Reviewer Comments and suggestions

Title: WHO considerations on Regulatory Convergence of Cell and Gene Therapy Products

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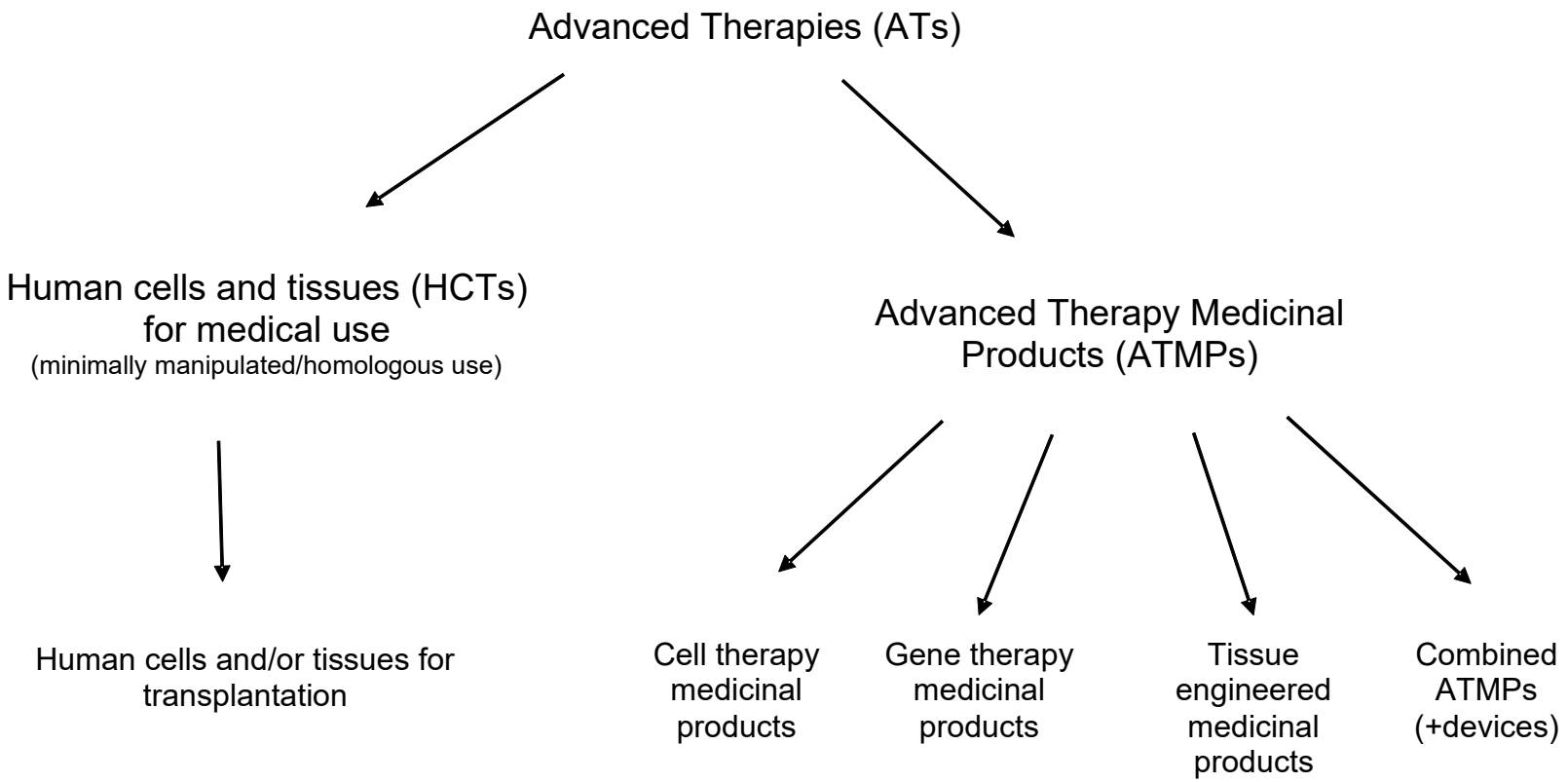
(Table is expandable)

General comment(s):
In general, we believe that WHO has achieved the appropriate balance in providing key principles for the "state of the art", without being overly prescriptive/too detailed, however, we have the following general comments: • We agree with the importance of developing regulatory requirements for CGTPs based on sound science and risk-based principles, and with the importance and need for regulatory convergence and harmonization in order to ensure safe and efficacious cell and gene therapy products are accessible in a timely manner globally. Encouraging NRAs, where possible, to adopt the scientific principles in guidelines from leading stringent regulators rather than developing their own national guidance will help build a path towards harmonisation (see line edits 295-297). • In general, we agree with the high-level approach WHO is taking in this paper, especially in light of the rapidly evolving scientific and regulatory environment of CGTPs, where too much detail would result in approaches being outdated very quickly. However, while collaboration of regulatory bodies is an important component, WHO should consider including statements for regulatory authorities to apply mutual recognition of GMP inspections of more experienced regulatory bodies. This is especially true in the near and mid-term, as it is expected to take some time for expertise to be gained. • We also urge regulatory bodies to ensure there is a mechanism for applicant-authority dialogue across the product lifecycle in place, as this is another key component in ensuring understanding for both parties. This should not mandate face-to-face meetings, however. • One area that could be considered for future guidelines is to discuss options for waivers considering the adverse impact of duplicative import/export release testing for ATMPs. This testing by NRAs adds no value where assurance exists of the company's control system. Considering the small batches involved for these products supplies for clinical trials must be prioritised over supplying samples for redundant testing. We appreciate the time WHO has taken in drafting this document, and it could be further strengthened by grouping together some of categories of definitions and terminology. Currently these can be found throughout the document, which distracts from other concepts and ideas being discussed. We suggest that these be grouped together at the start of the document, which will make for a more concise document. We understand further examples are to be provided in subsequent documents, but feel it is important to more strongly highlight the above points herein.

