EFPIA Position Paper on Gene Therapy Medicinal Products (GTMP) Definition

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Introduction

The European Federation of Pharmaceutical Industries and Associations (EFPIA) acknowledges the importance of defining Gene Therapy (GT) Medicinal Products (GTMP) within the framework of pharmaceutical legislation revision, to ensure clarity and consistency in the development and regulation of these innovative therapies. In response to the proposed definition of a GTMP by the European Commission (EC), EFPIA offers the following principles for consideration.

Proposed Definition

EFPIA generally supports the proposed revision to the definition of GTMP as outlined in the 2023 proposal for EC Directive under Article 4 (point 29) and presented in Table 1 (March 2024 ENVI compromise amendments). EFPIA welcomes the definition that encompasses substances or combinations of substances intended for sequence-specific genome editing and clarifies inclusion of both recombinant and synthetic nucleic acids used to regulate, replace, or add genetic sequences if acting by its transcription or translation. Excluding vaccines against infectious diseases from this definition is also supported. However, EFPIA recommends to clearly distinguish between genetically modified cells that are GTMP from those that are currently defined as somatic Cell Therapy and Tissue Engineered Products (as per EMA ATMP classification reflection paper 2015 EMA/CAT/600280/2010 rev.1), as both can now fall within the proposed GTMP definition.

Table 1: Current and proposed revision to the definition of a GTMP within the EU

Current GTMP definition per Directive 2009/120/EC (Section 2.1)	**Revised GTMP definition proposal per EU General Pharmaceutical legislation revision**
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;	'Gene therapy medicinal product' means a medicinal product, except vaccines against infectious diseases, that contains or consists of: (a) substance or a combination of substances intended to edit the host genome in a sequence-specific manner or that contains or consists of cells subjected to such modification or

(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.	(b) 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 contains or consists of cells subjected to these modifications.

EFPIA recognizes two main types of GT modalities introduced by the proposed definition, (a) gene editing and (b) gene transfer (see Table 2). The classification of gene transfer medicinal products is based on its therapeutic mode of action (effect mediated by transcription or translation of nucleic acids), regardless of manufacturing method. This approach provides clarity on a product that would fall under the scope of GTMP definition and is a good basis for further global harmonizations. EFPIA notes that the proposed definition does not differentiate between transient versus sustained effect, viral versus non-viral vectors, or *in vivo* versus *ex vivo GT*. It is noted that the proposed definition does not require that the therapeutic, prophylactic or diagnostic effect relates directly to the administered or edited nucleic acid sequence, and thus it does not differentiate GTMP from a product containing cells or tissues based on the "direct effect" or principal mode of action (see example in table 3).

Table 2: Type of GTMP according to the EU proposed definition

Type of GT	Materials	Mode Of Action
(a) Gene editing	***Substance or combination of substances*** (i.e., chemically synthesized and/or biological).	*Intended to* ***edit the host genome*** *in a sequence-specific manner or that* ***contains or consists of cells subjected to such modification.***
(b) Gene transfer	***Recombinant or synthetic nucleic acid.*** Independent of the vector (e.g., LNP, viral vector).	*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 contains or consists of cells subjected to these modifications.*

Considerations for specific cell therapies, mRNA and Oligonucleotide products within the definition of GTMPs

EFPIA underscores the importance to consider the mode of action and to not distinguish classification depending on how a product is manufactured. Table 3 illustrates the importance of considering the mode of action when assessing the classification of GTMP.

mRNA (excluding vaccines against infectious disease) utilized for expressing human or non-human proteins (e.g., chimeric antigen receptor (CAR), monoclonal antibody), or delivering gene editing substances *should* be considered GTMPs regardless of how they are generated.

The mode of action of oligonucleotides is not mediated by their transcription or translation. This is an important differentiator that excludes oligonucleotides used alone from the definition of a gene therapy. When combined with other substances in the view of performing gene editing or gene transfer, an oligonucleotide could be a component of the GTMP.

The primary mode of action is an important differentiator that can delineate genetically modified cells considered as GTMP vs those considered as somatic cell / tissue engineered products.

