19 February 2024
EMA/62329/2024
CAT

Overview of comments received on ' Guideline on quality, non-clinical and clinical requirements for investigational advanced therapy medicinal products in clinical trials ' (EMA/CAT/852602/2018)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	Alliance for Regenerative Medicine
2	Amicus Therapeutics Europe Ltd.
3	BioPhorum - Cell & Gene Therapy Regulatory Strategy Workstream Group
4	Cruelty Free International
5	EBE (European Biopharmaceutical Enterprises) - EFPIA
6	EuropaBio
7	Faculty of Pharmaceutical Medicine, UK
8	Fondazione Telethon, SR-TIGET San Raffaele Telethon Institute for gene therapy
9	Gilead Sciences International Ltd
10	Immunicum AB
11	International Society for Cell & Gene Therapy
12	Lonza Pharma and Biotech
13	LYMPHOMA COALITION EUROPE
14	Medicines Evaluation Board, Netherlands
15	Paul-Ehrlich-Institute, Germany
16	PPD Germany
17	SANOFI

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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1. General comments – overview

[Add tables with general overview as received from interested party.]

	General comment (if any)	Outcome (if applicable)
1.	General: In general, ARM welcomes this draft guidance which strikes the right balance between being comprehensive whilst offering the sponsor a fair amount of flexibility to justify the most scientifically rational path forward. The guideline proves to be useful for companies entering in clinical stage. ARM is hopeful the guidance will help to achieve a better alignment of requirements and expectations when clinical trial applications are reviewed by different national authorities in Europe, thereby facilitating the review and approval process, with more consistent conclusions. An alignment of this guide on FDA requirements would additionally help developers. As several other EMA guidelines on similar topics are in force, we suggest to clearly state which guideline(s) the "Guideline on quality, non-clinical and clinical requirements for investigational advanced therapy medicinal products in clinical trials" will supersede. Scope: The introduction mentioned that genome editing therapies would be discussed in the guidance, however these were not addressed in the non-clinical section. In general, the guidance is focused on viral and cell-based therapeutics (*ex vivo* and *in vivo*) with limited guidance on non-viral *in vivo* therapeutics. Considerations for genome editing- based products are very limited and should be elaborated, with clarity on what in the guideline is applicable or not applicable to such products. Use of modularity approaches to non-clinical assessments should be elaborated. In addition, as stated on lines 131-133, the focus of the guidance is mainly for exploratory trials whilst confirmatory trials are not discussed in great detail. However, ATIMPs trials collect efficacy data routinely in exploratory phase where safety is the primary focus, particularly for targeted cell therapies or personalised medicine. An expansion of section 2 of the draft guidance to include discussion around Adaptive Trial Design approaches and how quality needs to be managed in the context of such designs would be helpful. Fully synthetic products:	The comments are acknowledged. There is no other EMA guideline specifically dedicated to the clinical trial stage for ATMPs. Which ATMP-specific requirements are referred to here is unclear. Existing guidance on adaptive designs should be considered.

	General comment (if any)	Outcome (if applicable)
	Some genome editing products may be fully synthetic, e.g. nucleotide-lipid nanoparticles (LNP). The guidance refers to complexing products (LNP) in relation to non-viral vector for both drug substance (being part of the active) and drug product (as excipients). More clarity on whether the LNP should be considered as being part of the active substance or as an excipient would be needed. The approach should consider other LNP products, not necessarily classified as ATMP. For example, for patisiran-LNP (Onpattro®), a siRNA formulated as LNP the LNP was considered as an excipient by CHMP. Several considerations in this guideline are applicable to fully synthetic genome editing products. However, it is not entirely clear whether fully synthetic genome-editing products fall under the definition of ATMPs. Additional clarity on the classification for these products and whether this guideline (or parts of it) is applicable to them is sought. Given that products utilizing gene editing techniques span the boundaries of biological/synthetics, some guidance regarding such products is needed.	The guideline scope is restricted to products fulfilling the current ATMP definition.
	<u>Terminology and abbreviations:</u> We note that the document contains abbreviations that are explained in different places. It would be better to dedicate a section in the document with an exhaustive list of all abbreviations used in the document. We note the use of new abbreviations, with 'ATIMP' for 'Advanced Therapy Investigational Medicinal Therapy', as well as 'CBIMP' (Cell Based Investigational Medicinal Product) and 'GTIMP' (Gene Therapy Investigational Medicinal Product). In view of the fact that several other existing reference documents, such as the GMP for ATMPs or GCP for ATMPs and also that the title of this guideline uses the terminology 'Investigational ATMPs', we would recommend using this latter terminology throughout the document for consistency and clarity. The same approach could be taken to replace CBIMP and GTIMP by investigational CBMP and GTMP. Finally, it is proposed to correct "Pharmacokinetic" in "Pharmacokinetics" and "Pharmacodynamic" into "Pharmacodynamics".	A glossary is added.
	<u>Structure:</u> As the guidance jumps rapidly between advice specific for cell therapies and viral-delivered gene therapies, it is confusing to differentiate the guidance between these two modalities. We recommend to fully separate out the guidance offered for cellular and viral-delivered gene therapies. It might also be valuable to separate out cellular therapies where there has been no genetic modification, and those where there has. Similarly, it would be helpful to be clearer about what is applicable to allogeneic cell therapies versus autologous therapies. For instance, the information on lines 371-372 is	Rejected. The number of sections applicable to both outweighs the sections requiring dedicated text.

	General comment (if any)	Outcome (if applicable)
	likely most applicable to autologous cell therapies when the starting material is transported from the patient to the manufacturing site and back to the patient. Process controls: Section S.2.2. "Description of manufacturing process and process controls" makes several references to process control, whilst process controls are usually described more in details in Section S.2.4. "Control of critical steps and intermediates". It would be beneficial to clarify the information that needs to be included in both sections. Testing for Replication Competent Viruses (RCV): The guideline makes reference to the absence of replication competent viruses on non-replicating products in several sections (e.g. lines 396, 610, 695, 894). As new, more sensitive PCR based methods and new, more sensitive cell culture-based methods are developed, some products which have been previously shown to be free of replication competent viruses in the tested sample volume/concentration, may show to actually contain these in low levels. Therefore, the guideline should refer to the RCV limit based on safety data (non-clinical and clinical) rather than a total absence of RCV. Because there are products which are intended to replicate in the patient and are considered safe, the requirement for total absence of replicating viruses in non-replicating ones may not be justified from a safety point of view. There are some safety data showing that the low level RCV does not constitute a safety issue. The guideline should be adapted to accommodate for future improvement of detection methods, and a wording as used on lines 983-987 be adopted throughout the document. Convergence with other available international requirements: We noted some discrepancies with existing FDA guidelines and requirements, as detailed in the list of specific comments. In general, ARM pleads for a convergence of international regulatory requirements and would be grateful if the EMA and FDA could discuss the discrepancies we have identified to reach a common approach if possible. In particular, it would be helpful if there could be common agreement on how the different components and products used during the manufacturing process are evaluated and classified as starting materials, raw materials, drug substance or intermediates, especially for *ex vivo* gene therapies. For instance, a viral vector could be seen as a starting material or a drug substance depending on the jurisdiction. ARM believes that a risk-based approach should be adopted to determine whether plasmids, cells used to produce vectors or the editing machinery for *ex vivo* use, etc. should be treated as	Accepted. Wording and structure have been revised. Accepted. Wording has been revised. Differences are acknowledged. Where possible further alignment on concepts/terminology with FDA is sought, however in some cases this is not possible due to differences in legislation (e.g. definition of viral vector used to produce genetically modified cells as starting material vs. active substance)

