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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

European Federation of Pharmaceutical Industries and Associations - EFPIA. EFPIA is registered under “II – In-house lobbyists and trade/business/professional associations” with public ID number 38526121292-88.

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

Pharmaceutical, Research and Discovery, Medicinal

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

The European Federation of Pharmaceutical Industries and Associations (EFPIA) represents the pharmaceutical industry operating in Europe, having 36 national associations and 39 leading pharmaceutical companies as members.

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

Gene and cell therapy, gene editing

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

Yes, gene editing techniques are used in medicinal research to identify targets for future drugs and to generate optimised in vitro and in vivo models for testing allowing for evaluation of potential drug candidates. Besides providing tools for drug discovery, the gene editing techniques allow for generation of novel medicinal products for human use, designed to replace or inactivate disease causing genes, or to introduce new genetic sequences for therapeutic purposes.
New genomic techniques for that are increasingly being utilised and developed by the pharmaceutical companies to support patient access to the life-changing therapies include the following:

- Induced pluripotent stem cell therapies
- CAR-T-cells based therapies using gene editing
- CRISPR, Base editing, prime editing, Talen and Zinc-finger nucleases

The increasing use of genome editing technologies was addressed by the EMA in a 2018 report “Report of the EMA expert meeting on genome editing technologies used in medicinal product development” (dated 12 September 2018; https://www.ema.europa.eu/en/documents/report/report-ema-expert-meeting-genome-editing-technologies-used-medicinal-product-development_en-0.pdf)

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

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

* Please provide details

Yes, in general, the development and use of medicinal products, including cell and gene therapies, is highly regulated. The use of NGTs in research and development of cell and gene therapies (Advanced Therapy Medicinal Products (ATMPs)) follow established legislation and regulatory guidelines for medicinal products, which have a strong focus on the quality, efficacy and patient safety.

The manufacture, supply and testing of medicinal products in general are required follow strict standards captured in Good Manufacturing Practices (GMP), Good Distribution Practices (GDP) and Good Clinical Practices (GCP). Specific GMPs and GCPs have also been elaborated for ATMPs including those based on NGTs. These standards protect against unintentional use of NGT-products by establishing: principles for appropriate training and hygiene of personnel involved in manufacture of NGT-products as well as suitability of premises to minimise risks; minimum standards for ensuring the integrity of the supply chain for NGT-products and requirements for safe conduct of clinical trials with NGT-products.

In addition, as part of the environment risk assessment conducted in accordance with GMO legislation (in context of clinical trials) or Annex 1 of Directive 2001/83/EC (in context of marketing authorisation for medicinal products) applicants must ensure measures for storage, transportation and waste treatment as well as consider whether risk management strategies should be implemented.

Reference:
Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products (2017): https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-4/2017_11_22_guidelines_gmp_for_atmps.pdf

Guidelines on Good Clinical Practice specific to ATMPs (2019): https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/atmp_guidelines_en.pdf
Guidelines on Good Distribution Practice of medicinal products for human use: https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2013:343:0001:0014:EN:PDF

Guidelines on principles of Good Distribution Practice of active substances for medicinal products for human use: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A52015XC0321(01)

Good practice documents in GMO requirements for investigational products on EC website: https://ec.europa.eu/health/human-use/advanced-therapies_en

EMA Guideline on environmental risk assessments for medicinal products containing, or consisting of, genetically modified organisms (GMOs): https://www.ema.europa.eu/en/environmental-risk-assessments-medicinal-products-containing-consisting-genetically-modified

* 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

Yes, pharmaceutical companies are using NGTs to develop medicinal products, including ATMPs, to treat patients with serious conditions for which there are unmet medical needs. Several ATMPs have already been approved for use in Europe and many others are being developed and studied in clinical trials. These products are already having a transformative impact on patients. 500,000 patients are projected to be treated with ATMPs by 2030.*
The EU has a long history of supporting research and innovation in gene therapy for example through the FP7 Framework and Horizon 2020 funding programmes. There are also a number of public-private partnerships dedicated to development of gene therapies which may utilize NGTs such as: Innovative Medicines Initiative projects on Advancing the research and innovation of ATMPs and Supporting the development of engineered T cells.
Please also refer to Q1.

