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Opinion

What's in a word? Defining "gene therapy medicines"

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Gene therapy medicinal products (GTMPs) have emerged as a transformative class of medicines. Defining what a certain class of medicines encompasses, and what it does not, is key, with ample implications and consequential regulatory requirements. In April 2023, the European Commission proposed new pharmaceutical legislation safeguarding the public health within the European Union with a new, broader definition of GTMP, including genome editing medicines and nucleic acids of either source, regulating, replacing, or adding a genetic sequence that mediates its effect by transcription or translation. This definition is all-encompassing for any "genetic" intervention and is agnostic to mechanism of action, duration of action, location of action, and associated risk. Here, we take this as a paradigm to discuss how terminology and definitions are more than just words and can have meaningful regulatory, scientific, and public health implications.

INTRODUCTION

Gene therapy medicines have emerged as a transformative class of medicines, especially with recent breakthroughs like CAR-T cells, or gene editing approaches for sickle cell anemia.[1] Recent advancements, as different as permanent editing of the genome or the transient delivery of messenger RNA (mRNA) into human cells to temporarily express key proteins, are being subsumed under the term "gene therapy".

In April 2023, the European Commission (EC) proposed a new pharmaceutical legislation,[2] which includes a revised definition of gene therapy medicinal products (GTMPs). The currently proposed new definition of GTMP is broad and covers a wide range of product types which are on quite opposite sides of the spectrum. As such, the currently proposed definition is all-encompassing for any "genetic" intervention and is agnostic to mechanism of action, duration of action, location of action, and associated risk. In this article, we take this as a paradigm to discuss how terminology and definitions are more than just words and can have meaningful implications. We seek to show that legislative and scientific advancement can, and should, go hand in hand with a focus on advancement of public health, and add the dimension of risk into key definitions.

Currently, there is no global alignment on what a "gene therapy medicine" is. A gene is commonly understood to be "the basic unit of inheritance" and is "passed from parents to offspring and contains the information needed to specify physical and biological traits".[3] Inherited or acquired genomic mutations may lead to diseases, for which the only permanent treatment option would be correction or replacement of the disease-causing mutation in the respective cells. Currently, several "gene therapy" technologies allow for such corrections, targeting genetic diseases such as inborn errors of metabolism, spinal muscular atrophy, β-thalassemia, hemophilia, and Duchenne muscular dystrophy, or can be developed for the potential treatment of cancer, for example, with genetically modified cells targeting the tumor (e.g., CAR-T cells). In the following, we take a closer look to current gene therapy definitions, for illustration purposes focusing on Europe and the United States (Table 1).

Gene therapy definition in Europe

Under current European Union (EU) legislation (rather than the new proposal),[4] three categories of advanced therapy medicinal products (ATMPs) exist: gene therapy medicinal products (GTMPs), somatic cell therapy medicinal products, and tissue-engineered medicinal products. GTMPs constitute a biological medicinal product based on a recombinant nucleic acid that is "regulating, repairing, replacing, adding, or deleting a genetic sequence." Vaccines against infectious diseases are excluded from the GTMP definition (Table 1). A recent review by Guerriaud and Kohli addresses the challenges posed by this classification and calls for the development of specific guidelines tailored to RNA-based drugs.[5]

One could envisage a scenario where theoretical products based on other novel technologies, although mechanistically impacting the genome, would not be classified as GTMPs under this definition. For example, genome editing technologies like zinc-finger nucleases (ZFNs) or transcription activator-like effector nucleases (TALENs), are based on a nuclease protein introducing breaks into DNA; however, if provided as a protein, they would not meet the GTMP definition as they are not based on a recombinant nucleic acid.

Nucleic acids of synthetic origin are common for shorter sequences like small interfering RNA or antisense oligonucleotides; the development of longer synthetic origin nucleic acid molecules is progressing and might soon be a reality.[9,10] Nevertheless, from a practical point of view, the recombinant (covered by the current EU definition) or synthetic origin (not covered by the current EU definition) of a nucleic acid is not expected to change the mechanics and nature of the product or how it works.