	General comment (if any)	Outcome (if applicable)
	starting or raw materials. This is important as quality requirements depend on how every ingredient/component is viewed.	
2	Amicus Therapeutics Europe Ltd (ATEL) is pleased that this important guideline is moving forward and supports the efforts to give clarity on many areas of product development for ATMPs in the clinical phase. As a developer of medicines in the rare disease space, a common occurrence for ATMPs, ATEL has a general concern that only the rigid Phase I/II/III development paradigm has been presented in the Guideline; in the form of splitting between exploratory (Phase I/II) and confirmatory (Phase III) trials. Although many ATMP developments may follow this traditional route we feel that more flexibility should be included in the guideline for alternate developments paths. For example, for areas of high unmet medical need there could be the potential for Phase I/II data supporting approval and Phase III data or RWE data, potentially from a registry, provided post approval as part of post approval commitments. A second general comment is to request that as much alignment as possible is attempted with ATMP guidance developments in other key regions such as the US. **Please note:** In addition, Amicus Therapeutics Europe Ltd (ATEL) only comment as it relates to the quality section is the following: "There are no specific comments regarding the ATMP Quality aspects and requirements. The timing of Quality aspects should require some flexibility, particularly should they involve an unmet medical need	Acknowledged. The differentiation between "exploratory" and "pivotal" was chosen intentionally to reflect this flexibility and to communicate that the intended use of the data should be considered by the developer. Where possible alignment with FDA is sought, however in some cases this is not possible due to differences in legislation
3	Overall the flow of the quality portion of the guideline is very disjointed and hard to follow. Information on certain topics (e.g. starting materials) is spread across the guideline rather than being in one place making it difficult for the reader to see what information is expected in what section of the IMPD. In addition, the proposed placement for information does not seem to follow ICH M4Q in several places, making the structure of the dossier confusing and repetitive. In addition, there seems to be a lack of clarity in some parts on the level of detail expected for an early phase study vs a	Accepted. The structure has been revisited

	General comment (if any)	Outcome (if applicable)
	confirmatory study. Some of the guidance seems to be have expectations similar to MAA level of detail and is not always realistic. Including both gene therapies and cell therapies in one guideline is challenging. Jumping from one topic to another and mixing the two makes the guidance hard to follow. In addition, certain types of product (e.g. plasmid- based GT, mRNA products) are not really discussed much at all and are missing. We strongly recommend that EMA consider either issuing discrete guidance for CBIMPs and GTIMPs or reorganize this document into clearly delineated sections which outline the Quality aspects of each class of ATIMP.	Rejected. The number of sections applicable to both outweighs the sections requiring dedicated text.

4	Cruelty Free International appreciates the idea behind this guideline, which aims to provide more detailed guidance on the structure and data requirements for a clinical trial application with advanced therapy medicinal products (ATMPs). However, we have some serious concerns regarding; 1) the omission of reference to legislation relating to the protection of animals used for scientific purposes; 2) the lack of examples and limited guidance provided on non-clinical testing methods other than animal models, and 3) the unsubstantiated support for the use of animal models in the development of innovative medicines with increasing human target specificity. **1. Legislation relating to the protection of animals used for scientific purposes** In Europe there is a legal obligation to use alternatives to animal tests if available (i.e. Directive 2010/63) and to take the principles of the 3Rs into consideration – both of which should be clearly mentioned in the guideline so as to further encourage their implementation. We urge the Committee for Advanced Therapies (CAT) to reference legislation relating to the protection of animals used for scientific purposes, and to incorporate the principles of the 3Rs into the guideline where appropriate in the interests of animal welfare. This is in line with the EMA's ongoing commitment to support the implementation of the 3Rs principles: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_001916.jsp&mid=WC0b01ac0580d52a5e. The following text has been accepted into the final versions of other guidelines: 'In accordance with the provisions of the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes and Directive 2010/63/EU on the protection of animals used for scientific purposes), the 3R principles (replacement, reduction and refinement) should be applied'. **2. Limited guidance on other non-clinical testing methods** The focus of the guideline is on "quality, non-clinical and clinical requirements" for ATMPs in clinical trials. Therefore, we would expect to see more guidance on other non-clinical testing methods that should be considered before discussing the use of animal models. Section 5 of the draft guideline on 'non-clinical documentation' jumps from a general sub-section on the 'general aspects' of non-clinical requirements (5.1) to a sub-section (5.2) on 'animal models'. With the goals of minimising animal testing in mind, a new sub-section should be added in between sub-sections 5.1 and 5.2 to provide guidance on the use of in vitro, in silico and other non-animal methods as part of the non-clinical documentation package for ATMPs. It should also be made clear that, in accordance with the 3R principles, these methods must be prioritised before considering animal models, which come with many limitations with regards to their relevance and extrapolation to humans (e.g. starting dose, biodistribution, immunogenicity, on- and off-target effects and tumourigenicity), and should therefore be viewed as a last resort option under rare and clearly justified	Accepted. Wording has been added. Due to the rapidly evolving field of ATMPs it is not possible to include an exhaustive list of examples. Therefore, the non-clinical part of the guideline provides an overview of the broad principles for non-clinical studies for investigational ATMPs and each product should then be considered on an individual basis.

	General comment (if any)	Outcome (if applicable)
5	In general, we found this draft guidance to be comprehensive and offering the sponsor a fair amount of flexibility to justify the most scientifically rational path forward. We did however find it to be quite confusing with respect to the acronyms used (i.e., we are not clear what the difference is between ATMP and ATIMP, we also note that this is the first time the acronym "ATIMP" has been utilised in guidance). Including both gene therapies and cell therapies in one guideline is challenging. Jumping from one topic to another and mixing the two makes the guidance hard to follow. In addition, certain types of product (e.g. plasmid-based GT, mRNA products) are not really discussed much at all and are missing. Finally, the introduction mentioned that genome editing therapies would be discussed in the guidance, however these were not addressed in the nonclinical section. We recommend the agency settle on a smaller number of acronyms and to fully separate out the guidance offered for cellular and viral-delivered gene therapies. It might also be valuable to separate out cellular therapies where there has been no genetic modification, and those where there has. Overall the flow of the quality portion of the guideline is disjointed and hard to follow. Information on certain topics (e.g. starting materials) is spread across the guideline rather than being in one place making it difficult for the reader to see what information is expected in what section of the IMPD. In addition, the proposed placement for information does not seem to follow ICH M4Q in several places, making the structure of the dossier confusing and repetitive. In addition, there seems to be a lack of clarity in some parts on the level of detail expected for an early phase study vs a confirmatory study. Some of the guidance seems to be have expectations similar to MAA level of detail and is not always realistic. We recommend the Agency to amend the quality part of the guideline to improve the structure.	Accepted. A glossary has been added and the terminology revisited Rejected. The number of sections applicable to both outweighs the sections requiring dedicated text. Comment addressed Accepted Accepted, structure and wording have been revised

	General comment (if any)	Outcome (if applicable)
6	EuropaBio welcome the release of the draft "Guideline on quality, non-clinical and clinical requirements for investigational advanced therapy medicinal products in clinical trials". In general, we found this draft guidance to be comprehensive and offering the sponsor a fair amount of flexibility to justify the most scientifically rational path forward. We did however find it to be quite confusing with respect to the acronyms used (ie, we are not clear what the difference is between ATMP and ATIMP, we also note that this is the first time the acronym "ATIMP" has been utilized in guidance) as well as the guidance jumping rapidly between advice specific for cell therapies and viral-delivered gene therapies. It was very confusing to differentiate between guidance between these two modalities. Finally, the introduction mentioned that genome editing therapies would be discussed in the guidance, however these were not addressed in the nonclinical section. We recommend the agency settle on a smaller number of acronyms and to fully separate out the guidance offered for cellular and viral-delivered gene therapies. It might also be valuable to separate out cellular therapies where there has been no genetic modification, and those where there has. As several other EMA guidelines on similar topics are in force, we suggest to clearly state which guideline(s) the "Guideline on quality, non-clinical and clinical requirements for investigational advanced therapy medicinal products in clinical trials" will supersede. We propose to correct "Pharmacokinetic" in "Pharmacokinetics" and "Pharmacodynamic" in "Pharmacodynamics". We noticed the use of the acronyms "ATIMPs" for investigational ATMPs in the present guideline. In other guidelines or documents, the acronym "iATMPs" has been previously used. We therefore suggest harmonizing the terminology and the corresponding acronyms.	Accepted. A glossary has been added and the terminology revised There is no other EMA guideline specifically dedicated to the clinical trial stage for ATMPs. Accepted, acronyms have been revised

	General comment (if any)	Outcome (if applicable)
7	Upon review, the Faculty of Pharmaceutical Medicine (FPM) believes that these guidelines are logical, clear and comprehensive, and provided flexibility for dealing with these complex new agents and rare diseases. It is very helpful that the guideline gives clarification on certain points relating to the development of ATMPs that sponsors have had issues with, in the past. Such examples are: using terms like 'Exploratory and Confirmatory Trials' rather than Phase I, II & III etc., as this nomenclature does not logically fit with the clinical work for ATMPs (Summary, Sections 6.2, 6.3); advice on performing product comparability assessments during manufacturing and clinical development (Section S.2.6); use of animal models (Section 5.2); the ability to use data previously generated with other products relating to shedding and biodistribution assessments (Sections 5.3 and 5.5); and combination products involving ATMPs and Medical Devices (Section %.7). It is important that such clarifications are retained in the final guideline when it is completed It is noted that the quality and preclinical sections include many recommendations which overlap with existing guidance. The current text should be carefully checked for consistency between existing guidance and recommendations made in this overarching guideline. If it is intended that this new guidance replace previous documents, it should be explicitly stated.	The comments are acknowledged. This guideline is dedicated to the clinical trial stage rather than marketing authorization and therefore recommendations reflect the respective situations. There is no other EMA guideline specifically dedicated to the clinical trial stage for ATMPs.
10	In general, the draft guideline covers an extremely large spectrum of different ATMPs. This makes it sometimes difficult to follow, and to understand what is valid for all types and what is valid for specific types, as the information is mixed, sometimes with very specific examples.	The comment is acknowledged, terminology, structure and wording have been revisited