*MIT NEWDIGS. (2018). Research Brief 2018F210v027. https://newdigs.mit.edu/sites/default/files/FoCUS%20Research%20Brief%202018F210v027.pdf
References
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

(Presentation) 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 pharmaceutical industry adheres to global laws and regulatory guidelines for NGT-based products and follows all emerging science, diligently considering the ethical aspects. The medicinal products legislative framework already contains a number of provisions to guard against unintentional use. These are captured in legislation and the GMP, GDP and GCP standards mentioned in response to Q2.
New ATMPs also require sufficient evidence to justify initiation of controlled clinical trials in humans and later to demonstrate a positive benefit/risk balance before applying for market authorisation. Companies must submit applications for clinical trial(s) and a marketing authorisation that are evaluated by EU (EMA) and national medicines regulatory authorities. An authorisation must be granted before starting a clinical trial or placing a product on the market. Following authorisation, a monitoring system and risk minimisation measures are established to protect patients and healthcare professionals to mitigate risks of unintentional use. These measures include specific label information and risk management plans for the ATMP, which provide instructions on appropriate use of the product as well as how the therapy should be handled and given to the patient.
Furthermore, we are aware of the World Health Organisation initiative to develop global standards for governance and oversight of human genome editing (https://www.who.int/ethics/topics/human-genome-editing/en/)
Other international associations have also established ethical guidelines addressing issues important for gene editing such as the Alliance for Regenerative Medicine position statement: (https://alliancerm.org/bioethics/) and ISCT Presidential Task Force on the use of unproven and/or unethical cell & gene therapy (http://www.isct-unprovencellulartherapies.org/)

* 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

NGTs further extend the possibility to genetically tailor cells for treatment of disease and opens opportunities for gene editing products to correct genes leading to disease. The wider utility of medicinal products enabled using NGT should put a new focus on rationale for classifying ATMPs such as genetically modified cells and gene therapy delivered in non-viral vehicles as GMOs.
As explained above in response to Q2, the manufacture, development and supply of medicinal products is regulated to ensure high standards for quality, safety efficacy of products. At the developmental stage, therapeutic products containing GMOs, including those generated using NGTs, are required to make additional submissions in order to comply with GMO legislation.
Pharmaceutical companies are taking measures to comply with the GMO legislation during product development. Standard requirements as indicated by legislation are fulfilled with environmental risk assessment, evaluation of exposure or other aspects important to the environment. The resource requirements and expertise for the handling and conduct risk assessment of organism obtained by NGTs are not different to that for GMOs generated using other techniques. In addition, evaluation of risk benefit in terms of GMO needs to be provided as part of GMO application. They are submitted to GMO competent authorities before initiating clinical trials of gene therapies and cell therapies containing genetically modified cells that were developed using NGTs. These submissions are in addition to submissions to national medicines authorities for clinical trial authorisation and ethics committees, which are required for all medicinal products under Clinical Trials legislation.
In contrast, at the time of marketing authorisation for medicinal products containing GMOs, including those based on NGTs, the environmental risk assessment is integrated into the evaluation of the marketing authorisation application. (see EMA Guideline on environmental risk assessments for medicinal products containing, or consisting of, genetically modified organisms (GMOs) (https://www.ema.europa.eu/en /environmental-risk-assessments-medicinal-products-containing-consisting-genetically-modified) and EMA Standard Operating Procedure “Consultation of environmental competent authorities on genetically-modified organisms with respect to environmental risk assessment in product evaluation (human use)” (SOP/H/3191) https://www.ema.europa.eu/en/documents/sop/standard-operating-procedure-consultation-environmental-competent-authorities-genetically-modified_en.pdf)
Companies experiences have shown that the GMO assessment process for products in development can be lengthy and these additional GMO submissions can cause delays of up to 12 months before a clinical trial can be initiated (depending on the national requirements and competent authority procedures). This leads to delays in patient’s access to potential new therapeutic options and slows the innovation process.

* What best practices can you share?

Please refer to the previous answer.

* 5 bis. What challenges have you encountered?