The draft "WHO considerations on Regulatory Convergence of Cell and Gene Therapy Products" is a major milestone to drive global convergence on cell and gene therapy. We would like to express our appreciation and support for this very important document. The proposed classification delineating ATMPs and HCTs under the umbrella of CGTPs is an important concept that would benefit in being presented early in the document. While it is acknowledged that the proposed terms were carefully selected, we would propose the following terms and classification:



The reasons for the proposition are as follows:

- Advanced Therapies: the use of CGTPs maintains ambiguity on the possibility that both Cell therapy and Gene therapy products could be considered as "non-medicinal products". While it may be possible for some CT under certain conditions, it is not anticipated that it is possible for GT. The use of "Advanced" could nicely describe the intended class of products and exclude others (e.g., blood products for transfusion).
- Medicinal products: it would be helpful to consistently refer to Cell therapy MP or Gene therapy MP across the document to avoid

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misunderstanding of the type of products being covered (i.e., the term "products" alone can be understood as including both MP and "products for medical use"). Consequently, there may be a need to align the terminology used in the document to clearly refer to medicinal products (e.g., CTMP).

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N/A	General comment – traceability	BIO believes that the traceability of the cells or tissues from the donor to the recipient(s) and from recipient(s) to donor(s) (bidirectional) should be ensured.	BIO recommends mentioning this in the white paper.
N/A	General comment – acceptance criteria	Generally, there is limited material available for cell and gene therapy products and acceptance criteria may be wide due to limited data or lack of correlation of in vitro data with clinical efficacy.	BIO recommends mentioning the setting of acceptance criteria in the white paper.
73-75	These cell and gene therapy products (CGTPs) (1) encompass a remarkably broad range of complexity, ranging from unprocessed skin grafts (relatively simple) to gene therapies (highly complex).	BIO supports the statement about the broad range of complexity. There is also a wide range of complexity of gene therapy medicinal products: from less complex in vivo GT modalities like plasmid DNA to more complex ex vivo GT modalities like autologous CAR-T products. An important proposal in this paper is that the scope includes both ATMPs *and* HCTs. BIO suggests providing a clear statement of the intended scope in the introduction (otherwise, does not appear until line 267). BIO also suggests considering the nomenclature "Advanced Therapies" to include both HCT and ATMP. (CGTP may currently be perceived as equivalent to ATMP.)	These ~~cell and gene therapy products (CGTPs)~~ advanced therapies encompass a remarkably broad range of complexity, ranging from unprocessed skin grafts (relatively simple) to highly complex gene therapies ~~(highly complex)~~, and include HCTs and advanced therapy medicinal products (ATMPs)."
86-89	They also are emerging rapidly as potentially curative therapies that could		BIO suggests adding cancer indications as ATMPs have led to curative outcomes in

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	transform the management of diseases like thalassemia, sickle cell disease, hemophilia, spinal muscular atrophy (SMA), Lebers congenital amaurosis (LCA) and many other inherited diseases (7).		Hematological malignancies (e.g. DLBCL, Multiple Myeloma).
104-108	Furthermore, for therapeutic products that utilize genome editing technology, non-clinical testing to evaluate off-target effects generally requires use of human cells. Manufacturing of ATMPs can be highly complex and require very specialized facilities and techniques to allow product processing and formulation *(10)*. That is the case especially for genetically modified cells and directly administered gene therapy products *(11)*.	It is sometimes difficult to identify appropriate animal species due to multiple receptor ligand interactions for cell-based therapies. Regarding complex manufacturing for development or commercializing for small patient populations, there are often bottle-neck in the manufacturing process due to availability of starting material for cell and gene therapy products.	BIO suggests the following edit: Furthermore, for therapeutic products that utilize genome editing technology, non-clinical testing to evaluate off-target effects generally requires use of human cells. Regardless of species, the mechanism of action is often multi-faceted and complex, and this complexity further complicates the choice of an animal model. Manufacturing of ATMPs can be highly complex and require very specialized facilities and techniques to allow product processing and formulation That is case especially for genetically modified cells and directly administered gene therapy products. These manufacturing complexities are amplified when the patient population is small, as is often the case for ATMPs.
108-111	Clinical development may present a variety of challenges including the lack of adequately documented natural history for rare diseases as well as the need to evaluate clinical safety and efficacy in very small patient populations.	BIO suggests to add “durability” since many gene therapies are intended to be curative and, therefore, the duration of patient response needs to be monitored.	BIO recommends the following edit: “...evaluate clinical safety and efficacy and durability in very small patient populations
123-125	The regulatory framework should be based on sound scientific and ethical principles and comprehensive evaluation of risks vs	CGTPs is a subcategory of advanced therapies in many countries, e.g. US, EU, Japan (advanced therapies defined as	BIO recommends the following edit: The regulatory framework should be based on sound scientific and ethical principles and