	General comment (if any)	Outcome (if applicable)
11	ISCT endorses the need for more clarity on what is required for early clinical trials with ATMP. However, we question the value of the additional comments for confirmatory trials given these should be considering what is required for MAA, and thus should refer to MA-level guidances. We feel confining the scope to early trials would help to simplify the guideline (GL), which is otherwise quite long and perhaps too ambitious. We also appreciate that the quality part of the guideline is presented in CTD format since many of our members have limited experience with the CTD and are uncertain which data go where. Often developers struggle as much with the dossier structure as the scientific aspects, and this area has so far been overlooked by regulators but is a real need for industry. However, if the guideline is to follow CTD it would be appreciated that the text under each section is limited to the information and/or data required in that section; currently there are many comments that are not related to the content of the CTD heading used. For example, section S22 is a simple description of the manufacturing process and controls, but the guideline includes discussion on details that belong in S23, S24, S26, S31, and S42/43. It is suggested to align this guidance with ICH M4- CTD format and section headings. (e.g., subdivide section P2 into P2.1-P2.6 (see guideline EMA/CHMP/QWP/545525/2017). It would also be appreciated if some advice could be included on how to describe a continuous process that doesn't release a DS. We feel populating S.1 to S.3 then P.1, P.2, and P.4 - P.8 makes sense, but some chose to favour P-sections leaving S largely unpopulated (save S.2.3 and S.3). Any comments on the CAT's preference would be welcomed. It is suggested to include a list of definitions and a glossary of terms, aligning with ICH terminology. Any guidance on quality of comparator/placebo product to be provided in an ATMP CTA is missing. It is advised to include or refer to other applicable guidance's (e.g., EMA/CHMP/BWP/53498/2008 rev. 1; EMA/CHMP/QWP/545525/2017, etc.). It is suggested to include a section with examples of non-substantial and substantial modifications to the IMPD or reference section 6 of EMA/CHMP/BWP/53498/2008 rev. 1. Overall the text does not achieve the objective of clarifying what is required for early clinical studies, in part because much of the text re-iterates other MA-level guidance and doesn't provide clear insight into how expectations differ. ISCT expected specific advice as to the level of detail and degree of development required for exploratory CT; in this respect the guideline could be clearer.	Accepted. The structure and wording have been revisited for clarification. NC and C parts of this guideline follow the structure of other guidelines for MAA Structure and wording have been revised Accepted, wording has been added Accepted, information has been added

	General comment (if any)	Outcome (if applicable)
	Although the ambition to draft an overarching guideline on Q, NC, and C requirements for ATMPs is highly appreciated, the current draft becomes complicated to read (and comment on) as a result. We did not reach a consensus how it should be changed, but the following were discussed; 1. Since viral vectors are manufactured in a similar way to biotech products, these aspects could be directed to the guideline for biotech IMP (EMA/CHMP/BWP/534898/2008) and the MAA level guideline for GT products (EMA/CAT/80183/2014). Either then remove other text relating to these or only include any additional comments. 2. Focus the guideline to early/exploratory clinical trials only; those embarking on confirmatory trials should be considering MA-level guidance at this stage anyhow. It might be that the first version is more focussed, and later revisions add additional aspects, or are prepared separately. We consider this guideline requires a major rewrite; and we strongly recommend that the CAT release this for a second public consultation before finalising given the extent and level of detail required to make this document useful to the cell and gene therapy community.	The structure has been revisited.
14	The aim indicated in the introductory section ('help the developers of ATMPs to design their development programme') seems not fully in line with the executive summary of the GL where it is stated that the GL 'provides guidance on the structure and data requirements for a clinical trial application'. This ambiguity is also noted in the sections on the different parts of Module 3, where in some cases specific information requirements are provided, whereas in other cases it is stated what the applicant should do, rather than what should be laid down in the dossier. Further consistency could improve the document. The description of cell-based medicinal products and gene therapy medicinal products provided in the introduction to the GL is not in line with the usual definition, where genetically modified cells would be considered gene therapy products. The lack of a clear distinction between cell therapy medicinal products and cell based medicinal products (which also could include products containing genetically modified cells and tissue engineering products), and in vivo gene therapy products is confusing.. As a	Accepted, the wording has been revisited The wording has been revised

	General comment (if any)	Outcome (if applicable)
	consequence, it is not always clear to which type of product the guidance provided by the GL refers to. The clarity of the GL could be improved by further specifying the wording and guidance to make a distinction between these different types of ATMPs. In relation to the remark above, it is noted that not all sections on Module 3 are equally addressing cell based medicinal products, genetically modified cells, in vivo gene therapy products, and tissue engineered products. On some occasions, guidance appears to be focussed mainly on one product type (for instance section S.1.3 mainly addresses viral vectors, section S.2.4 and P.3.5 seem to be written only for cell based products, section S.4.1 only provides specific guidance for viral vectors, section P.3.4 only provides specific guidance on critical manufacturing steps for cell based medicinal products). Specific information for genetically modified cells or for tissue engineered products is often missing. For completeness of the GL, additional guidance may be provided, especially for genetically modified cells and tissue engineered products. The focus seems to be mostly on (ex vivo genetically modified) cell products. In vivo GTMPs seems not to get the same amount attention. If it is not the purpose to focus mainly on cell products, it is suggested to go critically through the text of at least the non-clinical requirements, to ascertain that both in and ex vivo modified GTMP gets equal attention. If it is the purpose to focus more on cell products, please state and explain this very clearly at the beginning of the document. The guideline is rather general, especially for the non-clinical and clinical parts. This is a consequence as ATIMPs includes a broad range of products. As scientific knowledge advances, it might become clear that certain studies are not (longer) needed for specific classes of products, or issues may appear that deserve more attention during the development phase of the product. When there is more scientific knowledge on such specific topics, for instance on the need for germline transmission for certain type of viral vector backbones, this may be rather communicated in a reflection paper. The non-clinical part of the guideline is expected to describe considerations for the non-clinical development of ATIMPs. The unique nature and intrinsic properties of ATIMPs requires a starting point different from conventional non-clinical development strategies as described in ICH S6 and M3 guidance. Animal models to establish Proof-of-Concept and safety (biodistribution, toxicity) are limited and may not always be informative. A risk-based approach is required, which focusses on in vitro investigation of the potential efficacy of the product that is fit for purpose and allows translation to the clinic, avoiding animal studies where possible. Only when in vitro approaches provide insufficient	Due to the rapidly evolving field of ATMPs it is not possible to include an exhaustive list of examples. Therefore, the non-clinical part of the guideline provides an overview of the broad principles for non-clinical studies for investigational ATMPs and each product should then be considered on an individual basis. As further knowledge becomes available, revisions to the guideline will be considered.

	General comment (if any)	Outcome (if applicable)
	information to support FIH, animal models could be considered when added value can be justified. Furthermore, it should be more clearly stated that not all aspects may be relevant for each specific ATIMP. Due to the limitations in non-clinical product development, some questions which are usually addressed, in part, by non-clinical (animal) studies, can only be done so by clinical investigations. As a consequence, specific attention should be payed to the design of FIH studies. It should be stressed that it is paramount to collect as much information as possible on the (pharmacodynamic) activity of the product in the FIH studies in order to address the issues which could not be studied in NC models.	
15	The Executive Summary states that the main focuses of the guideline are the requirements for exploratory trials. However, in many instances, the text seems to emphasize confirmatory trials or even requirements at the stage of MAA. We commented within the document on specific sections. It may be pertinent to check the revised document again for setting an adequate framework also for exploratory trials.	Accepted. The wording has been revised
17	Sanofi agrees that development of an ATMP should follow the same general principles as other medicinal products, except for where distinctive characteristics and features of ATMPs are expected to have an impact. It is recommended that sub-headings are used where (non-clinical and clinical) guidance is specific to cell-based medicinal products, or specific to gene therapy medicinal products (e.g. lines 1572-1584) Quality: - We ask agency to clearly identify and separate recommendations in the guideline related to early versus late phases of development -We ask agency to combine in one single guidance recommendations given in this draft together with those given in the Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products EMA/CAT/80183/2014 - This guideline does not provide guidance on changes to ATIMPs with a need to request a substantial modification to the IMPD. We ask the agency to provide this information.	Accepted. Structure and wording have been revised.

