited:
- IMI Supporting the development of engineered T cells: https://ec.europa.eu/info/funding-tenders/opportunities/portal/screen/opportunities/topic-details/imi2-2019-18-06
- IMI Advancing the research and innovation of ATMPs: https://ec.europa.eu/info/funding-tenders/opportunities/portal/screen/opportunities/topic-details/imi2-2019-18-05
- HORIZON 2020:The EU Framework Programme for Research and Innovation - Activities and initiatives in advanced therapies https://ec.europa.eu/health/sites/health/files/non_communicable_diseases/docs/ev_20180928_co01_en.pdf
- Advanced T-cell Engineered for Cancer Therapy (ATECT) https://cordis.europa.eu/project/id/602239

* **4. Do you know of any initiatives in your sector to guard against unintentional use of NGT-products?**

- ◉ Yes
- ○ No
- ○ Not applicable

* Please provide details

The medicinal product legislation and national regulations provide safeguard against unintentional use of NGT-products, e.g. by restricting their supply to some expert centres.

* 4 bis. Are you aware of any challenges encountered?

- ○ Yes
- ◉ No

* **5. Are your members taking specific measures to comply with the GMO legislation as regards organisms obtained by NGTs?**

Please also see question 8 specifically on labelling

- (●) Yes
- ( ) No
- ( ) Not applicable

* Please describe the measures and their effectiveness including details on the required financial, human resources and technical expertise

The EU Advanced Therapy Medicinal Product (ATMP Regulation (1304/2007) details the specific regulatory considerations for ATMPs including those consisting of or containing GMOs. In addition, products consisting of or containing GMOs need to comply with relevant European and national GMO legislation: before undertaking clinical trials with ATMPs consisting of or containing GMOs, sponsors need to seek the approval of national health competent authorities (as for any clinical trials on humans) as well as of national or regional GMO authorities for the environmental and biosafety aspects of GMOs.

* What best practices can you share?

The publication of a joint position paper in 2017 signed by ARM, EuropaBio, EFPIA and EBE with a series of recommendations, as well as contacts with the European Commission have stimulated the undertaking of an initiative by the European Commission, the EMA and competent authorities to address some of the difficulties for clinical trials with medicinal products containing or consisting of GMOs. A Good Practice document, Q&A and common application forms have been published and endorsed by several Member States, that facilitate the GMO review and approval process and ensure greater convergence of decisions for a same product in different countries (see https://ec.europa.eu/health/human-use/advanced-therapies_en). Several recommendations proposed in our joint position paper have since been implemented. Despite these improvements, difficulties subsist. For instance, ARM members recently indicated that even with the implementation of common application forms, national GMO submissions still require the use of national forms in addition to the common application form in some countries, with a sizeable dossier and a lot of redundancies between the different documents. Another example is that the process in some countries (e.g. Spain) is the same for every product, regardless of their risk classification, with no additional flexibility or speedier approval for class I products (the lowest risk class).

* 5 bis. What challenges have you encountered?

See also the response to Question 9. The GMO approval process for clinical trials with gene therapies is a complicated, sometimes very lengthy process. Divergent classification (deliberate release or contained use) in Member States requires different notification pathways, differing document requisites from national and/or regional authorities, public disclosure of IP information in certain Member States, different translation requirements and public consultations for the release of GMOs, etc. It constitutes major hurdles for therapeutic developers and is responsible for significant delays in the initiation of clinical trials. Despite recent improvement (see above), some difficulties remain and indicate that the approval for clinical trials with gene therapies continue to be delayed due to GMO requirements. This leads to a lack of early access to innovative medicines and competitiveness in Europe compared to other regions to attract new clinical trials with gene therapies, as shown in ARM study published in October 2019 (see https://alliancerm.org/wp-content/uploads/2019/10/Trends-in-Clinical-Trials-2019-Final_Digital.pdf): between 1 Jan 2014 and 30 June 2019, 55% of all new clinical trials with ATMPs were with gene therapies in Europe compared to 77% of all new clinical trials in North America. Delays in the initiation of clinical trials have serious financial implications for ATMP developers, particularly detrimental for the small and medium enterprises and lead to delays in access to these ground-breaking, life-saving treatments.