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	benefits for the different categories of CGTPs	regenerative medical products), Canada.	comprehensive evaluation of risks vs benefits for the different categories of ~~CGTPs~~ ATMPs.
133-138	As high-income countries work towards further regulatory convergence for these products, it is important to ensure that regulators in low- and middle-income countries (LMICs) are familiar with the scientific principles and regulatory issues for CGTPs also. Important factors include understanding of the scope (breadth and the nature of HCTs and ATMPs), risks and the key regulatory concepts relevant to ensuring that the more complex products are shown to be safe and effective prior to their widespread deployment. The importance of post-market	Convergence should not be limited to high income countries but may have different priorities. It would be recommended to promote convergence of technical aspects for all countries, while their applications/implementations should account for the countries' situation.	BIO recommends the WHO promote convergence of technical and practical aspects (e.g., GMP, in-country testing, qualification of SM/RM, comparability, stability) and participation of all countries in these discussions.
145-147	However, there potentially are high risks associated also with the gene therapy products, spanning from replicating virus contaminants to immunogenicity and tumourigenicity.	BIO recommends rephrasing as replication competent viruses may not always be related to contamination (e.g., recombination event).	BIO recommends the following edit: … spanning from ~~replicating~~ virus replication ~~contaminants~~ to immunogenicity and tumourigenicity.
147-149	Proper analytical testing and pre-clinical / clinical studies are required to identify and mitigate as many of the risks as possible to ensure patient safety.	BIO believes this addition would complement and explain the sentence on lines 153-155: “Similarly, raising awareness of the challenges, including manufacturing challenges, is critical to avoid unnecessary delays in access to these products.” The	BIO recommends the following addition: Proper analytical testing and pre-clinical / clinical studies are required to identify and mitigate as many of the risks as possible to ensure patient safety. Often, for complex

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		point of adding the above-recommended sentence is that Agencies should not just highlight the issues, they should provide clear guidance as well to avoid the issues. That seems an important concept for authorities in charge of putting new regulatory frameworks in place for cell and gene therapies.	cell and gene therapy products, manufacturing development is rate limiting to bring these innovative products to patients. It is critical for CGTPs regulatory frameworks to provide sufficient guidance on manufacturing regulatory requirements to avoid significant delays in the development of these products.
152-153	Preparing regulatory authorities in LMICs to assess the benefits and risks of such ATMPs is critical to avoid unnecessary risks to patients who receive them.	Timely access is one of the benefits.	BIO suggests the following edit: Preparing regulatory authorities in LMICs to assess the benefits and risks of such ATMPs is critical to provide timely access to these products and to avoid unnecessary risks to patients who receive them.
153-155	Similarly, raising awareness of the challenges, including manufacturing challenges, is critical to avoid unnecessary delays in access to these products.	Some countries may place the requirements for conventional product (e.g. in-country testing, pharmacopeia,etc) to ATMP without considering the specificity of ATMP, this may cause significant delays in access to these innovative treatment.	BIO suggests the following edit: Similarly, raising awareness of the challenges specific to ATMP, including manufacturing challenges, is critical to avoid unnecessary country-specific requirements and delays in access to these products.
167	Need for convergence on minimum global standards for ATMP quality	BIO recommends to promote technical convergence rather than "minimum standards".	BIO recommends the following edit: Need for convergence on ~~minimum~~ global standards for ATMP quality
172-173	areas covered could include definitions, quality attributes, standards, and clinical development pathways		BIO suggests the following edit: areas covered could include definitions, quality attributes, standards, nonclinical and clinical development pathways
180-182	Clearly describe what the CGTPs are, describe how the subsets of HCTs and ATMPs are defined from this larger class,	BIO agrees with this statement and suggests considering the need to provide detailed examples of what constitutes	BIO recommends the following edit: "...definitions of key terminology relevant in this area, including details of what is meant

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	and provide definitions of key terminology relevant in this area.	"substantial manipulation" since this has not been aligned internationally to date.	by minimal and substantial manipulation"
180-182	Clearly describe what the CGTPs are, describe how the subsets of HCTs and ATMPs are defined from this larger class, and provide definitions of key terminology relevant in this area	Since HCTs are not considered CGTs, this sentence should be rephrased.	Clearly describe what the ~~CGTPs~~ ATMPs are, describe how the subsets are defined from this larger class, and provide definitions of key terminology relevant in this area.
190-193	Provide the key elements of a regulatory framework that supports the safety and effectiveness of CGTPs including suggested regulatory controls for different risk categories of products covering key elements for adequate oversight spanning the entire product lifecycle from the investigational phase through post-market surveillance;	BIO supports the recommendation, but it should also include Quality. .	BIO recommends the following edit: Provide the key elements of a regulatory framework that supports the quality, safety and effectiveness of CGTPs including suggested regulatory controls for different risk categories of products covering key elements for adequate oversight spanning the entire product lifecycle from the investigational phase through post-market surveillance;
190 -193	Provide the key elements of a regulatory framework that supports the safety and effectiveness of CGTPs including suggested regulatory controls for different risk categories of products covering key elements for adequate oversight spanning the entire product lifecycle from the investigational phase through post-market surveillance;	This document mainly focuses on the regulatory framework as it relates to the safety and effectiveness of the CGTPs for patients. However, the regulatory framework for the biosafety/environmental impact of genetically modified products varies even more widely across the globe. This poses a significant hindrance to global access of CGTPs and should also be addressed when considering regulatory convergence.	BIO suggests adding a separate bullet to address the existence and need for convergence on the regulatory framework that supports the biosafety and environmental impact of CGTPs.
195-197	Develop a proposal for how the regulatory framework for the risk categories could be	We commend WHO for encouraging regulatory reliance for ATMPs and look	None