In view of this diversity and rapid development of products in this space, this current definition of gene therapy may no longer

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Table 1. Definition of gene therapy medicines

Region	Source	Gene therapy definition
EU and UK	Directive 2001/83/EC[a]	see Table 2 for new proposed definition by EC and EP; the current definition reads: "Gene therapy medicinal product means a biological medicinal product which has the following characteristics: (a) it contains an active substance which contains or consists of a recombinant nucleic acid used in or administered to human beings with a view to regulating, repairing, replacing, adding or deleting a genetic sequence; (b) its therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence. Gene therapy medicinal products shall not include vaccines against infectious diseases."
USA	58 FR 53248, October 14, 1993[6]	"Gene therapy products are defined (…) as products containing genetic material administered to modify or manipulate the expression of genetic material or to alter the biological properties of living cells. Some gene therapy products (e.g., those containing viral vectors) to be administered to humans fall within the definition of biological products and are subject to the licensing provisions of the PHS Act, as well as to the drug provisions of the act. Other gene therapy products, such as chemically synthesized products, meet the drug definition but not the biological product definition and are regulated under the relevant provisions of the act only."
	FDA guideline[b]	"Human gene therapy seeks to modify or manipulate the expression of a gene or to alter the biological properties of living cells for therapeutic use. FDA generally considers human gene therapy products to include all products that mediate their effects by transcription or translation of transferred genetic material, or by specifically altering host (human) genetic sequences."

PHS, Public Health Service.
[a]As amended by 2009/120/EC.[7]
[b]Definition in most recent guidance addressing gene therapy: "Manufacturing Changes and Comparability for Human Cellular and Gene Therapy Products."[8]

be fully adequate. Within the currently ongoing overhaul of EU pharmaceutical legislation,[11] a new definition of GTMP has been proposed by the European Commission (EC), subsequently amended by a draft of the European Parliament (EP). The revised draft definition provides a clear distinction between products that edit the host genome and those that do not, a differentiation agreed upon by both the EC (Table 2: categories a and b) and the EP (Table 2, types 1 and 2). Additionally, the category of nucleic acid has been expanded to include both synthetic and biological origins.

Like the current definition, the proposed 2023 European draft definition, as amended by the EP, is all-encompassing for any genetic intervention and is agnostic to the mechanism of action, duration of action, and specific location of action of the therapeutic intervention; it would include a wider spectrum of product types than what is available currently due to the inclusion of all synthetic nucleic acids. It still embraces all nucleic acid products, independent of their effect on the genome. If applied, it would classify products across the spectrum of all mechanisms of action under the same regulatory category and the same requirements: from (theoretical) products that might in future even permanently alter the human genome at the germline level (potentially irreversible genetic modification for future generations) to products that only contain mRNA to temporarily express therapeutic proteins such as enzymes or tumor antigens, without altering the genome of cells.

Gene therapy definition in the United States

In the United States, gene therapy products are regulated by the Food and Drug Administration's (FDA's) Center for Biologics Evaluation and Research, with various definitions in published guidelines (Table 1), including the following definition:[13]

"Human gene therapy seeks to modify or manipulate the expression of a gene or to alter the biological properties of living cells for therapeutic use. Gene therapies can work by several mechanisms:

- Replacing a disease-causing gene with a healthy copy of the gene
- Inactivating a disease-causing gene that is not functioning properly
- Introducing a new or modified gene into the body to help treat a disease."

There are a variety of gene therapy product types referred to by FDA guidance, including plasmid DNA, viral and bacterial vectors, gene editing technology, and patient-derived cellular gene therapy. Of the many FDA guideline documents associated with gene therapy,[14] one important document is "Guidance for Human Somatic Cell Therapy and Gene Therapy," which was last updated in 1998. Notably but understandably given the publication date, there is no reference to products such as mRNA in this guidance. More recently, other FDA guidance documents, including "Human Gene Therapy for Rare Diseases," published in 2020, and a draft guidance "Manufacturing Changes and Comparability for Human Cellular and Gene Therapy Products," published in July 2023, state that the "FDA generally considers human gene therapy products to include all products that mediate their effects by transcription or translation of transferred genetic material, or by specifically altering host (human) genetic sequences. Some examples of gene therapy products include nucleic acids (e.g., plasmids, *in vitro* transcribed ribonucleic acid (RNA)), genetically modified microorganisms (e.g., viruses, bacteria, fungi), engineered site-specific nucleases used for human genome editing, and *ex vivo* genetically modified human cells," Unlike the current European definition, in the United States there is no distinction between recombinant or synthetic nucleic acids; both are considered gene therapies. All such products are thus regulated as biologics.