2. Specific comments on text

[Add tables with specific comments as received from interested party.]

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
39-40	1	**Comment:** Add new lines under line 39 with headings "A.3. Excipients" and "A.4. Solvents for reconstitution and diluents" for completion and consistency in the table of content.	Accepted.
Executive summary			
58	5, 6	**Comment:** We are not clear on the difference between ATMP and ATIMP. Please provide clarification on this.	Acronyms have been revised.
60-61	15	**Comment**: No need to highlight a specific class of ATIMPs. **Proposed change** (if any): delete ~~Considerations on genome editing tools are included.~~	Accepted
63	15	**Comment**: In large parts of the document the focus rather lies on requirements for confirmatory trials or even MAA. We commented specifically in the document. However, there still may be requirements which appear highly challenging for phase I trials **Proposed change** (if any): delete	The comment is acknowledged. The guideline reflects requirements for exploratory and confirmatory clinical trials.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
.1. Introduction (background)			
64-92	11	**Comment**: We see no particular need for this text. **Proposed change (if any):** remove	Rejected. We consider this text relevant for early developers
65-66	17	**Comment**: to provide reference to legal definition of Advanced therapy medicinal products (ATMPs[i]) **Proposed change** (if any): Advanced therapy medicinal products (ATMPs[i]) **as defined in Article 2(1)(a-c) of Regulation (EC) No 1394/2007 (definition of advanced therapy medicinal product)** comprise gene therapy, somatic cell therapy medicinal products and tissue engineered products	Accepted, the wording has been inserted
66	5	**Comment:** Combined ATMPs should be included in the list.	Accepted, the wording has been inserted
69-93	1	**Comment:** A distinction is made between cell-based medicinal products and gene therapy medicinal products. However, as cell-based medicinal products may include products classified as gene therapy medicinal products as well as tissue-engineered products, this may lead to confusion. More clarity in the definitions should be provided and a reference to the EMA Reflection Paper on ATMP classification be made.	Accepted. The wording has been revisited for clarification.
70	1	**Comment:** It is stated that cells in cell-based medicinal products can be of human or animal origin. However, the document does not contain any specific recommendation for CBMP derived from animal cells (as starting material), whilst such product typically raise specific issues and would require specific guidance. The only other reference to cells of animal origin is made on line 592 in the section on starting	The guidance reflects current experience but will be revised as further experience is gained

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		materials for GTIMP but guidance on cells of animal origin for CBIMP lacks (see for instance lines 475-476).	
70-72	1	**Comment:** Considering the "stem cells" terminology and stem cells specific issues, it is suggested to also include references to the "reflection paper on stem cell-based medicinal products", It is suggested to include a references to the "reflection paper on stem cell-based medicinal products", EMA/CAT/571134/2009, providing additional background, definitions and considerations regarding stem cells.	Accepted. A reference to the document has been added in the reference list
75	1, 5, 6	**Comment:** Please note any other EMA guidances that should be referred to when developing cell therapies that utilize scaffolds or other device/materials. If any guidances take precedence over others, please mention this.	There is no other EMA guideline dedicated to the clinical trial stage for ATMPs.
77-87	1, 6	**Comment:** It is unclear if *ex vivo* genetically modified bacteria, or phage/phage-like particles designed to infect bacteria *in vivo* and deliver the gene of interest in bacteria cells instead of the patient somatic cells, are included in this definition of gene therapy medicinal products. From the rest of the document it is understood that genetically modified bacteria are included in the scope of this guideline. It is therefore proposed to modify the wording of this paragraph accordingly. **Proposed change**: "*By using such gene therapy constructs in vivo, genetic regulation or genetic modification of somatic* ***or bacterial*** *cells can be achieved in situ. The same gene therapy vector can be used ex vivo for the manufacture of genetically modified cells* ***(human, animal or bacterial)****. Quality aspects of vector and cell-based products need to be considered for the development of products consisting of genetically modified cells.* *Historically many gene therapy approaches have been based on expression of a transgene encoding a functional protein (i.e. a transgene product). Newer tools are under development that modify or edit directly the cellular* ***(including bacterial)*** *genome in vitro or*	Classification is addressed in other documents and not in scope of this guideline.

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		even in vivo. In both cases, the respective tools may be delivered by a viral vector or by a non-viral approach."	
77-78	5	**Comment**: The definitions used in the text are not clear and do not seem to be aligned with the definition in Annex I to Directive 2001/83/EC. Would a "genetic construct" be only a construct with elements of a gene, such as e.g. an open reading frame? Would "to express a specific transgene" mean that protein expression is required? Would a transient transcript (e.g. mRNA) which does not replicate, integrate into, change or modify the cellular genome be considered a GTMP? **Proposed change (if any)**: To add a more transparent definition of the GTMP, e.g. referring to the definition in Annex I to Directive 2001/83/EC.	Accepted. Reference to legal definitions has been added.
82	5	**Comment**: vectors and cells are classified as starting materials for genetically modified cells **Proposed change (if any)** : "starting materials" instead of "products"	Accepted. Wording has been revised
86	1	**Comment:** "*Newer tools under development that modify or edit directly the cellular genome*" : should this be consistent with other regulators e.g. FDA with respect to permanence?	Where possible further alignment on concepts/terminology with FDA is sought, however in some cases this is not possible due to differences in legislation. Permanence is not part of the current legal definition
93-116	11	**Comment**: All medicines take a risk-based approach to their development, and the intended difference of the so-called RBA for ATMP is not clear from this text, nor addressed in the RBA guideline or Annex I part IV. The RBA guideline is described as optional and addresses how to create a risk register and use this in the dossier to help the assessors understand why certain studies are conducted or not. While logical, our members do not see how this is different from normal development, other than consolidating these risks into a master risk register.	The comment is not fully understood. The risk based approach is specifically anchored in the ATMP Legislation.