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	implemented in countries with different levels of regulatory maturity. Examples will be provided in a subsequent document.	forward to the subsequent document expanding on the proposed approach. The assessments and decisions relied upon should be those made by stringent health authorities with experience in ATMPs.	
199-200	Provide an annotated bibliography to highlight key references relevant to the manufacture, product development, and regulation of ATMPs.	BIO suggests including a forward-looking statement since there are new CGTP modalities emerging, and this is expected to continue. We request that the annotated bibliography include relevant regulations, guidances and guidelines from developed countries with mature regulatory systems for ATMPs.	"...regulation of ATMPs, including relevant regulations, guidances and guidelines from developed countries with mature regulatory systems for such medical products, recognizing that novel CGT products will continue to emerge."
202-205	The WHO goal is to promote regulatory convergence for CGTPs to facilitate development and access to these novel products for patients in all regions of the world. In addition, the aim is to increase safety of patients treated with CGTPs by preventing exploitation of those jurisdictions with inadequate regulations in place for the safe oversight of such novel products (26,27).	Regulatory convergence is in the interest of patients in all regions of the world. LMIC that have less developed regulatory systems rely on the assessment in major ICH regions via CPPs. This is not different for CGTPs as compared to conventional treatments.	BIO recommends the following edit: The WHO goal is to promote regulatory convergence for CGTPs to facilitate development and access to these novel products for patients and to ensure safety of patients treated with CGTPs in all regions of the world. ~~In addition, the aim is to increase safety of patients treated with CGTPs by preventing exploitation of those jurisdictions with inadequate regulations in place for the safe oversight of such novel products (26,27).~~
204-205	In addition, the aim is to increase safety of patients treated with CGTPs by preventing exploitation of those jurisdictions with inadequate regulations in place for the safe oversight of such novel products	One important goal is to protect subjects participating in clinical studies of these products in LMICs (e.g., following ICH guidelines on GCP), in addition to protecting the patients being considered for treatment after product registration.	BIO suggests the following edit: In addition, the aim is to increase safety of study participants and patients treated with CGTPs by preventing exploitation of the vulnerable patients in jurisdictions with inadequate regulations in place for the safe oversight of such novel products

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208-209	The committee had a clear consensus that global harmonization in CGTPs is needed and that WHO should become engaged in this area.	BIO supports the global harmonization but assume something is missing here, e.g., in regulations/definitions etc. Fully agree that it is quite important that WHO become engaged in this area. Many ATMPs are being developed to treat rare genetic disorders. There are only a small number of patients world-wide, so having international alignment can be crucial.	BIO suggests the following edit: The committee had a clear consensus that global harmonization in the definition and regulation of CGTPs is needed and that WHO should become engaged in this area.
217	Terminology	The terminology in the white paper is helpful. Durability refers to the duration of the clinical effect. This is particularly important for products that are intended to provide a cure or lifelong benefit to patients.	BIO suggests adding the term “durability”.
224-225	Cell therapy product is composed of viable human or animal cells with nucleus, intended for treatment or prevention of human diseases or physiological conditions.	This definition doesn’t differentiate cell therapy from the HCT discussed in this document. As suggested in the general comment, it would be recommended to refer to CT Medicinal Products, and their definition could be amended to reflect it.	BIO suggests the following edit: Cell therapy medicinal product contains or consists of cells or tissues that have been subject to substantial manipulation so that biological characteristics, physiological functions or structural properties relevant for the intended clinical use have been altered, or of cells or tissues that are not intended to be used for the same essential function(s) in the recipient and the donor; and is presented as having properties for, or is used in or administered to human beings with a view to treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic action of its cells or tissues.
226-227	The products include plasmids and viral	Suggest adding messenger RNA (mRNA)	BIO suggests the following edit: The