Several additional challenges with the current process were highlighted in a position paper jointly published by EFPIA, Alliance for Regenerative Medicine and EuropaBio:*
- EU regulations and directives regarding GMOs are not specific to medicinal products. The requirements were drafted with a focus on plants and the authorities responsible for review have expertise in plants and foods. This can result in questions that are not applicable to pharmaceuticals and necessitates additional time for communication with the authority.
- GMO directives have been implemented differently by Member States, and the disparities in process and timing are challenging to manage. For example, in some EU member a pre-submission meeting is required which adds into the complexity; in some Member States, the GMO application must be approved before the CTA can be submitted while in other it can be done in parallel.
- In addition, some national laws require the GMO assessment process to be repeated for subsequent clinical trials, even if they involve the same product in the same indication and same method of administration.
- Environmental risk assessment can result in divergent conclusions in different Member States, even when the product, indication, method of administration, and study design are the same. Some Member States apply „contained use „requirements and others apply „deliberate use“ requirements.

* ARM, EBE, EFPIA, EuropaBio. (2017). Possible solutions to improve the European regulatory procedures for clinical trials with Advanced Therapy Medicinal Products consisting of or containing Genetically Modified Organisms. https://www.ebe-biopharma.eu/publication/arm-ebe-efpia-and-europa-bio-joint-position-paper-possible-solutions-to-improve-the-european-regulatory-procedures-for-clinical-trials-with-advanced-therapy-medicinal-products-consisting-of-or-cont/

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

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

* Please describe what type of support and what best practices you can share

Yes. In general, support has been received via dialogue with the national and EU authorities for medicinal products (e.g. EMA). However, the level of support available has been inconsistent across European Member States.
As stated earlier in this survey response, the GMO legislation is not adapted to the specificity and already highly-regulated nature of ATMP development. This has been acknowledged by the European Commission and medicines competent authorities at national and EU (e.g. EMA) level in their joint action plan on ATMPs.
* The European Commission's efforts with Member States to compile a repository of national GMO regulatory requirements on the Commission's website, including the common application forms and good practice documents that have been published have been useful.**
However, despite these efforts some challenges remain including the lack of harmonization in implementation of common forms and submission requirements. Such lack of harmonization is evident across the different GMO processes and available support for clinical trials at the national level, across EU member states.
In order to facilitate timely access to these innovative therapies for patients by reducing delays to clinical studies and also to maintain EU competitiveness for the development of ATMPs, we would welcome further efforts by the Commission and Member States. We would be pleased to participate in future dialogue with the European Commission and Member States on additional solutions that could further streamline the current process for the medicinal product sector. These could include:***
- Similar to the approach taken at the time of marketing authorisation application for a gene therapy or genetically modified cell therapy, GMO submissions could be fully integrated into the CTA submission process by ensuring the new CT portal has capability to accept GMO documentation.
- Furthermore, the authority in each Member State that is responsible for CTA review could act as the single contact with sponsors, in order to enhance the communication and collaboration between the GMO and CTA authorities. This process is currently used in Germany and Sweden.
- A GMO facilitation group could be formed to facilitate dialogue between GMO and CTA authorities, similar to the Mutual Recognition Facilitation Group for marketing authorisations or the Voluntary Harmonisation Procedure for clinical trials.
- The application process and requirements for GMOs could be harmonized through EU regulation similar to Clinical Trials Regulation.
References:
* see report on Outcome of a multi-stakeholder meeting with experts and regulators on ATMPs held at EMA on Friday 27 May 2016 (https://www.ema.europa.eu/en/documents/report/outcomes-workshop-multi-stakeholder-advanced-therapy-medicinal-products-atmps-expert-meeting_en.pdf) as well as the European Commission DG Health and Food Safety and European Medicines Agency Action Plan on ATMPs (https://www.ema.europa.eu/sites/default/files/documents/2017/10/20/action-plan-advanced-therapy_en.pdf)
** https://ec.europa.eu/health/human-use/advanced-therapies_en
*** ARM, EBE, EFPIA, EuropaBio. (2017). Possible solutions to improve the European regulatory procedures for clinical trials with Advanced Therapy Medicinal Products consisting of or containing Genetically Modified Organisms. https://www.ebe-biopharma.eu/publication/arm-ebe-efpia-and-europa-bio-joint-position-paper-possible-solutions-to-improve-the-european-regulatory-procedures-for-clinical-trials-with-advanced-therapy-medicinal-products-consisting-of-or-cont/

*** 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

Yes. Pharmaceutical development of ATMPs is highly regulated and no specific additional traceability strategies are required in addition to those currently established. The quality information on source on GMO organism techniques used to obtain them is part of regulatory information included in the clinical trial application and later in marketing authorisation application. The marketing authorisation holder is obliged to maintain this information and timely inform regulatory authorities up on change using established regulation process.
In addition, specific follow-up requirements on safety and efficacy outcomes of patients treated with ATMPs in clinical trials and post-marketing authorisation are established in regulatory guidelines for gene therapy and the ATMP regulation 1394/2007 and will be applied to any new ATMP using NGTs.