* **6. Has your organisation/your members been adequately supported by national and European authorities to conform to the legislation?**

- ○ Yes
- ◉ No
- ○ Not applicable

* What challenges have you encountered?

Despite support, particularly at European level, as described above under question 5., this proves insufficient to significantly improve the attractiveness of Europe for the development of gene therapies. Beyond the complexities and delays getting the authorisations for GMO aspects of clinical trials for gene therapies, an additional difficulty is anticipated with the forthcoming implementation of the Clinical Trials Regulation (EU) N°536/2014 since the EU portal, as defined in its article 80, to be used with the entry into force of this new regulation is not adapted to accommodate the specific requirements of the GMO approval process for medicinal products consisting of or containing GMOs.

* **7. Does your sector have experience or knowledge on traceability strategies, which could be used for tracing NGT-products?**

- ◉ Yes
- ○ No
- ○ Not applicable

* Please describe the traceability strategy, including details on the required financial, human resources and technical expertise

There is no specific traceability strategy for NGT-products. Traceability requirements as applicable for medicinal products will be followed for medicines based on NGT-products. In this regard, we can refer to:

- Guidance EMEA/CHMP/GTWP/60436/2007 requiring that 'The marketing authorisation holder or sponsor of a clinical trial with a GT products shall ensure that traceability data on the sourcing, manufacturing, packaging, storing, transport and delivery to the hospital, institution or private practice where the product is used, are in accordance with Regulation (EC) No 1394/2007 (art. 15), and upcoming guidelines related to ATMP Traceability and Good Clinical Practice.'
- Regulation (EC) No 1394/2007 – Art. 15, requiring that with the marketing authorisation application, a risk management plan has to be submitted in accordance with the current EU legislation and pharmacovigilance guidelines (see Guideline on Safety and Efficacy Follow-up – Risk Management of Advanced Therapy Medicinal Products). Marketing authorisation holders also need establish and maintain a system ensuring that the individual product can be traced through the sourcing, manufacturing, packaging, storing, transport and delivery to the hospital, institution or private practice where the product is used. They also need to keep these data for a minimum of 30 years after the expiry date of the product, or longer if required by the Commission as a term of the marketing authorisation.
- In addition, traceability requirements for cells and tissues used as starting materials for NGT-products also need to be complied with (Commission Directive 2006/86/EC, Commission Directive (EU) 2015/565, etc).

We consider additional traceability strategies not necessary for medicinal products consisting of or containing GMOs since (1) viral vectors and genetically modified human cells do not duplicate or cannot survive long in the environment, and (2) human individuals treated with in vivo therapies should not be considered as GMO. Traceability requirements for medicines are robust and are outlined in the regulation (EC No 1394/2007, art. 15).

* **8. Are your members taking specific measures for NGT-products to ensure the compliance with the labelling requirements of the GMO legislation?**

- ○ Yes
- ◉ No
- ○ Not applicable

* Please describe the measures and their effectiveness including details on the required financial, human resources and technical expertise

Labelling requirements for gene therapies are the same as for other types of medicinal products.

* What best practices can you share?

Labelling requirements for gene therapies are the same as for other types of medicinal products.

* Please explain why not

Not applicable since labelling requirements in the case of medicinal products consisting of or containing GMOs are defined by the pharmaceutical legislation.

* 8 bis. What challenges have you encountered?

-

* **9. Do you have other experience or knowledge that you can share on the application of the GMO legislation, including experimental releases (such as field trials or clinical trials), concerning NGTs/NGT-products ?**

- ◉ Yes
- ○ No
- ○ Not applicable

* Please describe for the:

