Reviewer Comments and Suggestions

Title: WHO Approach towards the development of a global regulatory framework for cell and gene therapy products (document WHO/BS/2022.2424)

Written comments proposing modifications to this Guideline MUST be received by **9 September 2022.**
Comments should be submitted electronically to the Responsible Officer: Dr. Richard Isbrucker at: isbruckerr@who.int

Reviewer(s) (Name, Organization, and contact details):	Katherine Donigan, Biotechnology Innovation Organization, kdonigan@bio.org

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Line No.	Original Text	Comment	Suggested Amendment	Internal Use Only
General / Overall comments on the document:				
BIO views the extensively revised document (WHO/BS/2022.2424)"WHO Approach Towards the Development of a Global Regulatory Framework for Cell and Gene Therapy Products" as a major milestone and will be the first global regulatory guidance on these innovative therapeutics. We would like to express our appreciation and support for this very important and thoughtful document. This paper sets out a risk-based approach for the proper regulatory oversight of ATMPs and HCTs. This paper also provides valuable terminology, which is important given the current global inconsistencies in nomenclature and definitions. We note the deletion of terms such as “Advanced Therapies (ATs)” and “cell and gene therapy products (CGTPs)” from the document and welcome the simplification of the terminology in the revision. As described in the paper, regulatory oversight should be commensurate with the risk posed by the product, which includes a wide spectrum of cell and gene therapeutic modalities. The extent of manipulation of cells and tissues is acknowledged, and some products will be in a “grey zone” where there may be debate about whether the manipulation can be considered minimal or substantial, thus we recommend that the guidance maintain clarity for when the therapeutic will be for heterologous use, so as to avoid ambiguity. The document emphasizes the potential of regulatory reliance mechanisms for certain National Regulatory Authorities (NRAs) to conduct reviews and make approval decisions where gaps in knowledge and regulatory capacity exist. However, additional details would be helpful to clarify how regulatory reliance mechanisms may address the challenges that are discussed. For example, it is unclear what qualifies an NRA as a “competent authority” or how to evaluate a regulatory authority’s maturity level, both of which will dictate the NRAs that are considered reference NRAs for relying countries and regions. Also, given the significant need for regulatory oversight and decision making in the post-approval setting, it would be helpful to more clearly understand how and if regulatory reliance mechanisms could also play a role to address those needs where a given NRA may not have the capacity and expertise to oversee post-marketing surveillance and to monitor long-term safety and efficacy. As the ATMP space continues to rapidly change, new issues that currently do not have a regulatory framework or relevant guidance will appear. It will be crucial for regulators to assess when new issues that need regulatory guidance arise and quickly provide guidance to ensure clear recommendations			

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and consistency. One current example would be a potential framework that allows for the administration of safe and efficacious yet out-of-specification (OOS) product. Given the critical importance of vein-to-vein time with cell therapy products, sponsors should work with regulators to ensure patients do not miss the therapeutic window for a last line of therapy.				
Abbreviations				
N/A	N/A	The abbreviation for critical quality attributes (CQAs) is missing. We recommend adding this abbreviation to this list.	We recommend adding the following to this list: "CQAs: critical quality attributes"	
1. Introduction				
96-97	Cells and tissues which have undergone minimal manipulation are often, but not necessarily, used to provide the same essential functions in the recipient as they do in the donor. These are defined here as human cells and tissues for medical use (HCTs).	This statement is significantly diverging from the commonly agreed definition that HCT fulfills the condition of minimal manipulation and homologous use as described in line 358. Recommend delete "but not necessarily" for the definition part, while it could be acknowledged in the later part that the risk-based approach should be used, and that risk related to minimally manipulated product for heterologous use are borderline between HCT and ATMP classification and may require customized framework. Not separating the criteria of homologous use and minimal manipulation. This is attempted under the section Classification of HCTs and ATMPs below line 351, but it remains unclear that such products must meet both conditions to be considered HCTs	BIO recommends the following text as replacement: We define human cells and tissues for medical use (HCTs) as meeting two basic criteria having undergone only minimal manipulation (if any) and exerting in the recipient the same essential functions as they do in the donor (homologous use).	
108-111	"Advanced therapy medicinal products (ATMPs) for human use are defined as cell and gene therapy products and tissue engineered products, which are produced not only from manipulated cells or tissues. ATMPs also include nucleic acids or suitable vectors like plasmids or viruses for either direct administration to a recipient or to isolated cells or tissues."	The way the sentence included in line 108-111 is presented could be understood as a definition. The difficulty to define "ATMP" is acknowledged, however it would be recommended to have definitions of HCT and ATMP included in the terminology. Furthermore, additional clarity of these definitions would be appreciated, as the second part of the sentence may not be sufficient to set conditions for being considered as an ATMP	We recommend the following editorial revision: "Advanced therapy medicinal products (ATMPs) for human use are defined as cell and gene therapy products and tissue engineered products~~, which are produced not only from manipulated cells or tissues~~. ATMPs are not exclusively produced from manipulated cells or tissues. ATMPs may also include nucleic acids or suitable vectors like plasmids or viruses for either direct	