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		Proposed change (if any): The text here does not clarify the RBA so could be shortened to simply say a RBA can be used, and cite the guideline.	
94	1, 6	**Comment:** The risk-based approach should be applied throughout the development of an investigational ATMP (and even in the commercial phase), not only to determine the content of the IMPD. **Proposed change:** "~~*In determining the content of the IMPD*~~ *Throughout the development of an iATMP**, a risk-based approach can be applied.***"**	Accepted. The wording has been adapted
94	5	**Proposed change (if any)**: "In determining the content of the IMPD, a risk-based approach **should** be applied."	Rejected, in line with legislation wording
100	5	**Proposed change (if any)**: The **risk-based** analysis should be updated by the applicant throughout the product life cycle as new data become available.	Rejected. It is an analysis of the risks
108-109	15	**Comment**: Increasing regulatory expectations is also attributable to NC and C and should be discussed there as well. **Proposed change** (if any): Add discussion to section 5 and 6.	Accepted
110	5	**Proposed change (if any)**: Suggestion to modify as follows: "The level of effort and documentation should be commensurate with the level of risk **and the nature of the ATMP."**	Rejected. Irrespective of the nature of the ATMP, the information provided should be comprehensive
114-116	1, 6	**Comment:** An immature quality development may compromise not only the clinical studies but also the non-clinical ones. Batches used for pivotal non-clinical studies (e.g. GLP toxicity and biodistribution, if appropriate) should be representative of the clinical (GMP) ones.	Acknowledged.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
115-116	15	**Comment**: Quality system is considered issue of GMP and not part of assessment for CTA. **Proposed change** (if any): delete ~~A weak quality system may also compromise the approval of the clinical trial if the safety of trial subjects is at risk.~~	Rejected. It is agreed that the quality system per se is not part of the assessment, the results of a poor quality system (e.g. inconsistent, incomplete IMPDs,…) however are.
117	5	**Comment**: a reference to art 2 of REG 536/2014/EC could be added to clarify definition of substantial modifications.	Accepted.
117	17	**Comment**: Quality Changes during the clinical trial: We suggest providing examples/non-exhaustive list of quality modifications that are typically considered as "substantial" (ie. need to be notified to the competent authorities) or "non-substantial" in a separate paragraph.	Acknowledged.
117-121	11	**Comment**: While not for ATMP, it would seem relevant to cite the guideline on biological IMP (EMA/CHMP/BWP/534898/2008) as this discusses what is or is not a substantial amendment for a biological IMP. **Proposed change** (if any): cite the guideline on biological IMP (EMA/CHMP/BWP/534898/2008 ;https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/2012-05_quality_for_biological.pdf) for advice on amendments to CTA.	Rejected. To the extent possible, this guidance is intended as stand-alone document.
118-119	12	**Comment**: Additional guidance by providing examples of substantial and non-substantial changes is requested. Proposed change (if any):	Partially accepted. General concepts are included, but detailed guidance is not meaningful due to the heterogeneity of ATMPs
119-120	5	**Comment**: Suggestion to add the following: Reference to the guidance where the changes to the clinical trial dossier can be considered as substantial.	Further information has been included.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
2. Scope			
124	1, 6	**Comment:** It is not necessary to continually define acronyms like "ATIMP". (See also under general comments). Please just provide the acronym after the initial definition (in the introduction).	Accepted. A glossary has been added.
126	15	**Comment**: No need to highlight a specific class of ATIMPs (see above comment on lines 60-61). **Proposed change** (if any): delete ~~Considerations on genome editing tools are included.~~	Accepted.
127-132	1	**Comment:** In monogenetic diseases, a well-controlled Phase ½ trial with an ATMP may be pivotal for a marketing authorisation application. Furthermore, a single dose ATMP may be administered in a Phase 1 study with intent of efficacy. It is suggested to delete the reference that FIH constitute a type of exploratory study, as FIH may be expanded to become pivotal in support of MAA. **Proposed change:** *"Clinical trial phases in ATMP development are usually not as clear-cut as they might be for other product types. Therefore, distinction is made between exploratory trials and confirmatory trials, where the latter are performed to obtain pivotal data for a marketing authorisation application (MAA).* ~~***First-in-human (FIH) studies constitute a subtype of exploratory trials where a given medicinal product is given to human study participants for the first time.***~~ *The requirements for exploratory trials are the main focus of this guidance."*	Acknowledged. The guideline generally reflects these concepts.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
127-133	2	Comment: In line with the general comment above, consider change from: Clinical trial phases in ATMP development are usually not as clear-cut as they might be for other product types. Therefore distinction is made between exploratory trials and confirmatory trials, where the latter are performed to obtain pivotal data for a marketing authorisation application (MAA). First-in-human (FIH) studies constitute a subtype of exploratory trials where a given medicinal product is given to human study participants for the first time. The requirements for exploratory trials are the main focus of this guidance. For confirmatory trials, developers should also take into consideration existing relevant guidelines outlining marketing authorisation requirements. Proposed change (if any): Clinical trial phases in ATMP development are usually not as clear-cut as they might be for other product types. In the majority of cases it is expected that there will be a distinction between exploratory trials and confirmatory trials, where the latter are performed to obtain pivotal data for a marketing authorisation application (MAA). However, where there is high unmet medical need and the overall data from a quality, non-clinical and clinical perspective supports an early MAA it may be appropriate to generate confirmatory data in the post approval phase. In this latter case, data quality principles applied to confirmatory trials for Quality, Non-clinical and Clinical sections should be applied to the so-called exploratory studies and be sufficiently addressed to support a positive benefit risk assessment at the time of the MAA. First-in-human (FIH) study constitute a subtype of exploratory trials where a given medicinal product is given to human study participants for the first time. The requirements for exploratory trials are the main focus of this guidance. For confirmatory trials, developers should also take into consideration existing relevant guidelines outlining marketing authorisation requirements.	Accepted. The wording has been modified.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
127-133	17	**Comment**: To clearly identify and separate recommendations in the guideline related to First in-human (FIH) studies (subtype of exploratory trials) versus late phases of development	Accepted. The wording has been revisited.
128	3	**Comment:** The intended definition for exploratory trials should align with Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products **Proposed change (if any):** The distinction is made between exploratory trials (Phase I/Phase I/II) or …the distinction is made between exploratory, early phase, trials	Accepted.
129-131	3, 5	Comment: Although it is agreed that standard trial phases are usually not as clear-cut for ATMPs, there may be scenarios with potentially curative therapies that a FIH study may act as confirmatory. Proposed change (if any): First-in-human (FIH) studies constitute a subtype of exploratory trials where a given medicinal product is given to human study participants for the first time (note that this does not prevent them also acting as a confirmatory trial).	Accepted. Wording has been updated.
135-137	1	**Comment:** National requirements for GMO clinical trials are referenced to the EC website. Given the extent of CMC information in GMO applications and different national requirements, it would be useful to have recommendations in this guidance to guide national CMC requirements towards harmonization.	Rejected. Relevant GMO guidance is reflected in the list of references, the detailed requirements are outside the scope of this guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
138-140	3	**Comment**: If exosomes are carriers for RNA, how do they not meet the criteria for ATMPs? 1) the product has to be a biological medicinal product and contains recombinant nucleic acid(s) and 2) the recombinant nucleic acid(s) should be directly involved in the mechanism of action (and hence therapeutic action) of the product.	Rejected. This comment refers to classification, which is not in scope of this guideline. Product specific EMA CAT classification is recommended.
138-140	12	**Comment**: Additional clarification is requested as exosomes are carriers for RNA and would meet the criteria for ATMPs: 1) the product has to be a biological medicinal product and contains recombinant nucleic acid(s) and 2) the recombinant nucleic acid(s) should be directly involved in the mechanism of action (and hence therapeutic action of the product). Proposed change (if any):	Rejected. This comment refers to classification, which is not in scope of this guideline. Product specific EMA CAT classification is recommended.
138-141	1	**Comment:** Please clarify whether fully synthetic genome editing products meet the definition of gene therapies and ATMPs and which parts of the guidelines are applicable to them – See also general comments above.	Rejected. Classification is not in scope of this guideline. Product specific EMA CAT classification is recommended.
138-141	7	**Comment**: There is much confusion amongst sponsors as to why extracellular vesicles and cellular fragments from human cells etc do not fulfil the definition of ATIMPs, yet it is stated in this section that the underlying scientific principles outlined may be applicable. It is recommended that clarification is given as to why such potential agents do not fulfil the definition of being an ATIMP, when after all they are derived from whole human cells, which do meet the definition. Such clarification would save resources and time both for the Agency and Sponsors who routinely seek clarification on an individual basis.	This classification issue is addressed in Reflection paper on classification of advanced therapy medicinal products. Classification is not in scope of this guideline. Product specific EMA CAT classification is recommended.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
3. Legal basis			