- ☐ Agri-food sector
- ☐ Industrial sector
- ☑ Medicinal sector

Medicinal sector

See also response under question 5. One of the main reasons for the difficulties gaining approval for GMO aspects during clinical trials with gene therapies is that the GMO legislation in Europe was not originally designed for medicinal products and is not fit-for-purpose. The GMO legislation was designed mainly to cover plant and animal genetic modification with a goal to protect food consumers and crops from contamination, not so much to protect patients or caregivers. The information and the application forms to apply for GMO approval were initially not adapted and contained a lot of information irrelevant for medicinal products. The regulatory agencies in charge of the GMO evaluations in Member States are often responsible for Environmental or Food, with insufficient specific expertise in medicinal product requirements to cope with the rising number of clinical studies with gene therapies. The applications for GMO aspects during clinical trials are very resource intensive and their review often lead to divergent opinions (deliberate release vs contained use or different risk classes for a same product), making it very complex and burdensome for the sponsors of clinical trials. Medicinal products are extensively regulated and undergo a thorough review by the health authorities and national ethical committees before they can be tested in humans. These are administered after explicit informed patient's consent in clinical studies and after due concertation between the prescribing physician and the patient in case of commercial product.
ARM believes that the GMO legislation is not adding value to protect citizens from the unwanted effects of the majority of medicinal products consisting of or containing GMOs.
We would ask for a reconsideration whether the GMO legislation should apply for medicinal products consisting of or containing GMOs. More specifically, we believe that the environmental and biosafety risk does not exist for non-replicating viral vectors or genetically modified human cells as these do not duplicate and cannot survive long in the environment. Additionally, human individuals treated with in vivo therapies should not be considered as GMO.
Alternatively, rather than having a separate, independent review of GMO aspects by GMO authorities for clinical trials with products consisting of or containing GMOs, we would propose a regulatory assessment that considers GMO aspects. Currently, when medicinal products for human use containing or consisting of GMOs apply for marketing authorization to the EMA, the GMO framework is not applicable (Article 12 Directive 2001/18/EC and Article 3.3 Directive 2009/43/EC): the assessment of environmental aspects of these products is performed by the responsible EMA committee (i.e. CAT for ATMPs) and the Rapporteur consults with GMO authorities to assess compliance with the safety requirements laid down by Directive 2001/18/EC. Given that GMO authorities have agreed specific Environmental Risk Assessment (ERA) for viral vectors and genetically modified cells, ARM believes that this should be sufficient to comply with the GMO directive requirements for these types of products. Completed ERA would be submitted with the Clinical Trial Application to regulatory authorities who have CMC, non-clinical and clinical data to assess the completed ERA, and regulatory authorities can consult with the GMO authorities. Such an approach would facilitate the implementation of the Clinical Trial Regulation, with a single clinical trial application, with ERA, through the portal, and a single approval.
ARM is willing and prepared to engage with the EC and other stakeholders to discuss the feasibility and acceptability of such proposals or any other that would significantly reduce the workload for applicants and reviewers, streamline the processes, harmonize decisions within Member States and can adapt with rapidly advancing science. A streamlined approach for clinical trials and GMO aspects is needed to support the competitiveness of Europe and increase its attractiveness as a region for the development of ATMPs.

Please upload any supporting documentation for this section here. For each document, please indicate which question it is complementing

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B - Information on research on NGTs/NGT-products

* **10. Are your members carrying out NGT-related research in your sector?**

- (●) Yes
- ( ) No
- ( ) Not applicable

* Please specify including subject, type of research, resources allocated, research location

The majority of therapeutic developers using genome editing technologies are still in preclinical stage: from the 66 companies currently developing gene edited therapies, 16 are in clinical stage and 50 in preclinical stage.
Out of a total of 1066 on-going clinical trials on human subjects with advanced therapies at the end of 2019, there were globally a total of 804 on-going clinical trials using gene therapies including gene-modified cell therapies, of which 32* active, interventional clinical trials using genome editing technologies, of which 6 have locations in Europe. These trials explore many different therapeutic indications – see some examples below. See more in ARM 2019 Annual Report available here.
Many of the companies using the new genome editing technologies for the development of new medicines are members of ARM, including: Adaptimmune, AskBio, Astellas (Universal Cells), bluebird bio, BlueRock Therapeutics, BMS (Celgene), Caribou Biosciences, CRISPR Therapeutics, Editas Medicine, Excision BioTherapeutics, Fate Therapeutics, Healios, Homology Medicines, Intellia Therapeutics, Kite Pharma /Gilead, LogicBio, , Mammoth Biosciences, MaxCyte, Novartis, Pfizer, Poseida Therapeutics, Precision Biosciences, Rocket Pharmaceuticals, Sangamo Therapeutics, Sanofi, Senti Bio, Takeda, Tmunity Therapeutics, Vertex Pharmaceuticals, Viacyte.
Further, the majority of our members are involved in the development of gene or gene modified cell therapies. See list of ARM members here
(*Phase 0 or early phase 1 trials are not included in this number.)