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		(e.g., no reference on “amount of manipulation” or its use).	administration to a recipient or to isolated cells or tissues.”	
110-115	ATMPs also include nucleic acids or suitable vectors like plasmids or viruses for either direct administration to a recipient or to isolated cells or tissues (3,5). ATMP product types are highly diverse and can include expanded autologous (patient) cells, engineered organs, viral products, genetically modified cells and novel gene editing/edited products (6,7) (see Table 1). ATMPs can also be combined with medical devices, such as scaffolds or matrices, as an integral part of the product (combined ATMPs).	Recommend reordering the sentence to start with the fact that ATMP are highly diverse and then list the different modalities.	BIO recommends the following edit: ATMP product types are highly diverse and can include: - nucleic acids or suitable vectors like plasmids or viruses for either direct administration to a recipient or to isolated cells or tissues (3,5). - expanded autologous (patient) cells, engineered organs, viral products, genetically modified cells and novel gene editing/edited products (6,7) (see Table 1). ATMPs can also be combined with medical devices, such as scaffolds or matrices, as an integral part of the product (combined ATMPs).	
117-120	These products are emerging rapidly as potentially curative treatments that could transform the management of diseases such as thalassemia, sickle cell disease, hemophilia, spinal muscular atrophy, Leber´s congenital amaurosis and many other monogenic diseases (8).	The stated indications for ATMPs are all monogenic diseases, and the sentence concludes with “and many other monogenic diseases” but ATMPs are used for other diseases and conditions, besides monogenic disorders. These types of therapies are also being applied with curative intent in cancer, particularly hematological malignancies.	BIO recommends the following edit: These products are emerging rapidly as potentially curative treatments that could transform the management of diseases such as thalassemia, sickle cell disease, hemophilia, spinal muscular atrophy, Leber´s congenital amaurosis, certain cancers, and many other ~~monogenic~~ diseases	
140-141	The nonclinical testing of ATMPs can be challenging for many new indications and especially for orphan diseases	These challenges are not limited to new indications nor to rare/orphan diseases and are in fact inherent to the characteristics of the ATMP’s themselves.	BIO recommends the following edit: The nonclinical testing of ATMPs can be challenging. ~~for many new indications and especially for orphan diseases~~	
145-147	Thus, whether evaluating an allogeneic or xenogeneic product within an *in vivo* model, there are likely to be differences in responses between the animal and the human.	We recommend the following editorial revision.	BIO recommends the following edit: Thus, ~~whether evaluating an allogeneic or xenogeneic product within~~ when an allogenic or xenogenic product is evaluated in an *in vivo* model, there are likely to be differences	