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	vectors that may be used in vivo or ex vivo.	products. The classification of mRNA-based gene therapy medicinal products, which require expression of a recombinant human gene for the mechanism of action, has been established for mRNA-based cancer immunotherapies.	products include plasmids and viral vectors and messenger RNA that may be used in vivo or ex vivo resulting in genetic expression of the sequence/modification of gene expression with a view to treating disease.
227	The products include plasmids and viral vectors that may be used in vivo or ex vivo. In addition, gene editing products when fulfilling this definition are gene therapy products.	Even though this type of product is a borderline case, mRNA-based therapeutics should be included here as potential gene therapy vectors too. mRNA-based vaccines should be exempted and should not be considered gene therapies even though the fundamental technology is the same. This would be in line with the already established and applied EU classification (Directive 2009/120/EC, EMA/140033/2021).	BIO suggests the following edit: The products include plasmids, mRNA-based vectors and viral vectors that may be used in vivo or ex vivo. In addition, gene editing products when fulfilling this definition are gene therapy products.
228	Viral products for infectious diseases are excluded and are not considered to be gene therapy products. Definitions of gene therapy products may vary between regulatory authorities.	This is related to the point above. If the vector, whatever its nature may be (may be plasmids or mRNAs or other vectors), is used to prevent infectious diseases, it should not be treated as gene therapy.	BIO suggests the following edit: Viral products or other vectors ~~for~~ to prevent infectious diseases are excluded and are not considered to be gene therapy products. Definitions of gene therapy products may vary between regulatory authorities.
233-234	**Combined ATMP** are cell or gene therapy products or tissue engineering products that include medical device(s) as an integral part of the product	In combination products for a biologic, either adding a device or a drug would meet the definition. In addition, it is unclear what is meant in the document by “an integral part of the product”.	BIO suggests the following edit: **Combined ATMP** are cell or gene therapy products or tissue engineering products that include ~~medical device(s) as an integral part of the product~~ other classes of therapies, such as drugs and / or medical device(s) as necessary for the clinical effect of the ATMP.
235-244	**Minimal manipulation** is the concept that a cell or tissue product does not undergo	The definition of minimal manipulation is confusing where it refers to acceptable cell	BIO suggests the following edit: **Minimal manipulation** is the concept that a cell or

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	processing other than certain rudimentary steps that do not alter the characteristics, functionality or the risk profile of the product. Acceptable cell or tissue processing steps might include sizing, rinsing, or washing with solutions such as saline. For example, rinsing a harvested tissue in normal saline to remove debris from the harvested material prior to storage would constitute minimal manipulation. Minimal manipulation may include cutting, grinding, centrifugation, antibiotic treatment, washing, sterilization/irradiation, cell separation, concentration, filtering, cryopreservation, lyophilization, vitrification; enzymatic digestion and short cell incubation are considered minimal manipulation if not involving cell division or altering relevant biological attributes of the cells	or tissue processing steps (rather ‘examples ‘) and with a granular listing below.	tissue product does not undergo processing other than certain rudimentary steps that do not alter the characteristics, functionality or the risk profile of the product. ~~Acceptable cell or tissue processing steps might include sizing, rinsing, or washing with solutions such as saline.~~ For example, rinsing a harvested tissue in normal saline to remove debris from the harvested material prior to storage would constitute minimal manipulation. Minimal manipulation may include cutting, grinding, centrifugation, antibiotic treatment, washing, sterilization/irradiation, cell separation, concentration, filtering, cryopreservation, lyophilization, vitrification; enzymatic digestion and short cell incubation are considered minimal manipulation if not involving cell division or altering relevant biological attributes of the cells
241-244	Minimal manipulation may include cutting, grinding, centrifugation, antibiotic treatment, washing, sterilization/irradiation, cell separation, concentration, filtering, cryopreservation, lyophilization, vitrification; enzymatic digestion and short cell incubation are considered minimal manipulation if not involving cell division or altering relevant biological attributes of the cells	BIO recommends replacing the term "altering" with another term expressing a change (e.g., change, modification, modulation), as significant enhancements should also be excluded.	
245-248	Same essential function (homologous use) is the concept that the essential function of the cells or tissues in the recipient should	While the example is helpful, the reference to a cadaveric donor may be mis-interpreted as a limitation.	BIO suggests the following edit: Same essential function (homologous use) is the concept that the essential function of the

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	be the same, or highly similar, to the function in the donor. For example, a bone graft from a cadaveric donor that is used to replace bone in the recipient would be considered homologous use.		cells or tissues in the recipient should be the same, or highly similar, to the function in the donor. For example, a bone graft from a ~~cadaveric~~ donor that is used to replace bone in the recipient would be considered homologous use.
255-258	For the purposes of this discussion, cells and tissues that are harvested and undergo only simple processing such as washing or sizing (minimal manipulation), and which are used to achieve the same essential function/s in the recipient as in the donor (homologous use) are defined as human cells and tissues for medical use, HCT.	BIO suggests placing the definition of HCT under the Terminology section.	
267	Figure 1	Figure 1 should be changed, since HCT are not considered CGTs.	BIO recommends the removal of the 3 HCT examples, or change the title of the table to "Examples of HCTs and ATMPs…"
279-281	Figure 1. CGTPs can be subcategorized according to the risk associated with their use. Cells and tissues in HCTs are mainly of human origin, whereas those in ATMPs may be of human or animal (xenogeneic) origin (see clarifications of the definitions of different ATMP classes in the glossary).	Why is 'mainly' used. Human cells and tissues for medical use are by nature of human origin?	BIO suggests the following edit: Figure 1. CGTPs can be subcategorized according to the risk associated with their use. Cells and tissues in HCTs are ~~mainly~~ of human origin, whereas those in ATMPs may be of human or animal (xenogeneic) origin (see clarifications of the definitions of different ATMP classes in the glossary).
283-285	In contrast to HCTs that are minimally manipulated and undergo homologous use, ATMPs are more complex because they require controlled steps for manufacturing and significant manipulation of the cellular or genetic starting material for the intended effect.	Significant manipulation is a term which is going to be open to interpretation. Recommend qualifying that by this we mean that this entails an intended alteration of the biological characteristics	BIO recommends the following edit: In contrast to HCTs that are minimally manipulated and undergo homologous use, ATMPs are more complex because they require controlled steps for manufacturing and significant manipulation of the cellular or genetic starting material that alters the biological characteristics for the intended effect.