* **11. Are you aware of other NGT-related research in your sector?**

- ( ) Yes
- (●) No
- ( ) Not applicable

* **12. Has there been any immediate impact on NGT-related research in your sector following the Court of Justice of the EU ruling on mutagenesis?**

Court of Justice ruling: Case C-528/16 http://curia.europa.eu/juris/documents.jsf?num=C-528/16

- ( ) Yes
- (●) No
- ( ) Not applicable

* Please explain why not

Most of the clinical trials with medicinal products using new genome editing (mutagenesis) techniques were initiated after the Court of Justice of the EU ruling on mutagenesis. Sponsors of these clinical trials comply with the GMO requirements as appropriate.

* **13. Could NGT-related research bring benefits/opportunities to your sector/field of interest?**

- (●) Yes

- ○ No
- ○ Not applicable

* Please provide concrete examples/data

There is rapidly growing number of gene therapies on the market. These products are one-time, durable treatments that are transformational in the lives of the patients they treat. NGTs will likely contribute significantly to the growing number of these transformational medicines that are available to patients. Investment in companies developing gene therapies in general, and gene therapies using genome editing technologies in particular has been very important during the last few years. From a total global financings of $9.8 Billion raised in ATMP/regenerative medicine in 2019, the total global financing in gene-based therapies was $ 7.6 B (€ 6.9 B), indicating investors' high interest and confidence in this technology.
This shows how vibrant and attractive this sector is, including in Europe, creating many jobs and economic growth. At the end of 2019, there were approx. 237 ATMP companies headquartered in Europe, representing approximately ¼ of all ATMP developers, of which 109 were active in gene therapies and 12 active in gene editing. These numbers, and the number of people employed in the sector are set to increase sharply over time, as reflected by investors' interest in gene therapies. However, most importantly are the benefits and opportunities in terms of healthcare and society: see answers to questions 16 & 17.

*** 14. Is NGT-related research facing challenges in your sector/field of interest?**

- ◉ Yes
- ○ No
- ○ Not applicable

* Please provide concrete examples/data

As explained above (see answers to question 5), the process for gaining approval of clinical trials with products consisting of or containing GMO is particularly complex and lengthy. This may explain why there are significantly less clinical trials with gene therapies in Europe compared to North America. Complex regulations and lengthy procedures significantly delay and limit patient access to these transformative treatments in Europe. See ARM report on clinical trials in Europe with advanced therapies: https://alliancerm.org/wp-content/uploads/2019/10/Trends-in-Clinical-Trials-2019-Final_Digital.pdf.
See also joint position paper on 'Possible solutions to improve the European regulatory procedures for clinical trials with Advanced Therapy Medicinal Products consisting of or containing Genetically Modified Organisms' published in September 2017: https://alliancerm.org/press-release/arm-ebe-efpia-and-europabio-jointly-publish-series-of-proposals-to-streamline-requirements-and-accelerate-approvals-of-clinical-trials-with-new-therapies-consisting-of-or-containing-genetically-modi/

*** 15. Have you identified any NGT-related research needs/gaps?**

- ○ Yes
- ◉ No
- ○ Not applicable

Please upload any supporting documentation for this section here. For each document, please indicate which question it is complementing

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C - Information on potential opportunities and benefits of NGTs/NGT-products

* **16. Could NGTs/NGT-products bring benefits/opportunities to your sector/field of interest?**

- (●) Yes
- ( ) No

* Please describe and provide concrete examples/data

Gene therapies typically treat the underlying cause of a disease or disorder rather than focusing on long-term symptom management. They can have profound and durable responses, perhaps with only a single administration, to patients with a diverse array of serious diseases and disorders, many of whom currently have limited or no treatment option available. Gene therapies have the potential to improve the standard of care for hundreds of thousands of patients worldwide and radically transform the healthcare landscape.
New genomic techniques are subject to intense research and investment in the field of advanced therapies. The majority of on-going genome editing clinical trials are in the field of oncology; other indications being studied include diseases such as: haemophilia, sickle cell disease, mucopolysaccharosis, transthyretin amyloidosis, methylmalonic acidemia, β-thalassemia, etc.
Examples of current clinical trials using NGT-products include:

- Allergan/Editas phase 1/2 clinical trial in congenital eye diseases
- Allogene phase 1 and 1/2 clinical trials (2) in large B cell/follicular lymphoma and multiple myeloma
- Cellectis clinical trials (3) in oncology (ALL, AMF, MM)
- CRISPR Therapeutics phase 1 and phase 2 clinical trials (2) in MM and NHL
- Precision Biosciences phase 1/2 clinical trials (3) in oncology (NHL, CLL, MM)
- Sangamo phase 1/2 clinical trials (2) in MPS I and II and Beta-thalassemia
- Vertex & CRISPR Therapeutics phase 1/2 clinical trials (2) in beta-thalassemia, sickle cell and other hematological diseases.

ARM's quarterly and annual reports on the sector provide regular update on clinical advancements. Additional information can be provided to the Commission or other stakeholders as needed.

* Are these benefits/opportunities specific to NGTs/NGT-products?

- (●) Yes
- ( ) No

* Please explain

Many of the conditions being addressed by medicinal products based on NGTs/NGT-products are not or insufficiently addressed by other types of products.

* **17. Could NGTs/NGT-products bring benefits/opportunities to society in general such as for the environment, human, animal and plant health, consumers, animal welfare, as well as social and economic benefits?**

- (●) Yes
- ( ) No

* Please describe and provide concrete examples/data

Products using NGT treat the underlying cause of a disease or disorder rather than focusing on long-term symptom management. They can have profound and durable responses, perhaps with only a single administration, to patients with a diverse array of serious diseases and disorders, many of whom currently have limited or no treatment option available. Genome editing and other gene therapies have the potential to improve the standard of care for hundreds of thousands of patients worldwide and radically transform the healthcare landscape. This technology is not a distant hope but a fast-approaching reality. Therapies using ZFNs have been in the clinic for several years, with the first results from a clinical trial to treat HIV published in 2014. Newer gene editing technologies, including CRISPR, have begun to enter the clinical as well.
See examples of clinical development above under question 16. The benefits for treating serious conditions with unmet medical needs are important for the patients, their families and caretakers, healthcare community and society at large. By profoundly changing the course of or curing diseases, gene therapies could bring important societal benefits as well as long-term savings in healthcare budgets (ref: https://alliancerm.org/sector-report/a-transformative-therapy-value-model-for-rare-blood-diseases).

* Under which conditions do you consider this would be the case?

Optimal patient access is necessary to fully exploit the benefits of these therapies. This requires in many countries adaptations in the health systems and market access procedures. See more on alliancerm.org/wp-content/uploads/2019/07/ARM-Market-Access-Report-FINAL.pdf

* Are these benefits/opportunities specific to NGTs/NGT-products?

- (●) Yes
- ( ) No

* Please explain

ATMPs are currently the only medicinal products able to correct the underlying causes of diseases such as genetic diseases, rare diseases, and many other, including more frequent, serious diseases. Most of the currently available medicinal products treat the symptoms and require chronic treatment but are not able to dramatically change the course of diseases.

* **18. Do you see particular opportunities for SMEs/small scale operators to access markets with their NGTs/NGT-products?**

- (●) Yes
- ( ) No

* Please describe and provide concrete examples/data

Most of the companies developing gene therapies currently are SMEs, as reflected in ARM membership: more than 70% of our member organizations (excluding non-profit, academic organisations and other types of members) have revenues < $50 Mil and <100 FTEs

* **19. Do you see benefits/opportunities from patenting or accessing patented NGTs/NGT-products?**

- (●) Yes
- ( ) No

* Please describe and provide concrete examples/data

Intellectual Property Rights (IPR) including patents are at the cornerstone of the biopharma industry and is the main driver to foster innovation. Strong IPR and particularly patent rights are pre-requisites for private placements, venture capital and other types of investment in a sector, particularly in high-risk sectors such as the health biotech industry.
An innovation friendly environment with strong IPR and reward mechanisms is needed to ensure Europe competitiveness in the field of gene therapies and NGT-products. Uncertainties on IPR would inevitably lead to rerouting of capital to different regions or different sectors, disincentivizing future innovation in Europe.