Table 2. Current proposals for a new gene therapy definition in Europe

EC proposal from April 26, 2023[2]	GTMP means a medicinal product, except vaccines, against infectious diseases, that contains or consists of:	
	(a) "a substance or a combination of substances intended to edit the host genome in a sequence-specific manner or that contain or consists of cells subjected to such modification; or	(b) a recombinant or synthetic nucleic acid used in or administered to human beings with a view to regulating, replacing or adding a genetic sequence that mediates its effect by transcription or translation of the transferred genetic materials or that contain or consists of cells subjected to these modifications"
EP amendment from April 10, 2024[12]	GTMP means a type 1 or type 2 medicinal product	
	"type 1 gene therapy medicinal product" means a medicinal product, that contains or consists of a substance or a combination of substances that edit the host genome in a sequence-specific manner or that contain or consists of cells subjected to such modification;	"type 2 gene therapy medicinal product" means a medicinal product, except vaccines against infectious diseases, that contains or consists of a recombinant or synthetic nucleic acid used in or administered to human beings with a view to regulating, replacing or adding a genetic sequence that mediates its effect by transcription or translation of the transferred genetic materials or that contain or consists of cells subjected to these modifications"

Another important medical research agency in the United States is the NIH, part of the US government's Department of Health and Human Services. The NIH publishes specific guidelines such as Research Involving Recombinant or Synthetic Nucleic Acid Molecules."[15] One aim of this guidance is to streamline oversight for clinical gene transfer protocols. In the 2019 update of this guidance, efforts were made to "streamline duplicative and burdensome oversight over gene therapy."[16] Despite these improvements, substantial challenges may remain for the appropriate management of clinical development of certain advanced therapy products such as mRNA, due to their continued classification as gene therapy, and some examples are discussed later in this paper. In an effort to harmonize terminology, organizations in the standardization and measurement space have put forward definitions, like the US National Institute of Standards and Technology (NIST), in their definition of gene therapy product, found in the NIST Bioeconomy Lexicon:[17] "Therapeutic product that mediates its effect by the expression of transferred genetic material(s), or by specifically altering a target genome," and an added Scope Note, "The expression referred to in a gene therapy product can occur via transcription or translation, and the target genome is not limited to human cells."

PUBLIC PERCEPTION OF GENE THERAPY MEDICINES

In recent years, gene therapy classification has had a greater chance of being misinterpreted by the public and thus may impact the adoption of potentially lifesaving medicines. Various factors influence the public's perception of gene therapies. The Edelman Trust Barometer 2024, a survey of over 32,000 respondents in 20 countries worldwide, reports high trust in the overall healthcare sector of 73%, but only 50% trust specifically in gene-based medicine.[18]

Healthcare professionals (HCPs) are trusted sources of medical information for patients and their families. The safety and long-term efficacy of gene therapy interventions are often cited as critical considerations raised by HCP and are associated with ethical considerations of potentially unintended genetic modifications.[19,20] A survey on the awareness of gene therapy medicines among HCPs conducted by IPSOS showed low familiarity with products, even at late-stage clinical development.[21] In general, studies among patients and the public indicate limited knowledge about cell and gene therapies, and that they would appreciate additional information on the topic.[22–24] It is notable that easily accessible information on gene therapy most often describes genomic integration as the main characteristic of gene therapy (refer to Table 3; top Google search definitions for "gene therapy"), which is not consistent with every category of product that falls into current gene therapy definitions in various parts of the world.

The COVID-19 pandemic further highlighted a need for greater understanding of gene therapies. Widespread internet and social media use facilitated the uncontrolled spread of disinformation and misconceptions about the first mRNA-based products to reach the market (i.e., SARS-CoV-2 vaccines). One of the most common public concerns was the incorrect association of mRNA vaccines with gene therapies able to integrate into and change the human genome.[30] Such misunderstandings, misconceptions, and lack of awareness may hinder public acceptance of new technologies and effective medicines. As vaccines are often indicated for the majority of the population, their safety and effectiveness are frequently a topic of public debate.[31–33] Notably, vaccine hesitancy was listed as one of the top 10 global health threats in 2019 by the World Health Organization,[34] which sadly contributed to a higher number of deaths from COVID-19 in the unvaccinated population.[35–37]

A survey conducted online in 2023 among a sample of 4,303 participants representative of the French mainland adult population reflects a nuanced view characterized by both