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			in responses between the animal and the human.	
151-153	"Furthermore, for therapeutic products which utilize genome editing technology, their nonclinical testing requires the use of human cells to evaluate potential off-target effects.	We recommend the following editorial revision.	BIO recommends the following edit: Furthermore, ~~for therapeutic products which utilize genome editing technology, their nonclinical testing~~ the nonclinical testing of therapeutic products which utilize genome editing technologies requires the use of human cells to evaluate potential off-target effects.	
155-157	Clinical development of HCTs and ATMPs require special regulatory considerations. This may include accounting for the lack of adequately documented natural history data for rare diseases as well as the need to evaluate clinical safety and efficacy in very small patient populations. Furthermore, interpretation of efficacy from controlled clinical trials for some ATMPs may be difficult if there is no suitable comparator or if the improvement in the recipients is minimal in response to the treatment.	Conflating issues related to rare diseases and clinical development of HCTs and ATMPs, which target rare diseases in many cases.	BIO recommends the following edit: Clinical development of HCTs and ATMPs require special regulatory considerations. In addition to the manufacturing and clinical intricacies, these products are often investigated and being developed for treatment of rare diseases, which create additional considerations.: These considerations ~~this~~ may include accounting for the lack of adequately documented natural history data for rare diseases as well as the need to evaluate clinical safety and efficacy in very small patient populations. Furthermore, interpretation of efficacy from controlled clinical trials for some ATMPs may be difficult if there is no suitable comparator or if the improvement in the recipients is minimal in response to the treatment.	
168-171	It is important for authorities to be aware of the regulatory considerations, challenges and needs for adequate data support for these products and address them to assure the safety and efficacy of the treatments and avoid unnecessary delays in patient access.	We recommend the following editorial revision.	BIO recommends the following edit: It is important for authorities to be aware of the regulatory considerations, challenges and needs for adequate data support ~~for these products and address them to assure the safety and efficacy of the treatments and~~ assuring the safe and efficacious use of these treatments to avoid unnecessary delays in patient access.	

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173-175	Due, in part, to the varied nature of HCTs and ATMPs, it is not surprising that national or regional regulatory frameworks for oversight of these products have evolved somewhat differently around the world.	We recommend the following editorial revision.	BIO recommends the following edit: Due, in part, to the varied nature of HCTs and ATMPs, it is not surprising that ~~national or regional regulatory frameworks for oversight of these products have evolved somewhat differently~~ different national or regional frameworks have evolved for oversight of these products around the world.	
182-184	The key elements of an effective regulatory framework include: a clear definition of the categories that constitute HCTs and ATMPs,	BIO supports this statement and emphasizes the need to propose clear definitions of HCT and ATMP in the terminology.		
186	• aligning the level of regulatory control based to the different risk categories.	We recommend the following editorial revision.	BIO recommends the following edit: • aligning the level of regulatory control based ~~to~~ on the different risk categories.	
210-211	As NRAs gain experience and expertise, they can review more complex applications in alignment with their increased capacity and resources.	While we strongly support the addition of encouragement to practice reliance, we would suggest rewording sentence 210 to not discourage reliance pathways once experience has been gained but rather to continue reliance pathways and further contribute to work sharing approaches where applicable.		
2. Purpose				
3. Terminology				
278	Autologous: referring to a patient's own cells	Definition would benefit from clarification and harmonization with definitions of allogeneic and xenogeneic	BIO recommends the following edit: Autologous: referring to ~~a patient's own~~ cells taken from and used to treat a medical condition in the same person.	
292-296	Gene editing: The use of guide RNA, which targets a nuclease enzyme to the site in the genome to be cleaved. The most commonly used approaches currently are based on zinc finger nucleases (ZFN), transcription activator-like effector nucleases (TALEN) or clustered regularly interspersed short	Not all gene editing technologies use guide RNA.	BIO recommends the following edit: Gene editing: ~~The~~ Use of ~~guide RNA, which targets~~ a nuclease enzyme to ~~the site in the genome to be~~ cleave at a specific site in the genome~~d~~ may use guide RNA to target the nuclease to the genome cleavage site. The most commonly used approaches currently are based on zinc finger nucleases (ZFN),	