Table 3: Classification of mRNA, oligonucleotide product and Cell therapies depending on their mode of action

Type of nucleic acid	Discussion on mode of action (MOA) / Intended use	GTMP ?
mRNA delivered by a non-viral vector [Ref 1,2]		
mRNA against infectious disease	Encoding antigen to elicit an immune response- Vaccines against infectious diseases are explicitly excluded from the definition of a GTMP	No
mRNA coding for a specific protein	mRNA encoding for a gene (e.g., antibody, cytokine, chimeric protein, CAR), and that mediates its effect by translation or transcription of the mRNA would be classified as a GTMP (per the proposed definition (b)).	Yes
mRNA coding for gene editing substances (e.g., CRISPR/Cas, TALEN)	mRNA used for the purpose of gene editing would fall within the definition of GTMP (a).	Yes
Circular RNA (CircRNA), single-stranded RNA (ssRNA), self-amplifying mRNA (samRNA).	Modalities increasing the duration of expression of mRNA would mediate their effect by translation or transcription of the nucleic acid and would be classified as GTMP (b). Depending on the protein being expressed and its intended use, there may be situations where they may not be considered as GTMP (e.g., vaccines against infectious disease).	Maybe
Oligonucleotide delivered by a non-viral vector [Ref 3,4,5]		
Antisense Oligonucleotide (ASO)	ASOs act by splicing modulators or steric blockers (leading to inhibition or degradation of a mRNA) or gene expression inhibitor (e.g., RNase H induced degradation). Their effect is not mediated by transcription or translation of the nucleic acid, and thus does not qualify as GTMP.	No
RNA interference (e.g., siRNA, miRNA)	RNA interference acts by inhibiting or degrading mRNA. Their effect is not mediated by transcription or translation of the nucleic acid, and thus do not qualify as GTMP.	No
RNA editing (e.g., antisense RNA-guided adenosine deaminase acting on RNA (ADAR)-based programmable A-to-I editing)	RNA editing to enable correction of mutations or modulate gene expression. While it acts by editing a sequence in a specific manner, it does not directly edit the genome / DNA, and thus does not qualify as GTMP.	No
CpG oligonucleotide	CpG oligonucleotides act as immunostimulant to cells expressing TLR9. Their effect is not mediated by transcription or translation of the nucleic acid, and thus do not fall within the definition of GTMP.	No
Aptamers	Aptamers selectively bind to their target. Their effect is not mediated by transcription or translation of the nucleic acid, and thus do not qualify as GTMP.	No

Guide RNA (e.g., crRNA + tracrRNA, sgRNA)	gRNA used in combination with appropriate enzymes (e.g., CAS-9, TALEN) to edit nucleic acid sequences would form part of a product falling within the definition GTMP (a). In some cases, the transferred nucleic acids are transcribed or translated, and thus could also fall within definition GTMP (b).	Yes

Genetically modified cells [Ref 6]		
Cells genetically modified by gene editing or gene transfer	Genetically modified cells could be considered as GTMP in accordance to definition part (a) or (b). However, genetically modified cells (by gene editing or transfer) which modification has no direct relationship with the primary therapeutic effect of the product (e.g., to replace the damaged/dead cells, "genetic modifications limited to secondary roles") should be classified as somatic cell therapy or tissue engineered products as appropriate, even if some GTMP requirements may be relevant.	Maybe

***LNP**: Lipid Nano Particle; **siRNA**: small interfering RNA; **miRNA**: microRNA; **crRNA**: CRISPR RNA; **tracrRNA**: trans-activating crRNA; **sgRNA**: single guide RNA.; **TLR9:** Toll Like Receptor 9*
***CRISPR**: Clustered Regularly Interspaced Palindromic Repeats; **TALEN:** Transcription Activator Like Effector Nucleases*

Risk-Based Approach

EFPIA advocates for a risk-based approach in assessing GTMPs, as introduced to the legislation with the revision of Annex 1, part IV of Directive 2001/83/EC as amended by Directive 2009/120 EC. The evaluation of the effect duration and the integration status are important considerations for a risk-based approach and contribute to determining the extent of quality, non-clinical and clinical data to be generated in the Clinical Trial Application (CTA), or Marketing Authorization Application (MAA). EFPIA emphasizes the need to also consider other pertinent factors (e.g., the expressed sequence and its effects, vector, patient population) when determining the risk profile of a GTMP. EFPIA believes that such a risk profile cannot be properly addressed within a legal definition and would recommend managing them through appropriate regulatory guidelines.