Table 3. Publicly available descriptions of gene therapy selection

Source	Gene therapy description
Medline Plus	"Gene therapy is a medical approach that treats or prevents disease by correcting the underlying genetic problem."[25] "Gene therapy works by altering the genetic code to recover the functions of critical proteins."[26]
FDA	"Human gene therapy seeks to modify or manipulate the expression of a gene or to alter the biological properties of living cells for therapeutic use. Gene therapy is a technique that modifies a person's genes to treat or cure disease."[13]
US National Human Genome Research Institute	"Gene therapy is a technique that uses a gene(s) to treat, prevent or cure a disease or medical disorder. Often, gene therapy works by adding new copies of a gene that is broken, or by replacing a defective or missing gene in a patient's cells with a healthy version of that gene."[27]
Mayo Clinic	"Gene therapy involves altering the genes inside your body's cells in an effort to treat or stop disease. Gene therapy is a technique that modifies a person's genes to treat or cure disease. Gene therapy replaces a faulty gene or adds a new gene in an attempt to cure disease or improve your body's ability to fight disease."[28]
UK National Health Service (NHS) England Genomics Education Program	"Gene therapy is a treatment that modifies the genome of specific cells to treat or prevent a genetic condition or disease."[29]

concerns about potential long-term side effects and optimism about the technology's promise for future medicine. However, 62% do not disagree that mRNA vaccines modify the DNA of the vaccinated person (42% do not know, and 20% agree).[38]

Overall, the public, whether educated or lay, seem to follow considerations that are often based on misinformation, perceptions, and poor understanding, with the "manipulation of the genome" being center stage. Efforts to facilitate and enable public understanding, including patients and healthcare providers, such as that brought forward by the US National Bleeding Disorders Foundation's Medical and Scientific Advisory Council (MASAC) or the European Patients Academy on Therapeutic Innovation (EUPATI), are important initiatives in this respect.[39,40]

ADDING THE GENOMIC MODIFICATION AS A DIMENSION TO A GENE THERAPY DEFINITION

Regulatory systems are designed to provide guidance and requirements for the clinical development and marketing authorization of medicinal products. For gene therapy medicines, since multiple products are subsumed under this definition (as discussed above), multiple levels of risk that the human genome is actually impacted are included. In this paper, we focus on risk as it relates to the modality's potential for genome modification. We do note that the identification of risk is multidimensional, and a product that integrates into the human genome, if adequately developed and understood, is not necessarily a high-risk product. Another obvious risk dimension, which is not a focus of this paper, is the risk inherent to the product's intended pharmacological mode of action (i.e., its therapeutic effect). We also stress that even if a medicinal product is considered to have inherent risk of any kind, appropriate risk assessment and mitigation strategies can mean that such a product still has an appropriate risk:benefit profile for relevant patients. For this paper's risk-based considerations, we propose reduction to the common denominator, which is whether or not the genome is altered. This is not only an important risk aspect but it is also central to public perception about what gene therapy does.

A variety of biological tools and vectors are used in the field of gene therapies, all of which differ mechanistically in how they interact with the genome (if at all), and how they deliver the genetic information contained in them (if any). These are mRNAs (for transient cytosolic translation into proteins), plasmids (no to low potential integration into the genome), adenoviral vectors and adeno-associated vectors (episomal persistence rather than genomic integration), lentiviral and retroviral vectors (integrating into the host genome), and genome editing tools (acting directly on the genome, using various tools, including ZFNs, TALENs and CRISPR-Cas9).

mRNA-based therapeutics can serve as a paradigm case for where a gene therapy is not providing therapy to the gene (the genome) but may be perceived as such due to classification. mRNAs are single-stranded nucleic acid molecules present in every cell after transcription from a DNA template. Under physiological conditions, mRNA, with the exception of a few mitochondrial transcripts, is produced in the nucleus, transported to the cytosol, and translated by ribosomes into a protein. The mRNA is then quickly metabolized. mRNA in the cytoplasm has a short half-life due to the abundance of RNAses in the environment or natural RNA decay mechanisms in the body and provides only a transient template for protein synthesis. mRNAs can be optimized for pharmacological use to result in reduced immunogenicity or increased expression of protein, together with an appropriate pharmaceutical formulation, and are generated by *in vitro* transcription delivered directly into the cytoplasm by lipid nanoparticles.[41] Current mRNA products may be considered not to impact the genome and have only a very transient pharmacological action after administration.