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295-297	Products consisting of or containing replicating viral vectors require an environmental assessment to evaluate the potential adverse effects that could occur if the viral vector is released into the environment. Strategies need to be in place to mitigate such occurrence.	Evaluation of Environmental Risk Assessments for medicinal products containing or consisting of Genetically Modified Organisms should be performed by medicinal product reviewers within the regulatory framework for the assessment of medicines and not outside of it. There have been significant issues particularly in Europe and Japan where these products are impacted by legislation that was designed for crop protection and not for medicines. National regulatory authorities looking to establish their guidance in this area can avoid this pitfall by deciding from the outset to having such issues included in the review of medicines.	BIO recommends the following edit: Products consisting of or containing replicating viral vectors require an environmental assessment to evaluate the potential adverse effects that could occur if the viral vector is released into the environment. Strategies need to be in place to mitigate such occurrence. NRAs who plan to introduce guidance in this area should aim to have such guidance/legislation under the jurisdiction of medicinal product review not crop protection.
298	Table 1. Examples of CGTPs demonstrating broad range of product complexity and risks	The risks of disease transmission to recipients of all allogeneic products need to be carefully assessed as the risks and concerns that exist for blood donors are the same concerns that exist for cell donors for allogeneic products. However, in Table 1, disease transmission is listed for only certain allogeneic products.	BIO recommends adding disease transmission as a specific risk for all allogenic products (HCTs, CTPs, GTPs).
298	Table 1. Examples of CGTPs demonstrating broad range of product complexity and risks	Table 1 lists several vectors used for CGTPs with their potential long-term effects. However, there are several more commonly used vectors that are omitted from this table.	BIO recommends expanding Table 1 to include additional vectors for CGTPs with their potential long-term risks.
298	Table 1	HCT Allogeneic amniotic membrane: it is not clear why specific risks presented as minor without mentioning viral safety	BIO suggests that viral safety for all allogeneic products be mentioned.
298	Table 1	HCT allogeneic virus specific T-cell: the terms "virus specific" may lead to	BIO recommends the deletion of these terms and rather mention these in the

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		confusion;	indication column.
298	Table 1	Specific risks: BIO asks WHO to please define or explain "immuno-toxicity" it may be confused with "immunogenicity" which would apply to all allogeneic products as well.	
298	Table 1	BIO suggests including messenger RNA (mRNA) gene therapy product as GTMP example.	BIO suggests the following edit: Product class: ATMP/GTP in vivo Product type: mRNA-based cancer immunotherapy encoding neoantigens Processing: Linear DNA template encodes mRNA generated by in vitro transcription Indication: Solid tumors Specific Risks: Minor
298	Table 1	While the classification and definitions are appreciated, there is potential confusion with ATMP and CTP and GTP. Perhaps GTP could be GTMP to be consistent with EMA definitions?	
298	Table 1 Immunotoxicity	Immunotoxicity is very broad. This risk seems specifically refer to GVHD. We would suggest revising the term.	BIO recommends using the term “alloreactivity” instead of “immunotoxicity.”
298	Oncogenesis	Both tumorigenicity and oncogenesis are frequently used in this table, however, the line differentiating these two terms can be very blurry. We recommend being consistent.	BIO recommends the use of the term “tumorigenicity” instead of “oncogenesis.”
Table 1	Genotoxicity	This risk seems to specifically refer to genomic editing related off target etc. Genotoxicity is not the correct term for this.	Off-target and structure variation related to genetic modification
Table 1		A general comment: autologous CD19 CAR T are the most approved CAR cell therapies; it may be helpful to include this fact to use as a reference point in relation	

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		to complexity/risk	
Table 1		The most complex cell therapy program would likely be iPSC derived, genetic modification evolved, allogenic CAR T cells. We suggest including these examples in the table to represent the most complex and likely highest associated risks,	
Table 1. row 5	Allogeneic pluripotent stem cells (iPSC[2] / hESC[3]), etc	In Specific risks, add alloreactivity in addition to immunotoxicity and tumorgenicity.	BIO recommends adding alloreactivity in addition to immunotoxicity and tumorgenicity.
Table 1. last row	Hematopoietic malignancies, off-the-shelf	CAR-T no longer limited to targeting Hematopoietic malignancies. Consider broaden to cover solid tumors (although no approvals yet for solid tumor indications). Given the recent Tmunity data showcasing PSMA-TGFB CAR-T toxicity leading to 2 patients deaths, most likely attributed to armoring, consider adding a new row to the table to show case the complexity of regulatory considerations for armoring/payloads of ATMPs that present new challenges for development from a safety perspective	BIO suggests adding a new row to the table to show case the complexity of regulatory considerations for armoring/payloads of ATMPs that present new challenges for development from a safety perspective.
314-316	An example of a critical quality attribute could be a specific cell surface marker, determined by a methodology such as flow cytometry, that should be present on a minimum percentage of a certain cell type in the product.	BIO suggests adding clarity and specificity to the type of product that would have this CQA.	BIO recommends the following edit: An example of a critical quality attribute could be a specific cell surface marker, determined by a methodology such as flow cytometry, that should be present on a minimum percentage of a certain cell type in the cell therapy product.
313-314	Ideally, a critical quality attribute would correlate with clinical effectiveness also.	The word “ideally” is not informative.	BIO recommends removing this text: ~~Ideally~~ A critical quality attribute would correlate with clinical effectiveness also.