142-183	4	**Comment**: Reference to Directive 2010/63/EU on the protection of animals used for scientific purposes should be included in the 'legal basis' section. **Proposed change**: Add the following document to the list: **Directive 2010/63/EU (regarding the protection of animals used for experimental and other scientific purposes)**	Accepted
143-183	11	**Comment**: The guideline relates to investigational ATMP, yet this section cites Directives that relate to market authorisation. Directive 2001/83/EC for example makes only a single reference to clinical trial (article 107) with no relevance to this GL. This seems off-topic given the guideline specifically states the primary purpose is for exploratory trials. Confirmatory trials which would obviously need to take those into consideration, but we recommend removing these from the scope. Specifically, the legal basis of clinical trials comes from the clinical trials directive/regulation. We note the current anticipated date for implementation of Regulation (EU) No 536/2014 is not until 2020 meaning Directive 2001/20/EC will remain in force for the time being; it would be helpful to address this point rather than merely citing both instruments. We suggest limiting section 3 to the actual legal basis and providing guidance in a separate section for guidance (or change the heading for section 3). It would be helpful to identify Directives 2004/23/EC and 2002/98/EC as the EUTCD and blood directives, since not all will recognise them. Line 152 should be corrected – they apply to testing of the starting material NOT the cell-based product made from them.	Accepted. The section has been reworded.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Guidance We suggest simply stating compliance with Eudralex volume 4 is legally required (to make text succinct and clear). We recommend identifying the two GMO directives, and potentially a link to the Commission resource on GMO (https://ec.europa.eu/health/human-use/advanced-therapies/gmo_investiganional_en). Ph.Eur. also relates to approved products, e.g. Ph.Eur. 5.14, to what degree could an early clinical study deviate? There is also some repetition; e.g. Line 147-149 and 160-162 cover the same. **Proposed change** (if any): Correct the legal basis, separate legal basis from guidance.	
150	5	**Comment**: Any reference to Dir 2001/18/EC and/or Dir 2009/41/ECC	Accepted. The section has been reworded.
150-151	12	**Comment**: Additional guidance on the types of ATIMPs that are considered as GMOs and a complete reference to the Legislation is requested. Proposed change (if any):	Accepted. Reference to the legislation is included in the text, relevant documents are included in the reference list
152-153	1	**Comment:** Directives 2004/23/EC and 2002/98/EC are mentioned here but there is no mention of these directives in the non-clinical data or the quality section. A mention of the interplay between the directive and regulation would be useful in terms of timing of viral testing of excised tissue within the framework of the AMTP Regulation and the Human Tissues and Cells Directive 2004/23/EC.	Accepted. The text has been revised.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
158-159	1	**Comment:** It might be worthwhile including relevant monograph numbers and chapters in the Eur. Ph. In addition, the following change is proposed: **Proposed change:** *"The following documents should be consulted ~~from~~ **for** all clinical trials,…"*	Rejected. Ph.Eur. monographs are modified and added regularly. Adding the current relevant Ph.Eur. monographs would lead to an incomplete/incorrect listin the near future. The editorial comment has been addressed.
158	7	The wording … be consulted *from* all clinical trials….. should read ….. be consulted *for* all clinical trials.	The editorial comment has been addressed.
160	1	**Comment:** It is suggested that all of Volume 4 is referenced.	Accepted. Vol 4 is referenced.
167	5	**Comment**: Consider adding reference to GCLP (Good Clinical Laboratory Practice Guidelines) guidelines	Partially accepted. Referenced in the appropriate (non-clinical) section
168 – 170	1	**Comment**: It is proposed to clarify this sentence. **Proposed change**: *"In addition, relevant European guidelines and reflection papers **that** provide information on the requirements ~~at~~ **for** Marketing Authorisation and ~~thus~~ ~~inform~~ **information** on the drug development process should be taken in consideration"*	The need for clarification is acknowledged, the wording has been modified: - With a view towards MAA, relevant European guidelines and reflection papers. They are listed in the "Reference" section and specifically referred to in the respective sections of this document.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
171	1	**Comment**: There does not appear to be a "Section 8'' in the guidance, though Section 8 is referred to in the sentence "They are partially listed below and referred to in the respective sections of this document and a cumulative listing is provided in section 8:'' Please cite the correct section for the cumulative listing of relevant European guidelines and reflection papers, if there is one.	Accepted. They are listed in the "References" section and specifically referred to in the respective sections of this document.
172-183	1	**Comment**: It is not clear what the criteria were for listing the cited European guidelines and reflection papers. Others such as the guideline on Quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells (EMA/CAT/GTWP/671639/2008 Rev 1) is also relevant and important for this broad guideline. **Proposed change:** Include the following in the list of European guidelines and reflection papers: • Quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells (EMA/CAT/GTWP/671639/2008 Rev 1)	Partially accepted, wording has been changed.
173	15	**Comment**: Relevant related Guidance documents are missing and should be added **Proposed change** (if any): add Guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells. Guideline on the non-clinical studies required before first clinical use of gene therapy medicinal products GL on NC requirements for FIH trials with ATMPs Guideline on plasma-derived medicinal products (EMA/CHMP/BWP/706271/2010)	Partially accepted, Relevant guidance is in the References section.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		CHMP/CAT position statement on Creutzfeldt-Jakob disease and advanced therapy medicinal products (EMA/CHMP/BWP/353632/2010) CHMP Position Statement on Creutzfeldt-Jakob disease and plasma-derived and urine-derived medicinal products. (EMEA/CHMP/BWP/303353/2010)	
183	3, 5	**Comment**: Consideration might be given to including reference to the Draft discussion paper: Use of patient disease registries for regulatory purposes – methodological and operational considerations (when approved) as this is relevant to establishing registries and conducting registry studies. **Proposed change (if any):** Guideline on follow-up of patients administered with gene therapy medicinal products 182 (EMEA/CHMP/GTWP/60436/2007). Draft discussion paper: Use of patient disease registries for regulatory purposes – methodological and operational consideration, EMA/763513/2018	Accepted. The Discussion paper is included in the References section.
4. Quality documentation			
185-225	11	**Comment**: While we appreciate agencies accept IMPD that are not in CTD structure, we feel this should not be encouraged. 186-188 adds nothing useful 189-201 – we suggest narrowing the scope and removing this. Process control is achieved primarily through control of the process parameters, with test parameters and in-process controls for the most part only confirming a unit operation was successful (not actually controlling the unit operation). Yet process parameters are not mentioned; the operating ranges are more important to	Partially accepted, the wording has been revisited. Accepted, the structure and wording have been revisited.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		controlling consistency than testing (which merely confirms the outcome). However, we don't see why this has been included in an introduction to M3, it would be better addressed within the relevant section (S24, S42 etc). 202-204 – we suggest removing, sentence is unclear 218 225– it would be more helpful to explain traceability in the CTD section where you would like the information to be presented. **Proposed change** (if any): Needs editing for relevance and clarity	
190-197	3, 5	Comment: Editorial changes are suggested to ensure greater clarity between what the expectation is during early development vs late. The current text is not very clear, and reference to MAA expectations is not relevant here. Proposed change (if any): Data requirements evolve as development progresses from exploratory to confirmatory clinical trials: • Quality data compiled in the IMPD are expected to reflect increasing knowledge and experience during product development. ~~At marketing authorisation it needs to be demonstrated that the medicinal product can be produced consistently and with reproducible quality. For example,~~ ~~a~~Acceptance criteria for ~~tests/~~ process parameters/in-process controls, even based on limited data should be set for exploratory trials, and they should be reviewed at later stages of development. • During development, the addition or removal of parameters and modification of analytical methods may be necessary. ~~In all cases~~At all stages of development, the suitability of the analytical methods used should be demonstrated.	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
191-192	3	**Comment**: What are the requirements for demonstrating process consistency during the continuum of product development? For example, what are the expectations for demonstrating consistency for an ATIMP manufactured for an exploratory study?	Following the risk based approach, no general statements are possible. Safety of the patient and robustness of data guide clinical trial assessment.
191-192	11	**Comment**: Clarification/guidance is requested for the requirements demonstrating process consistency during the continuum of product development. For example, what are the expectations for demonstrating consistency for an ATIMP manufactured for an exploratory study?	Following the risk based approach, no general statements are possible. Safety of the patient and robustness of data guide clinical trial assessment.
192-193	17	**Comment**: …. acceptance criteria for tests parameters/in-process controls, even based on limited data should be set and they should be reviewed at later stages of development. It will be helpful to have the expectation of the agency how to manage the information already submitted to agency (whether it is required or not to submit amendment)	Rejected. Submissions need to follow the definition of substantial/non-substantial modification according to art. 2 of REG 536/2014/EC
193-194	3	**Comment**: acceptance criteria implies a range or acceptable limit and may not always be appropriate with limited data. **Proposed change** (if any): Should also include action limits that if exceeded are investigated for process and product impact	Accepted. Wording has been modified