IMPLICATIONS OF BROAD DEFINITIONS

The definition and resulting classification of a medicinal product have numerous regulatory implications and consequences, many of

which are important and intended, but also some that are impactful and potentially overlooked. Due to significant differences in the underlying definition, the consequences for the same product may even vary by geographic region. Classification as a gene therapy results in various regulatory and practical implications for everyone involved: drug developers, regulatory authorities, HCPs, patients, and the general public.

When a product is classified as a gene therapy medicine, it may be subject to specific regulatory requirements tailored to its class, such as potential germline integration, shedding of the product, and the need for long-term follow-up proportional to the risk assessment, among other factors. Depending on the assessed risks, containment measures and specific protocols for the clinical application of gene therapy medicines may be mandated.

In the United States, using mRNA as an example, one consequence of mRNA products falling into the gene therapy classification is that clinical trial protocols are required to be assessed by both local institutional review boards (normal for any clinical trial protocol), and local institutional biosafety committees (IBCs; specifically required for research utilizing recombinant or synthetic nucleic acid molecules). IBCs assess biohazard and biological containment of investigational products, and they typically require dedicated application forms in which the applicant is required to answer many specific questions pertaining to gene therapy hazards and risks. The nature of such questions can also vary between IBCs at different clinical institutions. Often, the questions are not scientifically relevant for products like mRNA that provide their biological effect via translated proteins without ever entering a cell nucleus or modifying genes. Example questions include the following:

(1) Does the investigational product contain a "kill switch"?
(2) Will shedding of the investigational product occur at any time during the trial?
(3) Describe the derivation of the delivery vector system, including the source; give specifics.
(4) Is the investigational product replication incompetent?
(5) Describe the transgene or nucleic acid being delivered, its species source, any modifications, and the regulatory elements contained in the construct.
(6) Is there a risk of vertical transmission to offspring?
(7) Describe the gene transfer agent delivery method.

While the answers to such questions may ultimately be "no," "not applicable," or "none," a high degree of specialist knowledge is required to accurately complete the applications. This can result in delays to the clinical trial start-up process since multiple players have to be involved along the way.

Similar issues can be experienced during other types of local oversight review, for example, by pharmacy departments or hazardous drugs oversight committees. However, challenges of this nature are not unique to the United States. When products are classified as hazardous or potentially hazardous by an institution due to their inclusion in gene therapy definitions, additional controls are sometimes required in the dose preparation and administration process, such as the use of closed system drug-transfer devices (CSTDs). CSTDs are devices that mechanically prevent the escape of hazardous drug or vapor concentrations outside the system. Apart from the potential for disproportionality of having to use these measures where there is scientifically no risk of shedding, their use may also have practical adverse implications—for example, the use of CSTDs may impact the stability of mRNA products due to shear forces.

By a wide definition of gene therapy, despite very different mechanisms of action and risk of the respective products falling under it, mitigation strategies may be required by institutions that are not relevant to the true hazard profile of the respective product. This could prevent sponsors from running clinical trials at some institutions, which may disadvantage patients who consequently might not gain access to new technology and treatments as part of clinical trials. These real-life examples illustrate the impact of definitions and classifications on the development of new therapeutic products and the increasing need for more educational efforts directed at healthcare providers, clinical monitors, and patients to ensure appropriate understanding and use of gene therapies. This is especially true for products that currently fall under the gene therapy definition but provide their biological effect without making any changes to the human genome.

DISCUSSION

Finding a definition for a complex and heterogeneous entity such as gene therapies is challenging. A broad definition might encompass products that do not necessarily meet all regulatory criteria, complicating compliance, and potentially obscuring critical risk assessments. A too-broad definition may also be confusing to or misleading for stakeholders, including patients, HCPs, and the public. However, a very narrow definition, which may be perfectly suitable at the time it was developed, may result in the exclusion of potentially relevant products in the future. For gene therapy medicines, the inherent concern is causing long-term or permanent changes to the genome of cells. If this was included as a demarcation factor, then a definition could consist of several dimensions:

(1) Molecular modality (nucleic acids): many nucleic acids do not alter the human genome. Furthermore, future non-nucleic acid modalities (e.g., nuclease proteins) might interfere with the genome but would not be categorized as gene therapy. Is modality a scientifically valid criterion for classification?
(2) Source (biotechnological or synthetic): the impact on the genome might be the same, regardless of a given nucleic acid's origin. How pertinent is the source as a classification criterion?
(3) Mechanics: mechanics involves regulating, replacing, or adding a genetic sequence that exerts its effects through transcription or translation of the introduced genetic materials. Currently, this broad criterion encompasses a wide range of products, including those functioning through the translation of

mRNA, which does not involve genetic integration. Should this dimension be refined for clearer classification?