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317-326	The duration of such safety surveillance needs to be carefully considered to ensure optimal collection of events, yet not unduly burdensome for the patients who receive the gene therapy product.	It is important to remind the reader that the duration of follow-up should be evaluated based on the type of gene therapy product.	The duration of such safety surveillance should take into account the type of genetic modification, the type of vector, and the type of cells, which needs to be carefully considered to ensure optimal collection of events, yet not unduly burdensome for the patients who receive the gene therapy product.
345	Is the product based on viral vector, plasmid or genetically modified cells or is it gene editing product?	As above. mRNA vectors should be included.	BIO suggests the following addition: Is the product based on viral vector, plasmid, mRNA or genetically modified cells or is it a gene editing product?
347-365	Figure 2	BIO suggests it should be clarified that xenogeneic cell products are in scope for this schematic overview or not – and under which classification category/ies.	
364-365	Figure 2. A proposed schema for the regulatory path based on classification of the CGTPs. The definitions of minimal manipulation and homologous use are provided in the glossary.	Clarify that the definitions are found in the section “Terminology”.	BIO recommends the following edit: Figure 2. A proposed schema for the regulatory path based on classification of the CGTPs. The definitions of minimal manipulation and homologous use are provided in the ~~glossary~~ Terminology section.
367	A risk-based approach could be a feasible way to regulate CGTPs, depending on maturity level of the regulatory authority and its expertise and available resources.	While cell and gene therapies can have transformative benefit, they can also have known and still yet unknown effects. The “risk” is twofold: the risk of the therapy and the ability of the government to identify those risks. In this new frontier, it is critical that governments work together in reliance or work share models to exchange	BIO recommends the following edit: A risk-based approach could be a feasible way to regulate CGTPs. Depending on maturity level of the regulatory authority and its expertise and available resources, it may benefit from working with a more experienced government. WHO encourages governments to share knowledge and work together in reliance and work share models.

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		knowledge.	
377-380	It is critical to understand the nature of the products and the appropriate level of regulation required for different categories of CGTPs to prevent unscrupulous developers from taking advantage of vulnerable patients and less advanced regulatory environments.	Isn't this also true to allow timely access to patients?	BIO suggests the following addition: It is critical to understand the nature of the products and the appropriate level of regulation required for different categories of CGTPs to prevent unscrupulous developers from taking advantage of vulnerable patients and less advanced regulatory environments, as well as to ensure timely access of these products to patients with unmet medical need.
341 & 381		Recognizing the science is evolving at a rapid pace, it is important that regulatory authorities at various stages of maturity and expertise consult with more experienced authorities on best approaches to regulation of novel classes of products.	
381-382	A risk-based approach could be a feasible way to regulate CGTPs, depending on maturity level of the regulatory authority and its expertise and available resources.	In addition to the very useful definitions and examples of HCTs and ATMPs, it is important that regulatory bodies have a system to adjudicate novel products based on level of risk and complexity, as scientific knowledge is moving fast in this area.	BIO suggests the following addition: A risk-based approach could be a feasible way to regulate CGTPs, depending on maturity level of the regulatory authority and its expertise and available resources. Regulatory authorities should have consultative bodies ad systems to adjudicate and classify novel products not yet described in the current classification systems, based on complexity and risk.
381-405	A risk-based approach could be……. in the event issues such as bacterial or viral contamination are identified	The text starts with what is recommended/ aspired (381-393) and continues describing what is done. Suggest adding a few sentences at the end of the paragraph to also describe what the recommendation for	BIO suggests the following addition after line 405: For global distribution of HCTs or (off the shelf) ATMPs irrespective of the country of collection or manufacturing, it would be recommended to have a

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		screening is. For global distribution of HCTs or off the shelf ATMPs, it would be recommended to have a harmonized approach for screening donor of cells, tissues or starting material for ATMPs. In this context it might be helpful to clarify that the potential infectious diseases that need to be screened for may be more depending on the residence, previous residences, and travel history of the donor rather than the screening regulations in place or infectious disease in the country of import or residence of the patient.	harmonized approach for screening donor of cells, tissues or starting material for ATMPs. Donors should be screened for global relevant infectious agents and additionally for local relevant infectious agents depending on current and previous place of residence and travel history of the donor.
407-418	In addition, ATMPs require oversight of other key regulatory issues including: 1. manufacturing and quality controls of the ATMPs, including process changes and comparability assessments, for clinical trials and commercial production under Good Manufacturing Practice (GMP)	While it is acknowledged that HCT may be regulated with "less stringent regulations", these should, at the very minimum, comply with appropriate Quality (control and manufacturing) and Safety standards before being used in human patients. BIO recommends expanding the expectations for HCT as it may be understood that only infectious disease mitigation and traceability is needed for these products.	
432-444	For jurisdictions with minimal experience with ATMPs and rudimentary or less well-developed safety surveillance systems, it could be possible to have cell therapy or tissue engineering products marketed following a review process that leads to local approval based on sufficient data. There are intermediate states between these various options that a jurisdiction	It would be helpful if the logistic challenges of small batches and short half-lives was lifted as an issue where harmonisation and reliance could be helpful without jeopardizing patient safety. Hence, to facilitate clinical trials with ATMPs in countries with less developed regulatory frameworks and to avoid repeat testing for import, it is recommended to adopt a	BIO suggests the following addition: "To facilitate clinical trials with ATMPs and to avoid repeat testing for import, it is recommended to adopt a reliance approach with regard to testing for import and to establish common shipping and stability protocols for import"