Global Regulatory Impact

EFPIA acknowledges the global trend, as recognized by the World Health Organization (WHO), to include mRNA within the definition of a GTMP, and to exclude vaccines to prevent infectious disease (Table 4). Excluding mRNA from this classification would not align with such international standards and may have implications for regulatory harmonization and product naming conventions.

Table 4: World Health Organization definition of GTMP [Ref 6]

Gene therapy product:
"A medicinal product containing nucleic acids (for example, plasmids, messenger RNA (mRNA) or DNA) that are intended to regulate, repair, replace, add or delete a genetic sequence. The intended therapeutic effect is dependent upon the encoded gene used. Gene therapy products include those containing non-viral vectors (for example, lipid nanoparticles) or viral vectors that are used in vivo, as well as cells that have been modified by these types of vectors ex vivo. They may contain plasmids, mRNA or DNA, and may also include oncolytic viruses that are not genetically modified to express a transgene.

Within this definition, gene edited products are considered to be gene therapy products. However, vaccines intended to elicit an immune response to prevent infectious diseases (for example, mRNA, plasmid DNA or viral-vectored vaccines) are excluded from this definition and are not considered to be gene therapy products within the definition of an ATMP. It should be noted that the scope of what constitutes a gene therapy product may vary between regulatory authorities and, in some jurisdictions, might include prophylactic vaccines against infectious diseases".

Discussion

A medicinal product falling into the definition of GTMP would be classified as an ATMP. Such classification can be negatively perceived as it may lead to prolonged timelines for Clinical Trial Applications (CTA) and trigger higher review scrutiny for CTA and Marketing Authorization Application (MAA). On the other hand, it can also bring advantages, including a basis for a risk-based approach, a range of advisory services and incentives (e.g., adapted GMP framework and technical guidelines, Scientific advice and protocol assistance with adapted fees). As a consequence, it is important that the revision of the GTMP definition properly addresses the new modalities that have been recently developed, without negatively impacting products that have already been classified. The proposed definition improves the clarity on what should be considered a GTMP and widens the scope to include gene editing products and synthetic nucleic acids mediating its effect by its transcription or translation. Extension of definition to include synthetic nucleic acids is driven by consideration to mode of action and Table 3 illustrates the impacted products and the importance of applying the same classification as for recombinant mRNA to avoid a heterogeneous field.

Considerations related to the modalities intended to increase the duration of expression (e.g., CircRNA) or the lack of integration into the human genome (e.g., mRNA) are not considered sufficient to conclude whether or not nucleic acid based medicinal product should be considered a GTMP. Other factors (e.g., mode of action (MOA), primary MOA, effect of expressed sequence, intended use) needs to be properly considered. Exclusion from the GTMP definition based on duration of expression or lack of integration (e.g., mRNA technology) could lead to divergent classification of products that have similar effect or MOA but mediated through different technologies (e.g., CAR-T obtained from gene editing versus mRNA technologies). Furthermore, such exclusion would deviate from the current international trends, which do not exclude mRNA derived products from the GTMP definition.

While EFPIA generally supports the proposed definition, it introduces some ambiguity for certain genetically modified cells which could all fall into the new definition of GTMP (see table 3). In this context, EFPIA recommends that the GTMP definition clarifies the delineation with somatic cell therapies and tissue engineered products or address this point in appropriate guidance document. EFPIA would also like to stress the need to maintain transparent and accessible classification services, and to update guidance documents to better address risk-based approaches depending on the modality/technology used.

Conclusion

EFPIA supports the proposed definition of GTMP, which accounts for currently approved classifications and upcoming modalities under development. However, EFPIA anticipates ambiguity in

the classification of genetically modified cells that should be addressed in an amended GTMP definition and or appropriate classification guidance.

References

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