References:
- Annex 1 Directive 2001/83/EC
- Directive 2001/20/EC (Clinical Trials Directive)(https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/dir_2001_20/dir_2001_20_en.pdf)
- Volume 10 Clinical trial guidelines (https://ec.europa.eu/health/documents/eudralex/vol-10_en)
- Guideline on follow-up of patients administered with gene therapy medicinal products (2009) (https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-follow-patients-administered-gene-therapy-medicinal-products_en.pdf)
- Guideline on safety and efficacy follow-up and risk management of Advanced Therapy Medicinal Products (https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-safety-efficacy-follow-risk-management-advanced-therapy-medicinal-products-revision_en.pdf)

* **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

Yes. Laboratory and Clinical Trial Materials (CTM) manufacturing facilities are compliant with guidelines and regulations related to NGT based products. Further, labelling information for pharmaceutical products including e.g. gene therapy is regulated by existing EU medicinal product regulation (see Directive 2001/83/EC). Process is clear and requirements for labelling as well. Marketing authorisation holders and sponsors are responsible for maintaining the regulatory labelling information including implementation of changes into the currently approved label. Label contains efficacy and safety information that is kept up to date and used by healthcare professionals.

* What best practices can you share?

Please refer to the previous answer.

* 8 bis. What challenges have you encountered?

Not applicable

* **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
- [x] Medicinal sector

Medicinal sector

Yes. Please see responses to Q5 and Q6.

The process to gain approval to initiate a clinical trial including a GMO is challenging in Europe, with different national requirements and differences in approval timelines at the national level. Challenges are related to the different interpretation and implementation of GMO legislation on country/national level. Different requirements are in place regarding the information that should be provided along the clinical trial application (CTA) before initiation of the study. And frequently there is no harmonised GMO/CTA process (site versus national submission). In some EU countries GMO and CTA documentation is submitted together and assessment runs in parallel (Germany), in others like Netherlands GMO is a separate process with independent, unclear timelines in addition to CTA process. Individual site notifications are required in Czech Republic. For GMO submission in Ireland a pre-submission meeting is required which adds into the complexity.

Further, the process of GMO application maintenance with regards to changes into the quality of the product or to the clinical study is unclear. Some EU countries will require amendment submission of changes to the existing GMO application, some will not. Timelines for processing and approval of GMO on national level are very diverse. Long timelines such as GMO application approval took for CTA Phase 1/ 2 more than 1 year impacting opening the clinical trial sites.

As previously mentioned, the medicinal product sector is already well regulated, and initiation of a clinical trial requires prior assessment by national medicines authorities and ethics committees. We acknowledge the steps taken by the Member States and Commission to voluntarily align on interpretation of GMO aspects and submission requirements in the context of clinical trials. This has been useful in making incremental improvements to the processes at national level. However, the added value of an additional separate review of GMO aspects for clinical trials with medicinal products containing GMOs, including NGT-based products, remains unclear. A more streamlined and harmonised approach that fully integrates GMO aspects into the CTA application process should be considered. A harmonisation of GMO process would facilitate for companies to run clinical trials in Europe and speed access to new potential new NGT-based treatments in development for patients.