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	palindromic repeats (CRISPR) together with Cas9-endonuclease (CRISPR Cas9) (29).		transcription activator-like effector nucleases (TALEN) or clustered regularly interspersed short palindromic repeats (CRISPR) together with Cas9-endonuclease (CRISPR Cas9) (29).	
343	N/A	As discussed at multiple points in this document, the term "regulatory reliance" is a critical concept to support global access to safe and effective cell and gene therapy products. Although there is an existing definition developed by WHO, it is not listed in the terminology section. The WHO definition for "regulatory reliance" should be included in this section.	We recommend adding the following definition: "Regulatory reliance: Act whereby a regulatory authority in one jurisdiction may take into account/give significant weight to work performed by another regulator."	
N/A	N/A	The abbreviation "ATMP" is used throughout the document and is defined on lines 108 to 111. However, for ease of reference, we recommend that the definition of ATMP also be provided in the terminology section.	We recommend adding the following definition: "ATMPs: Refer to cell and gene therapy products and tissue engineered products, which are produced not only from manipulated cells or tissues."	
N/A	N/A	The term "competent authority" is mentioned throughout the document but is not clearly defined in the terminology section. A definition for competent authority should be included in this section.	We recommend defining the term "competent authority" in the terminology section of this document.	
4. Classification of HCTs and ATMPs				
353-359	Minimal manipulation and homologous use are the concepts that have been embraced by multiple regulatory authorities for making the distinction between HCTs and ATMPs (see clarifications of the definitions in the Terminology section) (2,3,18,20,30). For the purposes of this document, cells and tissues that are harvested and undergo only minimal manipulation (simple processing such as washing or sizing), and which are used to achieve the same	BIO supports this paragraph. The introduction and definitions of the document should be aligned to this text (i.e., including minimal manipulation and homologous use).		

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	essential function/s in the recipient as in the donor (homologous use) are defined as human cells and tissues for medical use or 'HCT'.			
364-365	"When the intention is homologous use of the HCTs, product specific clinical studies are usually not required."	We recommend the following editorial revision.	BIO recommends the following edit: "When the intention is homologous use of the HCTs, product-specific clinical studies are usually not required."	
377-383	In addition, the regulations for ATMPs based on replicating viral vectors and oncolytic viruses should include separate considerations to address the potential for their release into the environment and induction of viral disease in, or transmission to, third parties. Strategies need to be in place to mitigate the risk of such an occurrence; therefore, products consisting of, or containing, replicating viral vectors should be subject to an environmental assessment to evaluate the potential adverse effects that could occur if the viral vector is released into the environment.	Clarification of the scope of this statement would be helpful (i.e., Marketing Authorization vs development phases). We would recommend that: - At the stage of a clinical trial application (CTA), a GMO risk assessment should not be required if the GMO-ATMP is not able to survive and replicate outside of the intended clinical trial recipient, or if the transgene sequence is not harmful. - Where GMO risk assessment exemptions do not apply, promote the use of a "universal" or at least, harmonised principles. - If required for registration, and if policy frameworks allow, an approved GMO risk assessment performed in reference countries/regions should be recognized.		
403-405	Ideally, CQAs would correlate with clinical outcome, although this is not always possible or feasible as ATMPs are most likely to have multiple CQAs.	The difficulty to identify CQAs is not limited to their multiplicity but also due to the lack of appropriate predictive models and many other factors. It would be recommended to delete the last part of the sentence.	BIO recommends the following edit: Ideally, CQAs would correlate with clinical outcome, although this is not always possible or feasible ~~as ATMPs are most likely to have multiple CQAs~~.	
409-411	For example, Lentivirus vector-transduced CD34+ cells that are systemically administered to correct a genetic defect could exert their effect for years through the	We recommend the following editorial revision.	BIO recommends the following edit: For example, ~~Lentivirus~~ lentivirus vector-transduced CD34+ cells that are systemically administered to correct a genetic defect could	