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	could consider."	reliance approach with regard to testing for import.	
433-437	For jurisdictions that have already some experience with cell therapy and tissue engineering products and have an adequate safety surveillance system in place, it may be easier to proceed to review and approve less complex gene therapy products that do not have severe risks. For jurisdictions with more extensive experience with the approval of simple ATMPs…	BIO recommends avoiding the introduction of subclassifications that are not clearly defined, e.g. what are "less complex gene therapy products that do not have severe risks" or "simple ATMPs"? It seems contradictory to say above that gene therapies are highly complex and then say here 'simple ATMPs'. *ATMPs vary in their complexity from relatively simple products like plasmid DNA and mRNA … to more complicated like AAV and LVV products… and even more complex products like genetically engineered human T-cells … and ultimately tissues like thymic tissue. It's a whole spectrum of complexity.*	
436/437	less complex gene therapy/ simple ATMP	In the previous text (e.g. Figure 2, table 1), ATMPs and gene therapy products are classified as complex and high risk	BIO requests that clarifications or definitions in table 1 or align text in 436/437 with previous explained terminology.
440-444	For jurisdictions with minimal experience with ATMPs and rudimentary or less well-developed safety surveillance systems, it could be possible to have cell therapy or tissue engineering products marketed following a review process that leads to local approval based on sufficient data. There are intermediate states between these various options that a jurisdiction could consider.	It would be helpful to indicate that for ATMPs for authorities with minimal experience that reliance on stringent authority approvals may be appropriate. Suggest adding a sentence to give this direction. Furthermore, it is time consuming and arguably not a good use of resources for less resourced /experienced regulators to establish their own scientific guidelines especially where scientific thinking is rapidly evolving. Recommend adding a sentence that there is an option to adopt	BIO suggests the following addition: For jurisdictions with minimal experience with ATMPs and rudimentary or less well-developed safety surveillance systems, it could be possible to have cell therapy or tissue engineering products marketed following a review process that leads to local approval based on sufficient data. For ATMPs it may be helpful to rely on approvals from stringent regulatory authorities to the extent the marketing application and characteristics of the local target population are applicable. NRAs who are less resourced and lack experience

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		the scientific principles in guidelines from stringent regulators rather than developing their own national guidance.	could also elect to adopt the scientific principles in guidelines from stringent regulators instead of developing specific national guidelines. There are intermediate states between these various options that a jurisdiction could consider.
445-448	To increase access to quality-assured, safe and effective ATMPs, it is encouraged to promote collaboration between regulators regionally and globally and leverage resources more efficiently. Collaboration among regulators currently takes place through regulatory networks that promote cooperation for carrying out various regulatory processes for medical products.	BIO supports the proposed paragraph and notes that it would benefit from further expansion. The concepts of recognition and reliance could be presented as equally applicable to ATMPs and across their lifecycle. Reference to relevant WHO guidance on that topic would also be beneficial.	
445-470		Many regional/global groups (APEC countries, IPRP, AVAREF, ASAEN member states and PIC/S for inspection cooperation) are mentioned as working together in an attempt to coordinate/harmonize regulatory activities. Is there any working relationship with ICH to harmonize regulations/reviews across regions?	BIO suggests considering how best to take advantage of the ongoing cooperative efforts at ICH aimed at harmonizing regulatory approaches for CGTPs.
456 - 457	PIC/S increases mutual confidence in GMP inspections among member countries.	In addition to mutual recognition of GMP inspections, Mutual Recognition Agreements (MRAs) for CGTP batch release testing is also critical, especially for rare diseases.	BIO recommends the following addition: PIC/S increases mutual confidence in GMP inspections among member countries. Mechanisms to enable mutual recognition of CGTP batch release testing will also increase global access.
462-463	Through various initiatives for regulatory reliance regionally and internationally, it is	BIO agrees with the opportunity for convergence and harmonization in the field	

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	hoped that regulatory convergence will ultimately lead to regulatory harmonization.	of ATMPs. Not only will reliance lead to convergence, but convergence of definitions and regulatory requirements will be an important enabler for reliance.	
498	References	While the list is not all inclusive, BIO suggests including the referenced EMA guidance.	3 July 2017 EMA/CAT/216556/2017 Inspections, Human Medicines, Pharmacovigilance and Committees Division-Development of non-substantially manipulated cell-based ATMPs1 : flexibility introduced via the application of the risk-based approach https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/development-non-substantially-manipulated-cell-based-advanced-therapy-medicinal-products-flexibility_en.pdf

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