The EC's proposed subcategory of GTMP definition ("a substance or combination of substances intended to edit the host genome in a sequence-specific manner or that contains or consists of cells subjected to such modifications") explicitly addresses genomic impact. The broadness of the secondary subcategory, which includes any use of recombinant or synthetic nucleic acids in humans, is inclusive (a recombinant or synthetic nucleic acid used in or administered to human beings with a view to regulating, replacing, or adding a genetic sequence that mediates its effect by transcription or translation of the transferred genetic materials or that contain or consist of cells subjected to these modifications). A more targeted definition might specify GTMPs as medicinal products that alter the genome sequence. This approach would exclude therapies, like non-gene-modifying mRNA treatments, that function solely through translation without altering the genome sequence. Could a categorization of nucleic acid and other products according to their potential to modify the genome help to regulate these products in a more differentiated and risk-based manner?

Redefining gene therapy leads to two distinct scenarios for non-gene-editing therapeutics—for example, those mRNA therapeutics that do not act on the human genome.

(1) Inclusion of medicines not impacting the human genome in the gene therapy definition:

Exemplified by mRNA-based therapeutics; including all mRNA-based therapeutics in the gene therapy definition would ensure that any future variation of mRNA product potentially impacting the genome are covered, making relevant regulatory requirements applicable. This inclusion requires sponsors to extensively justify non-applicable elements in regulatory submissions (e.g., dossiers for a Marketing Authorization Application). Patients may receive information that might lead them to believe they are receiving a therapy with gene-altering effects, even if that is not the case (i.e., for most mRNA products currently in development). They may wonder why reference is made to gene therapy but receive explanations that their genes are not impacted, which may sound contradictory to them and may impact their understanding and trust of information.

However, developers would gain access to supporting benefits provided in Europe specifically for ATMPs only. For example, ATMP developers are supported by regulators with the so-called ATMP certification procedure. This certification procedure is a unique scientific assessment conducted prior to Marketing Authorization and provides sponsors with an important benchmark of their product`s regulatory status.

(2) Exclusion of medicines not impacting the human genome from the gene therapy definition:

Excluding those therapeutics from the gene therapy definition would align their regulatory status with other medicinal products (note again, that here we are considering only the isolated risk of genome sequence alterations and that there are other risk dimensions relevant to the encoded protein which may still apply). While sponsors need to comply with relevant general regulatory requirements, the drug development and approval process may more accurately reflect the actual character of the product. The risk of patients misunderstanding the mechanism of action and fearing alteration of their genome would be reduced since their therapy would not be defined as gene therapy. Sponsors, in turn, would not have access to specific incentives for ATMPs, unless such products (non-genome-impacting nucleic acids) were to become their own ATMP subclass.

CONCLUSION

Specific and carefully considered regulatory definitions for new healthcare technologies including medicinal products are necessary to everyone in society, to support continued development and approval and their use by all those who could benefit from them. The legislative process of defining a medicinal product class would ideally include an assessment of whether misperception could occur and how to avoid it. With the EC's and EP's revision of the definition of gene therapy medicine, there is an opportunity to reflect and consider how this definition could more consciously be based on mechanics. We acknowledge it is rarely possible to completely future-proof definitions involving complex biological interventions; however, we believe that with novel technologies arriving and a major definition being opened up in the EU, it is a good time to reflect on how to embrace the progress of new technologies that have emerged over the past decade and will continue to emerge in the future with a balanced definition taking account of risk—in this case of impacting the human genome—and which strikes the appropriate balance between regulation and requirements on one side and a correct perception in the medical and patient community on the other side. In addition, international efforts (e.g., by the International Organization for Standardization) could in the future play a role in helping harmonize standards for terminology for gene therapy.[42,43]

It is a common dilemma to develop a definition of a given entity. If it is too wide, virtually all products are included, which may not be the intention. If it is too narrow, it may result in problems should future products not thought of when the definition was written fall outside the definition but scientifically should be included, or if current products would with future research subsequently fall under it but not be included. We submit that a mechanics-related definition for GTMPs could be a viable approach. Legislators, possibly supported by the scientific community, will have to discuss the pros and cons of such an approach, including the question: should non-genome-modifying nucleic acid-based therapies have their own category, in Europe under the ATMP umbrella, and be regulated by specific scientific guidelines rather than by a priori categorization?

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