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	integrated presence of the vector in cells.		exert their effect for years through the integrated presence of the vector in cells.	
409-414	For example, Lentivirus vector-transduced CD34+ cells that are systemically administered to correct a genetic defect could exert their effect for years through the integrated presence of the vector in cells. Thus, the risk of insertional mutagenesis should be addressed in non-clinical and clinical studies and the safety surveillance monitoring systems that allow longer term follow-up of all treated patients should be in place to identify any emerging serious adverse events, including the development of malignancy (31).	The sentence could be misleading or understood as persistence of the vector is responsible for insertional mutagenesis; while it is probably a contributing factor, the vector characteristics and tropism to certain insertion sites could also contribute and thus may not be limited to persistence of the vector.		
5. Regulatory expectations for HCTs and ATMPs				
449-450	In addition, the facilities and establishments dedicated to the procurement and processing of HCTs may also require approval/licensing by competent authorities.	We believe it's valuable to acknowledge that patient sample collection centers also require oversight. It may be helpful to mention some examples of the types of site certifications that can be relevant. In this case, FACT and/or JACIE certifications may be appropriate.	BIO recommends the following edit: In addition, the facilities… by competent authorities. Examples that may be appropriate include FACT and JACIE.	
457-460	For those countries developing regulatory frameworks for HCTs and ATMPs, it is strongly recommended to ensure the regulations are aligned with any other relevant regulations that may already be established in the jurisdiction, such as those for medical devices.	The example of medical device regulation is confusing as it could be understood as a recommendation to align ATMP regulation to MD regulation, or to use medical devices regulation where available. It would be recommended to delete the last part of the sentence or clarify the intent of that example to avoid misinterpretation.	BIO recommends the following edit: For those countries developing regulatory frameworks for HCTs and ATMPs, it is strongly recommended to ensure the regulations are aligned with any other relevant regulations that may already be established in the jurisdiction, ~~such as those for medical devices.~~	
6. A risk-based approach for the regulatory oversight of HCTs and ATMPs				
500-502	However, there remains other risks associated with gene therapy products, including replication competent virus contaminants, undesired immunogenicity and	We recommend the following editorial revision.	BIO recommends the following edit: However, there ~~remains~~ remain other risks associated with gene therapy products, including replication competent virus contaminants, undesired immunogenicity and	

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	insertional mutagenesis leading to tumourigenicity.		insertional mutagenesis leading to tumourigenicity.	
525-539	ATMPs require the same risk-based approach as HCTs to prevent the transmission of infectious diseases and the mitigation of any other potential risks which may be inherent in the product. In addition, ATMPs require compliance with other key regulatory practices including GMP…GLP…	While the GxP descriptions for ATMP are fully supported, there is no reference to any Quality or laboratory standard for HCT which may suggest that no standard needs to be followed for HCT. Similar high-level recommendations could be included such as recommendation on the collection and manipulation of biospecimens.		
533-536	Good Laboratory Practices (GLP) are used where possible in safety and other non-clinical studies used to generate pharmacodynamic (PD), pharmacokinetic (PK), biodistribution and safety data for the products to ensure the risks are understood and mitigated before use in humans;	GLP is required for non-clinical safety studies.	BIO recommends the following edit: Good Laboratory Practices (GLP) are used where possible in ~~safety and other~~ non-clinical safety studies used to generate pharmacodynamic (PD), pharmacokinetic (PK), biodistribution and safety data for the products to ensure the risks are understood and mitigated before use in humans;	
7. Considerations in the development of a regulatory framework				
550-559	The diversity of HCTs and ATMPs may require tailoring of the regulatory framework to adapt to the range of products that a country may authorize for use within its jurisdiction.	The first section mainly refers to HCT although the first sentence starts wider and also includes ATMP. For clarity purposes, it may be useful to skip a line after the first sentence to mark the different section and make clear that the following text is for HCT only.		
556-557	It also is important to ensure that mechanisms are in place for both ethical and inspectional oversight and so the products can be traced and recalled if necessary.	Minor grammatical error that may impact clarity as ethical and inspectional oversight is not directly linked to traceability.	BIO recommends the following edit: It also is important to ensure that mechanisms are in place for both ethical and inspectional oversight and ~~so~~ that the products can be traced and recalled if necessary.	
8. Collaboration and strengthening regulatory capacities for the oversight of HCTs and ATMPs				
581-588	Depending on the maturity level of the regulatory authority and its expertise and available resources, it may benefit from collaborating with a more experienced regulatory authority. WHO encourages regulatory cooperation and reliance	BIO supports this section advocating for reliance. The paragraph would further benefit in promoting recognition of classification published by “mature regulatory authorities” (e.g., classification performed by EMA CAT). Transparent communication of decisions would also foster collaboration and knowledge sharing.		

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	between authorities and other entities that have a role in the oversight of HCTs and ATMPs. Existing opportunities for joint reviews and inspections, agency visits, collaboration for review of products for rare/ultrarare diseases, regulatory actions based on reliance etc. could be further expanded. Sharing of knowledge, expertise, and experience is crucial for strengthening global regulatory capacity for oversight of HCTs and ATMPs in all regions of the world.	Mentioning reliance approaches across the lifecycle of products would also be an important aspect to highlight.		
9. Conclusion and next steps				
Acknowledgements, References, Appendix 1				
Table 1				
Figure 1				