Please upload any supporting documentation for this section here. For each document, please indicate which question it is complementing

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D - Information on potential challenges and concerns on NGTs/NGT-products

* **20. Could NGTs/NGT-products raise challenges/concerns for your sector/field of interest?**

- (●) Yes
- ( ) No

* Please describe and provide concrete examples/data

As with any new technology, there are many difficulties and challenges to be addressed before NGT-products can be brought on the market to transform and improve patient lives.
These range from ensuring large-scale, consistent and high quality product manufacturing, finding efficient and safe delivery tools, to avoiding and controlling 'off target' effects.
A major concern is the oversight by too many different authorities in Europe and the lack of sufficient specific expertise on gene therapies by GMO authorities to cope with the rising number of applications with gene therapies: national or regional Agriculture or Environmental Authorities oversee the GMO aspects of investigational medicinal products, whilst national health authorities oversee all other aspects of investigational medicinal products, leading to a lot of complexities, divergent opinions and inefficiencies in the system (see more information in the responses to Q5 & 9).

* Are these challenges/concerns specific to NGTs/NGT-products?

- (●) Yes
- ( ) No

* Please explain

The above mentioned challenges are shared and specific to gene therapies and NGT-products. In addition, each specific product may have unique challenges to address before they can be successfully developed. The development process for these products is very long (typically 10+ years) and is resource and capital intensive

*

21. Could NGTs/NGT-products raise challenges/concerns for society in general such as for the environment, human, animal and plant health, consumers, animal welfare, as well as social and economic challenges?

- ○ Yes
- ◉ No

* Please explain why not

Modified viral vector and genetically modified human cells do not replicate and cannot survive in the environment. Further, human individuals treated with in vivo therapies should not be considered as GMO's. There is thus no major environmental risk associated with the development and use of gene therapies, including NGT-products. Further, medicinal products consisting of or containing GMOs are highly regulated by competent authorities and ethics committees and their use is allowed only after thorough review of all the required data, including environmental risk assessment, concluding to a positive benefit/risk ratio of the treatment.
As confirmed in our Statement of Principles originally published in August 2019 and signed by 15 of the preeminent companies active in developing therapeutic human genome editing technologies, ARM supports the use of gene editing techniques for therapeutic modifications to somatic cells under the oversight of relevant national or regional regulatory bodies (see on https://alliancerm.org/therapeutic-developers-statement-of-principles-2/). We do not support gene editing of the germline (sperm, eggs, fertilized embryos) for the purposes of human implantation. Further, we do not support implantation of a human embryo carrying gene modified cells. Most genetic diseases can be treated directly in affected somatic cells without modifying the germline, and we support such therapeutic use.

* **22. Do you see particular challenges for SMEs/small scale operators to access markets with their NGTs /NGT-products?**

- ◉ Yes
- ○ No

* Please explain and provide concrete examples and data

SME typically lack the human and financial resources to handle the complex and lengthy GMO assessments for the clinical development of their products. As every Member States follow their own GMO assessment process at national or regional levels independently of health authorities, this multiplies the number of procedures for multinational trials and delay the approvals to start clinical studies. Bigger organisations are better equipped and have affiliates in most European countries which are more familiar and able to handle local processes.
Additionally, while regulators from European health authorities have worked to adopt frameworks to ensure the appropriate, rapid approval of ATMPs in Europe, payers and health technology assessment bodies have not yet established the necessary specific mechanisms to ensure timely patient access to these therapies post-approval. Most payers and health technology assessment (HTA) bodies have not established specific mechanisms to adequately capture the full benefits of ATMPs. Consequently, there are many systematic barriers that may hinder ATMPs from reaching patients in need in a timely manner. To lift these barriers and ensure timely access to ATMPs, ARM published a series of recommendations to be implemented at European and national levels: see on alliancerm.org/wp-content/uploads/2019/07/ARM-Market-Access-Report-FINAL.pdf.