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
195-197	12	**Comment**: In light of the statements given in lines 118-121, additional guidance/clarification is requested whether changes in parameters and analytical methods would be substantial and requiring submission prior to implementation. Proposed change (if any):	Rejected. Submissions need to follow the definition of substantial/non-substantial modification according to art. 2 of REG 536/2014/EC
196	10	**Comment: '**the suitability of the analytical methods used should be demonstrated' **Proposed change:** Add in cross reference to S.4.3./P.5.3	Accepted
198	17	**Comment**: The term "mature" manufacturing process and specifications is not clear **Proposed change** (if any): To be removed or clarified	Accepted. Additional wording at first mention
198-199	3, 5	**Comment**: The first two sentences of this paragraph refer to conducting confirmatory clinical trials on a product based on a mature manufacturing process without further defining what is meant by 'mature' in this context. **Proposed change** (if any): Further explanation of the point referring to a "mature manufacturing process" would provide helpful clarity.	Accepted. Additional wording at first mention
198-201	1	**Comment:** It is agreed that conducting a confirmatory trial with product from a mature manufacturing process is the ideal scenario. However, an	Accepted. Additional wording at first mention

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		ATMP may progress quickly to confirmatory trials, e.g. gene therapy in monogenetic disease, and the manufacturing process will be likely still maturing. ATMPs may be also developed based on prior knowledge of a similar product(s) or utilising a manufacturing platform. The manufacturing process may not be mature for the new product but the level of process knowledge is higher based on prior experience. **Proposed change:** ***~~"It is expected to conduct~~*** *~~c~~Confirmatory clinical trials* ***should be conducted*** *with a product based on a* ***~~mature~~*** *manufacturing process* ***that is as mature as feasible*** *and* ***with*** *specifications that match those for marketing authorisation as closely as possible.* ***~~Deviations from this principle will lead to~~*** ***Ccomparability*** *issues, a* ***particular challenge for ATMPs,*** ***can arise if the manufacturing process is revised*** *and may raise questions on the representativeness (validity) of the data obtained."*	
198-201	12	**Comment**: As changes may occur during development additional guidance/clarification is requested around requirements for product used in confirmatory trials "matching" product used in marketing authorization. In addition, references to guidances on comparability during development of IMPs and marketing authorization would be helpful. Proposed change (if any):	Accepted. Reference is made to the Questions and answers on Comparability considerations for Advanced Therapy Medicinal Products (EMA/CAT/499821/2019)
199-201	10	**Comment:** The principle of using optimised and qualified assays could be added to the sentiment here as this also has the potential to impact on the demonstration of comparability **Proposed change:** It is expected to conduct confirmatory clinical trials with a product based on a mature manufacturing process and specifications that match those for marketing authorisation as closely as possible. Optimised and qualified non-compendial release assays should also be implemented. Deviations from this principle may lead to comparability issues at the time of MAA evaluation if the process to be	Partially accepted, the wording has been updated.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		used commercially differs from that used in confirmatory studies and may raise questions on the representativeness (validity) of the data obtained.	
200-201	3, 5	**Proposed change** (if any): Deviations from this principle may lead to comparability issues, a particular challenge for ATMPs, and may raise questions on the representativeness (validity) of the data obtained.	Partially accepted, the wording has been updated.
200-201	17	**Comment**: It is emphasis that comparability is a particular challenge for ATPMs: It would be helpful to provide more recommendations on the methodology to be applied for ATMPs.	Accepted, reference to the Questions and answers on Comparability considerations for Advanced Therapy Medicinal Products (EMA/CAT/499821/2019) has been added
202-204	5	**Comment**: This information seems out of place here. This information is already covered in S.2.2 on manufacturing info to be included for CBIMP, so propose to delete here. **Proposed change (if any)**: ~~For cell-based investigational ATMPs (CBIMP), the guideline describes activities by manufacturers following procurement of the cells and tissues or blood. CBIMP often contain, or consist of cell preparations of limited size and many are intended to be used in a patient-specific manner.~~	Accepted. Deleted
206-207	5	**Comment**: "When a CBIMP incorporates a medical device as an integral part of the active substance, the medical device will be considered a starting material." Please consider providing an example of when a medical device would be considered a starting material.	Accepted.
209	5	**Proposed change (if any)**: "When an ATMP~~s~~ necessitates a medical device as part of the final formulation, but the medical device is not **an** integral part of the active substance…"	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
205-217	1	**Comment:** Considerations for drug-device combinations, ATMP classification as a combined product and the implications for the applications of guidelines (including the recently published draft guideline on the quality requirements for drug-device combinations currently under public consultation) become quite complex. Additional clarification, with some examples is therefore sought. It would also be helpful to add references to the guidelines for combination products under the medicines framework. **Proposed change:** *"(…)* *- When a CIBMP incorporates a medical device as an integral part of the active substance**, the product is classified as a combined ATMP and,** the medical device will be considered as a starting material**.*** *- (…)**-** When **a** medical device is used as the container closure system (see section P.7) or is intended to administer an ATMP ~~and~~**, with** the administration device and the ATMP marketed as a single integral product and the device is not reusable **(e.g. a prefilled syringe),** the combination will be regulated under the medicines framework* ***and is not specifically addressed in this guideline"***	Accepted. Clarification is provided in the now finalized Guideline on quality documentation for medicinal products when used with a medical device (EMA/CHMP/QWP/BWP/259165/2019). Additional wording has been included.
213-217	10	Would be helpful to include reference to EMA Guideline on the quality requirements for drug-device combinations, EMA/CHMP/QWP/BWP/259165/2019. The consequences during development of Article 117 in the Regulation (EU) 2017/745 on medical devices as integral device components of medicinal products. **Proposed change:** When medical device is used as the container closure system (see section P.7) or is intended to administer an ATMP and the administration device and the ATMP are marketed as a single integral product and the device is not reusable, the combination will be	Partially accepted, wording has been updated.

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		regulated under the medicines framework. The latter scenario is not however specifically addressed in this guideline. For more information, see EMA Guideline on the quality requirements for drug-device combinations, EMA/CHMP/QWP/BWP/259165/2019.	
213-216	17	**Comment**: Delivery devices available at the market and at the clinical sites that surgeons use to administer the product to the patient. What data the agency expects from the Sponsor for this kind of devices e.g. which device compatibility, in-device hold data before administration etc.	Partially accepted. Wording in P.2 expanded
218-221	1	**Comment:** It is suggested to clarify that the traceability requirements applies to cell-based ATMPs. **Proposed change:** "*The traceability from the recipient of the **cell-based** product to the donor of the cells or tissues should be ensured*".	Accepted.
218-225	5	**Comment**: the flow of information on tissue regulation is quite disjointed and hard to follow. It would be good to move all legal and background information on human tissue regulation (donation, procurement, traceability etc) to be in one place in the guideline. **Proposed change (if any)**: Relocate lines 218-225 to sit under line 153. "Line 152: Donation, procurement, and testing of human cell-based products need to comply with the requirements of Directive 2004/23/EC or where applicable Directive 2002/98/EC. The traceability from the recipient of the product to the donor of the cells or tissues should be ensured. The traceability system should be bidirectional (from donor to recipient and from recipient to donor). Data should be kept for 30 years after the expiry date of the product, unless a longer time period is required in the clinical trial authorisation.	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		The requirements for traceability are without prejudice to the provision Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data. Therefore, the system should allow full traceability from the donor to the recipient through a coding system." Line 218: ~~The traceability from the recipient of the product to the donor of the cells or tissues should be ensured. The traceability system should be bidirectional (from donor to recipient and from recipient to donor). Data should be kept for 30 years after the expiry date of the product, unless a longer time period is required in the clinical trial 38inimize38zed38.~~ ~~The requirements for traceability are without prejudice to the provision Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data. Therefore the system should allow full traceability from the donor to the recipient through a coding system.~~	
218-225	16	**Comment**: It should be specified what kind of traceability is meant here. There is traceability in the broader sense applying to traceability of all study data for all types of studies, or the very narrow definition of traceability solely in the context of tracing donor cells to the recipient. **Proposed change** (if any): Please make it clear that only the second is meant here, in the sense of tracing donor cells to the recipient and NOT in the broader sense of tracing all study documentation.	Accepted, wording has been changed.
220	7	For the statement 'Data should be kept 30 years after the expiry date of the product', it would be helpful to refer to Eudralex Volume 4 Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products.	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
224-225	5	**Comment**: For consistency, it is proposed that the guidance is aligned with provisions for traceability as laid down in Directive 2004/23/EC, i.e., "*a minimum of 30 years after clinical use*" and that Directive 2004/23/EC is referenced in the guidance. **Proposed change (if any)**: "Therefore the system should allow full traceability from the donor to the recipient through a coding system **and should be kept for a minimum of 30years, in line with Directive 2004/23/EC [reference to** *Directive 2004/23/EC***]."**	Accepted.
224-225	12	**Comment**: Specific reference to directives or guidances on requirements for traceability for donor material would be beneficial. Proposed change (if any):	Accepted.
S – Active substance			
227	1	**Comment:** This sentence suggests that there is only ever one DS in a DP. It is proposed to add a comment that there could be multiple DSs.	Accepted.
227-231	5	**Comment**: Information on overall structure of the IMPD would sit better under heading 4. It is proposed that lines 227-231 are moved to the section on general Quality structure as these are not just related to active substance. Additional editorial changes are also suggested. **Proposed change (if any)**: Relocate lines 227-231 to be after line 188. Line 185: "The data on quality aspects of ATIMP should be presented in a logical structure, ~~ideally~~ according to the specified structure of the **Module 3** common technical document (CTD) ~~such as that of Module 3~~. The data submitted in this module should be consistent with and complement other parts of the clinical trial submission package.	Accepted, the wording has been revised.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		The IMPD should be divided into a drug substance (DS)[4] and a drug product (DP)[5] section. For certain ATIMPs, the starting material, the active substance and the finished product can be closely related or nearly identical. The active substance, any intermediate and the final product should be identified, if possible. In those cases where ~~the ATIMPs~~ production of the ATIMP is a continuous process, it is not necessary to repeat the information that was already provided in the DS part in~~to~~ the DP section." Line 227: ~~The IMPD should be divided into a drug substance (DS) and a drug product (DP) section. For certain ATIMPs, the starting material, the active substance and the finished product can be closely related or nearly identical. The active substance, any intermediate and the final product should be identified, if possible. In those cases where ATIMPs production is a continuous process, it is not necessary to repeat the information that was already provided in the DS part in the DP section.~~	
227-231	9	**Comment**: Some ATMPs may consist of more than one drug substance. Could this be confirmed within the text?	Accepted.
227-251	11	**Comment**: 227-231: It would be useful if the last sentence could be addressed in the CTD structure since many of our members are uncertain how to do this when the process is continuous (most CBMP). As written, it implies all DS sections would be completed, and only those P sections that do not have an S-equivalent would be used (i.e. P4). It does not address for example whether the process description would be spread across S22 and P32 or only described in one of those sections (which we fell would be more logical). It would be useful to have a recommended approach, to this end we feel, broadly speaking, S1-S3 should be used but S4-S7 cross referenced to the equivalent P-section. P3 would cross reference back to S, and only those sections in P1-P2 that are not covered by S would be populated. 232-251: this is clear from Annex I part IV; and reiterated in other guidance, we feel it is unnecessary here, or could be very much simplified, e.g. table/figure.	Accepted, wording has been revised. Rejected. Included for early developers.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Proposed change (if any): revise to make more succinct.	
227-254	10	As multiple types of products are discussed here, subheadings would improve readability.	Accepted. The structure has been revisited.
229	1	**Comment:** In a continuous manufacturing process, the active substance may be identical to the Drug Product, so we suggest deleting the word "nearly". **Proposed change:** *"For certain ATMPs, the starting materials, the active substance and the finished product can be closely related or ~~nearly~~ identical"*	Rejected. The wording is needed.
230	5	**Comment**: Suggested editorial change **Proposed change (if any)**: …where the ~~ATIMPs~~ production is a continuous process…	Accepted, wording has been changed
230-231	10	*In those cases where the ATIMPs production is a continuous process, it is not necessary to repeat the information that was already provided in the DS part, into the DP section.* This implies the preference from the regulator's perspective would be put the bulk of the information in the DS section. We would agree with this approach and suggest it should be more explicably written rather than just implied.	Accepted, wording has been added.
232-251	3, 5	**Comment**: The flow of information on starting materials is very confusing and hard to follow. **Proposed change** (if any): It is proposed that all definitions of starting materials are moved to be together under Section S.2.3, as currently some is in Section S and some in S.2.3. This would give a section S covering the definitions of active substance, and S.2.3 covering the definitions of	Partially accepted. The starting materials section text and structure have been revisited