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

The maximum file size is 1 MB

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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

Yes, pharmaceutical companies are using NGTs for drug discovery and for generation of advanced therapy medicinal products including gene and cell therapies: induced pluripotent cells, gene editing platform, development of human compatible tissues, cells, single cell genomics platform to dissect the biology of immune cells in human tumours, adults stem cells, cell therapies are in preclinical development, and others are currently being studied in clinical trials. There are 260 ongoing clinical studies of ATMPs in EU.* Globally, the number of studies are increasing; between 2014-2018, the number of new clinical trials per year increased by 32%. However, the increase in new clinical trials initiated per year in Europe was only <2%.** Some members report conducting research primarily in Sweden and UK, with various external collaborations cross Europe and beyond.
*https://alliancerm.org/wp-content/uploads/2020/02/CBX-Meeting-7-Feb-2020-FINAL.pdf
** Alliance for Regenerative Medicine. (2019). Clinical Trials in Europe: Recent Trends in ATMP Development. https://alliancerm.org/wp-content/uploads/2019/10/Trends-in-Clinical-Trials-2019-Final_Digital.pdf

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

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

* Please specify

Yes. There are other approaches such as RNA targeted therapies. See Q 10

*** 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 describe

For pharmaceutical companies, human gene therapies and cell therapies comprising cells modified using NGT continue to be subject to Directive 2001/18/EC. We understand that certain in vivo techniques using NGTs for therapeutic purposes in humans are still not subject to GMO legislation even after the Court of Justice ruling on mutagenesis as human beings cannot be considered GMOs according to the legislation.

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

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

* Please provide concrete examples/data

Yes, as mentioned in response to Q1, NGT facilitate and open-up new avenues in drug target identification and validation, including the generation of animal and cellular models of disease for study of candidate drugs. As an example, NGT facilitates studies to find drug resistance to chemotherapeutic drugs.
NGTs also open up for generation of novel advanced therapy medicinal products, targeting genetic diseases. This includes orphan diseases and patient populations with high unmet need. It should be noted that NGTs allow targeting genetic diseases that would be difficult or impossible to target using conventional drugs.

NGTs represent a new wave of innovation in the medicinal products sector, driving additional investment in companies who are conducting research and development in this space, including those based in Europe. Development of NGTs also create job opportunities within the academic research setting.

“Report of the EMA expert meeting on genome editing technologies used in medicinal product development” (dated 12 September 2018; https://www.ema.europa.eu/en/documents/report/report-ema-expert-meeting-genome-editing-technologies-used-medicinal-product-development_en-0.pdf).

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

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

* Please provide concrete examples/data

Yes. As this sector continues to rapidly grow, fuelled by the evolving science, it is particularly challenging to maintain sufficient expertise across the field of NGTs, increasingly sophisticated and novel methods, the latest products and their potential reimbursement. This is true for many stakeholders, including industry, regulators, payers, and physicians.
Regulatory requirements for quality and safety assurance of ATMPs based on NGTs are different depending on the region, country and authorities. A more harmonised global approach will facilitate global development.
NGTs open up the possibility to target very small patient populations or even develop individualised medicines. To enable this, from a manufacturing scale and patient benefit risk assessment perspective, the concepts of technical platforms need to be built. Manufacturing platforms for medicinal products generated using NGT could be standardised and tailored as required to generate specific medicinal products for a certain genetic disease, or even for a single patient. In this context it would be advantageous if a regulatory approval for such product could be based on an already approved technical platform, with only the changes to that platform being evaluated and risk assessed for a new product. Such concept would largely facilitate development of and investments in novel advanced therapy products utilising NGTs.

Further, we would like to also point out the disproportional number in clinical trials (general and based on technology) especially Phase 1 and Phase 2 on European level as indicated in the figures below. (Source: https://alliancerm.org/wp-content/uploads/2019/10/Trends-in-Clinical-Trials-2019-Final_Digital.pdf). There is considerable country-by-country variability in the number of clinical trials, speed of assessment, and time for approval of clinical trials in the different countries analysed in Europe. In Europe, the UK, Spain, and France attracted the highest absolute number of ATMP clinical trials during the period analysed. Some smaller countries are, relative to their size, outperforming: Belgium, Denmark, and Switzerland attract proportionally more new ATMP clinical trials per capita than other countries. In our view, it will be important access the differences and present more harmonised framework for ATMPs.

ATMPs may face challenges with current HTA principles and practices. Consideration of ways of dealing with increased uncertainty; for example, by developing out-come-based payment models, and dialogue regarding the economic, social, and ethical aspects of the implications of discounting given the differential between payment of costs and receipt of benefits, will be key. In particular, ATMPs may face a challenge in demonstrating value within current evaluative frameworks. It will be important to improve the HTA methods used for the assessment of ATMPs which would enable healthcare systems to manage some of the uncertainties presented by early data from these products.