* **23. Do you see challenges/concerns from patenting or accessing patented NGTs/NGT-products?**

- ◉ Yes

No

* Please describe and provide concrete examples/data

As mentioned above (see answer to question 19), patents are required to foster innovation and ensure safe, effective and quality products can be put on the market for patients' benefits . A substantial amount of information is included in the "SNIF" form which is to be published on several Member State Health Authorities' websites for up to 30 days. In addition, Ireland requires the entire GMO application (not just the SNIF) to be published for 30 days. Such disclosure may contain confidential and/or competitively sensitive information.

Please upload any supporting documentation for this section here. For each document, please indicate which question it is complementing

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E - Safety of NGTs/NGT-products

*** 24. What is your view on the safety of NGTs/NGT-products? Please substantiate your reply**

As for any medicinal products, the safety of these products needs to be thoroughly characterized and their benefit/risk ratio be deemed favourable before they can be placed on the market. The European Medicines Agency is fully competent to assess the safety of new medicines products, including NGT-products, and can be entrusted to carry out an objective, high-standard safety evaluation before they can be granted marketing authorization.

*** 25. Do you have specific safety considerations on NGTs/NGT-products?**

Yes
No

* Please explain

As with all new ground-breaking technologies, genome editing presents some new challenges, including on safety. Safety of these technologies, including specific safety concerns such as off-target effect for human genome editing, must be demonstrated in controlled clinical trials and their long-term safety be evaluated under the oversight of the appropriate regulatory authorities

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F - Ethical aspects of NGTs/NGT-products

*** 26. What is your view on ethical aspects related to NGTs/NGT-products? Please substantiate your reply**

ARM released a Therapeutic Developers' Statement of Principles, setting forth a bioethical framework for the use of gene editing in therapeutic applications. Originally released on 27 August 2019, and signed by 15 of the preeminent companies active in developing therapeutic human genome editing, the Statement of Principles specifies five key principles for the ethical use of gene editing and genetic modification. See more on https://alliancerm.org/therapeutic-developers-statement-of-principles-2/
ARM supports the use of gene editing techniques for therapeutic modifications to somatic cells under the oversight of relevant national or regional regulatory bodies. We do not support gene editing of the germline (sperm, eggs, fertilized embryos) for the purposes of human implantation. Further, we do not support implantation of a human embryo carrying gene modified cells. Most genetic diseases can be treated directly in affected somatic cells without modifying the germline, and we support such therapeutic use.
Other international organisations such as WHO or the international commission convened by the UK Royal Society, the U.S. National Academy of Sciences (NAS) and the U.S. National Academy of Medicine (NAM), with the participation of science and medical academies around the world, are also engaged in initiatives to develop global standards for governance and oversight of human genome editing and frame recommendations for its responsible use.
ARM is monitoring and, where relevant, engaging with these international initiatives.

*** 27. Do you have specific ethical considerations on NGTs/NGT-products?**

- (●) Yes
- ( ) No

* Please explain

See above, under question 26

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G - Consumers' right for information/freedom of choice

*** 28. What is your view on the labelling of NGT-products? Please substantiate your reply**

Labelling on new medicines based on NGT-products should follow the same rules as for any other medicines, with no additional or different specific requirements. The decision for prescription of a specific product treatment is left to physicians who have to adequately inform patients before treatment initiation.

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H - Final question

*** 29. Do you have other comments you would like to make?**

- (●) Yes
- ( ) No

Please provide your comments here

A conference on “Conversations on Science, Regulation and Society – the Future on Genome Editing in European healthcare systems” was held in the European Parliament on 25 October 2018, hosted by MEP Maria Teresa Giménez Barbat. This conference provided an overview of the growing prevalence of genome editing technologies in healthcare, their enormous potential in providing new approaches and cures to serious diseases, the perspectives from many different stakeholders and the need for cross-sectoral collaboration to ensure that patients in Europe can benefit from these new advances. The report on that conference has been released in September 2019 and is available on https://alliancerm.org/wp-content /uploads/2019/09/Future-of-genome-editing_FINAL-Sept-2019.pdf

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