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

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

* Please specify which needs/gaps, explain the reasoning and how these needs/gaps could be addressed

These technologies are still in their infancy and most methods have relatively low on-target efficiency and some off-target effects. Moreover, for the use in vivo, there is challenge of delivery methods. More research should be directed to further develop these technologies, reduce off-targets and increase efficiency to allow for these techniques to facilitate for development of new medicinal products. Despite challenges, the area of human somatic genome editing has potential benefit for patients on a global level. Two important aspects need to be considered: high precision and accuracy of gene editing technologies to achieve desired therapeutic effect with acceptable safety for the patient. NGT approaches will be a potential answer for high unmet medical need once challenges outlined above are resolved.
Clinical trial regulation national instead of EU wide – as per Clinical Trial Facilitation Group (CTFG).
Further there are IMI cell and gene therapy program focusing on developing tools and assays to assess and predict immunogenicity of NGTs.

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

Yes, Reference is given to responses for Q1 and Q13. In addition, the NGTs enables a more robust pre-clinical assessment of candidate drugs prior to start of clinical trials, and with availability of tailored cell systems for characterisation, a reduction in animal testing is likely. Consequently, it is suggested that use of NGTs can save resources and accelerate drug development.

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

- (●) Yes
- ( ) No

* Please explain

Please refer to the previous answer.

*** 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

Yes, gene and cell therapies offer the potential to treat, and potentially even cure, patients with serious diseases or conditions, orphan genetic based diseases for which there are currently limited or no treatment options cure or where response to conventional therapies is very low. By 2030, 500.000 patients are projected to be treated with ATMPs.* The benefit of these type of treatments is not only symptom treatment but provides the opportunity to change the course of a disease and the potential for real cures. NGT based drug products enable cure of complex genetic disease which have not otherwise been amenable to development of small molecule or simple biologic therapeutics. This leads to broader societal benefits and potential for long-term savings for healthcare systems**.

Risk benefit is to be established per product. If the safety of the platform is established, please see also answer on Q16. Ethical and legal aspects are to be considered too (e.g., heritable aspects following a gene therapy with an NGT).

* MIT NEWDIGS. (2018). Research Brief 2018F210v027. https://newdigs.mit.edu/sites/default/files/FoCUS%20Research%20Brief%202018F210v027.pdf
** Second Generation Cell and Gene-Based Therapies. 1st Edition. Biological Advances, Clinical Outcomes and Strategies for Capitalisation by Alain A Vertès, Devyn M Smith, Nasib Qureshi, Nathan J Dowden https://www.sciencedirect.com/book/9780128120347/second-generation-cell-and-gene-based-therapies

Reference is given to Q1, Q13 and Q16

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

* Please refer to the previous answer.

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

- (●) Yes
- ( ) No

* Please explain

Please refer to the previous answer.

* **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

Yes, SMEs companies are very innovative and generate a lot of the early discovery research in this space. Methodology and technical development of NGTs can be the base for start-up companies. There are several IP applications in the field of genome editing held by SMEs, with potential to bring value to the healthcare sector. Of note, most of gene and cell therapy drug products such as AAV and CAR-T products currently on the market are originally created by biotech companies (e.g. spun-out from Universities).

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

- (●) Yes
- ( ) No

* Please describe and provide concrete examples/data

Yes, pharmaceutical companies invest a significant amount of time and resources in order to research, develop, and manufacture gene and cell therapies. For each product that is approved, there are many products that were unsuccessful. A strong protection of intellectual property is necessary to enable innovation and to enable innovative pharmaceutical companies to recover the cost of product development. This will help them to continue developing therapies for high-unmet medical need for the benefit patients suffering from deliberating diseases.
Strong IP protection is essential for continued investment in the research and development of novel medicinal products including those based on or utilising NGTs.

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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

Yes, the challenge is in translating the transformative value of ATMPs when compared with either standard of care or conservative treatment into our health care system. Often clinical studies employ new endpoints and data set is based on small population which may add additional layer of complexity for establishing the transformative value of ATMP.
Gene therapy is a radical shift in the approach to disease treatment. By modifying the expression of a patient' s genes or repairing abnormal genes, gene therapy often has potential to address the root cause of diseases. The newly approved gene therapies offer substantial benefits to patients who otherwise have little to no hope of cure or even meaningful improvement. For example, they treat non-Hodgkin's lymphoma, an acute form of leukemia, or a hereditary genetic defect that nearly always leads to blindness. Each therapy is a potentially one-time treatment, just a single infusion, that may provide long-term, durable efficacy. These new treatments have initiated an important discussion about how to place a value on gene therapies and how the health care system will pay the upfront costs for these often one-time treatments. Assigning value to gene therapies and comparing them with potentially lifelong illness is a complex task. ATMPs may face challenges with current established HTA principles and practices. Consideration of ways of dealing with increased uncertainty be developing appropriate HTA methodological models to capture elements of ATMP value not captured in established QOL tools or developing payment models are important aspect for ATMP market access.
Finally, there are many concerns are on the ethical aspect of the human genome editing, especially regarding germline (heritable) editing, but somatic editing is ethically justified because it can help treat serious diseases.

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

- (●) Yes
- ( ) No

* Please explain

Please refer to the previous answer.

*** 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 describe and provide concrete examples/data

Gene and cell therapies offer the potential to treat, and potentially even cure, diseases or conditions that are currently life-threatening or require long-term treatment. The research and development costs of these therapies will have to be recovered over different time spans than current treatments and will require a new financing model including pricing and reimbursement. Pharmaceutical companies develop innovative therapies which require substantial investments, and therefore we support the development of a framework that allows sustainable investments in research and development to safeguard a continuous supply of

innovation.
Stakeholders including sponsors and health technology assessment agencies should collaborate to better understand approaches to understand the value of these therapies, manage uncertainty, and consider what changes in the health care system may be necessary to facilitate access to patients.

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

Please refer to the previous answer.

* Are these challenges/concerns specific to NGTs/products obtained by NGTs?

- (•) Yes
- ( ) No

* Please explain

Please refer to the previous answer.

*** 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

SMEs may face challenges obtaining the necessary manufacturing and distribution capacity to bring gene and cell therapies to market, which will likely require partnering with larger pharmaceutical companies. In general, biotech companies have lower budget and capability than big pharma in terms of addressing regulatory requirements, preparing regulatory applications, GxP experience, compliance, manufacturing (high manufacturing costs), clinical development (high clinical trial costs) and sales.

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

- (•) Yes
- ( ) No

* Please describe and provide concrete examples/data

Yes, further guidance is needed on how the similarity of gene and cell therapies will be interpreted for the determination of orphan designation and later 10 year market exclusivity in view of current Orphan Medicines Regulation (EC) No. 141/2000.
Currently the IP situation for NGT are challenging and hard to navigate as there are many players and different patents in place. Uncertainties concerning the IP situations can hamper beneficial use of NGTs.

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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 with all medicines, gene and cell therapies carry not only benefits but also potential risks that need to be understood and managed. There is uncertainty of safety risk of NGTs/NGT-products. Good product characterisation (purity, identity, potency, stability) is very important including assays to monitor product safety (genotoxicity, tumorigenicity).
Pharmaceutical companies are committed to ensuring the highest level of safety for patients who are being treated with gene and cell therapies in clinical trials or on the market. Nonclinical studies and clinical trials help us understand specific safety considerations for individual products. Risk mitigation measures and regulatory requirements should focus on addressing specific risks which vary depending on the nature of the product. We also support the collection of long-term safety data on these products to better understand potential risks.

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

- (●) Yes
- ( ) No

* Please explain

Yes, techniques are constantly improving to evaluate and predict off-target human genome editing. Special ethical concerns exist with respect to the potential for human germline editing. NGTs can have unintended effects that are unknown and not predictable based on animal data. Long term safety follow-up is needed for some product categories in order to monitor for delayed adverse reactions.

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

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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**

CRISPR and similar NGTs represent the next generation of genome engineering and are opening new and exciting doors to drug discovery and development, as well as to the role that genes play in disease pathology. In practice, these technologies are enabling us to accelerate and improve the drug discovery and development process, specifically in the identification and validation of new targets and in our ability to test potential new therapies for safety and efficacy.
Genome editing technologies offer the potential for the treatment of genetic diseases in the future. The development of such medicines requires the establishment of methods to enable the efficient modification of the target gene with no effects elsewhere in the genome. We are developing methods to improve the efficiency and specificity of precise genome editing to minimise off-target effects.
We support the general principle of cell and gene therapies in human somatic cells, but we are aware of risks due to: unwarranted on-target effects; possible off-target effects; unwanted germline (i.e. sperm, egg or embryo) modification. Any possible future pre-clinical or clinical work in this regard would be subject to

existing standards for medicinal product development with respect to their biosafety and safety and be subject to ethical review.
Innovative pharmaceutical industry neither practices nor endorses human gene therapies which target the germline and Directive 2001/20/EC on Clinical Trials states that no gene therapy trials may be carried out which result in modifications to the subject´s germline genetic identity. The ethical and scientific risks inherent in such practice are a topic of intense global discussion and deemed illegal in many countries.
NGTs are often limited to a single lifetime dose due to the development of antibodies against the viral vector. Therefore, both dose selection for clinical study and the anticipated duration of effect for a given NGT construct are also ethical considerations in this field as well as recruitment of patients in placebo-controlled trials.
In addition, there is a need for public discussion how NGT products remain affordable for society whereas an acceptable price can be set for organisations that take a reasonable return of investment into account.
As an innovative medicines industry, we remain committed to active participation in the debate on precise genome editing.
References:
WHO Expert Advisory Committee on Development Global Standards for Governance and Oversight of Human Genome Editing https://www.who.int/ethics/topics/human-genome-editing/WHO-Commissioned-Ethics-paper-March19.pdf
ASCGT Position Statement https://www.asgct.org/research/news/november-2018/asgct-statement-on-germline-gene-editing-practices”

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

- (●) Yes
- ( ) No

* Please explain

Yes, See also responses to Q26.
The true long-term environmental aspects and safety aspects for patients and their relatives remain an uncertainty. Genome editing could potentially be used not only for genome modification to prevent or cure diseases, but to enhance specific phenotypic characters.
Any unintentional modification to the germline will be transmitted to the progeny, thereby introducing modified genomes in the human pool. The consequences of this are unpredictable and impacts may be observed only in a timeframe measured by generations rather than years follow up to a clinical trial with such a gene therapeutic.

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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**

As for other pharmaceuticals, labelling of NGT products such as gene and cell therapies should clearly describe the benefits, risks, and instructions to facilitate safe use of the product.

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

The maximum file size is 1 MB

H - Final question

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

- (●) Yes
- ( ) No

Please provide your comments here

Yes. The EU regulatory framework is constantly evolving for the benefit of patients and medicine developers. For cell and gene therapies, the EU ATMP regulation was the first move in this respect. This was elaborated further by the risk-based approach to development and description of the technical requirements expected of ATMPs being developed for commercialization laid down in Directive 2009/120/EC. Lessons from the experience with ATMP development since the introduction of the ATMP regulation are also being applied to the evolution of regulatory guidance and procedures, however there is still need for more harmonized framework on the European level with regards to the GMO aspects important for clinical development in EU. To reiterate, Companies developing ATMPs, including those utilizing NGTs, have experienced several challenges in navigating the GMO legislative requirements in the context of clinical trials. This has led to delays in authorization of clinical trials for products containing GMOs with slowing down patient access and innovation as well as potentially lowering the competitiveness of EU as a place for conducting clinical trials with these emerging therapies. We would welcome a discussion on how to better streamline and harmonize the current approach by fully integrating GMO aspects into the CTA application process.
Further, traditional cost-effectiveness analysis conducted as part of HTA focuses on life-years gained, improvements in patient quality of life, and cost savings within healthcare. While the current framework may be appropriate for the assessment of ATMPs, it is also important that the full potential value of ATMPs is recognised. We suggest that this will involve incorporating of a consideration that other aspects of value could be considered as add on into the current evaluative framework for reimbursement.
We hope that some responses to the NGT questionnaire will be translated into actions that lead to further improvements in the ATMP landscape in Europe. EFPIA and its member companies welcome further collaborative discussions with the European Commission and Member State on how to address the challenges raised in the best interests of European patients and the public.

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Contact

SANTE-NGT-STUDY@ec.europa.eu