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		starting materials (see proposed edits S.2.3). Propose to use bullets to separate out text to make easy to follow. - The active substance of a CBIMP is composed of the manipulated or non-manipulated cells and/or tissues. ~~Additional substances (e.g. scaffolds, matrices, devices, biomaterials, biomolecules and/or other components) when combined as an integral part with the manipulated cells are considered part of the active substance and are therefore considered as starting materials, even if not of biological origin. Information on relevant manufacturing and control and viral safety aspect of these additional substances need to be provided.~~ • The active substance of a gene therapy medicinal product based on gene transfer methods in vivo is composed of the recombinant nucleic acid and the viral or non-viral vector used to deliver it. In the case of in vivo genome editing approaches, active substances normally comprise the tools used for the intended genome edition. This can be as diverse as a recombinant nucleic acid, a recombinant protein, a synthetic oligonucleotide or RNA, a ribonucleoprotein, etc. and the viral or non-viral vectors used to deliver them. • In the case of gene therapy ex vivo (i.e. genetically modified cells), the active substance is composed of the modified cells. ~~The unmodified cells, the viral or non-viral vectors and any other nucleic acid and/or protein used in the genetic modification of the cells are considered starting material. The requirements for the gene/vector component should additionally be taken into consideration. In this case of ex vivo use, viral vectors, plasmids, recombinant proteins and recombinant mRNA, the components to produce them (e.g. plasmids, cells) are also considered starting materials.~~ **~~In this case, the principles of GMP, as provided in the General Principles in the Guidelines for GMP for ATMP, should be~~**	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		~~**applied from the cells bank systems used to produce the starting materials, when applicable.**~~	
233-237	15	**Comment**: Repetition of lines 206/207. **Proposed change** (if any): delete here ~~Additional substances (e.g. scaffolds, matrices, devices, biomaterials, biomolecules and/or other components) when combined as an integral part with the manipulated cells are considered part of the active substance and are therefore considered as starting materials, even if not of biological origin. Information on relevant manufacturing and control and viral safety aspect of these additional substances need to be provided.~~	Accepted.
236	1	**Comment:** Correct 'safety aspects' to the plural form **Proposed change:** *"Information on relevant manufacturing and control and viral safety aspect**s**"*	Accepted.
236	15	**Comment**: Biological safety should not be restricted to viruses but also include microbial contamination and prions **Proposed change** (if any): Information on relevant manufacturing and control and ~~viral~~ adventitious agents safety aspects of these additional substances need to be provided	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
238-239	1	**Comment:** This sentence suggests that lipids in LPN used as non-viral vectors are part of the active substance. However, it is stated later that complexing materials (such as nanoparticles or lipids) for formulating the GTIMP drug product are considered as excipients (lines 1228-1229). Additional clarification is sought on whether lipids in LNP are considered as part of the active substance or excipients in the drug product. In addition, as stated under 'general comments', clarification is being sought on whether genome editing products that are completely synthetically produced, e.g. sgRNA and mRNA, are considered as GTIMP and covered by this guideline.	Accepted. Wording has been revised. Rejected. Classification issues are outside the scope of this guideline. Reference is made to the current legal ATMP definition which is restricted to biologics.
238-239	5	**Comment**: We are wondering whether it is intended that the definition of active substance applies to all kinds of GTMPs. For example, in case of mRNA formulated with LNP as a non-viral delivery system, we consider the active substance to be composed of the nucleic acid only and formulation with LNPs as part of the drug product manufacture. **Proposed change (if any)**: Please acknowledge that for certain GTMP the active substance can be defined differently.	Accepted. Wording has been revised
238-246	1	**Comment:** In this paragraph, it is stated that the gene/vector component used in *ex vivo* modified cells is considered a starting material. On line 560, it is stated that vector information should be provided in the "starting material section". The FDA has taken a different approach and has required BLA submissions to include vector information in a separate drug substance section of the BLA, implying that the viral vector is considered as an active ingredient. ARM would encourage the FDA	The comment is acknowledged. Where possible further alignment on concepts/terminology with FDA is sought, however in some cases this is not possible due to differences in legislation (e.g. definition of viral vector used to produce genetically modified cells as starting material vs. active substance)

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		and the EMA to discuss and take a similar approach as to how viral vector should be considered. Clarification on whether non viral vectors, such as LNP, should be considered as starting materials or drug product would be welcome. A definition and requirements for non-viral vectors would be helpful.	
240-241	5	**Comment**: Reconsider choice of "editing" in this context (in vivo). Propose "modification" instead. Editing infers permanency using more recent CRISPR-Cas approaches, when still, there are many GTMPs in development that do not "edit" the genome, but modify the expression from the sequence, by complementary base-pairing. For example, rAAV delivered nucleic acids that can decrease expression of a specific sequence [same applies to line 241 and "edition"].	Rejected. Context refers to genome editing.
241	1	**Comment:** The term "edition" is not a commonly used term relative to genome editing. **Proposed change:** *".. comprise the tools for the intended genome ~~edition~~ **editing**."*	Accepted.
241-243	15	**Comment**: This sentence is not fully clear and may become clearer by the proposed change. **Proposed change** (if any): This can be as diverse as a recombinant nucleic acid, a recombinant protein, a synthetic oligonucleotide or RNA, a ribonucleoprotein, etc. ~~and~~ or the viral or non-viral vectors used to deliver them.	Accepted.
244-246	1	**Comment:** "The unmodified cells, the viral or non-viral vectors and any other nucleic acid and/or protein used in the genetic modification of the cells are considered starting material."	Accepted.

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		This sentence needs to be rephrased to cover in cases where the initial cellular material has already been modified by other means, e.g. iPSCs used as starting material **Proposed change:** "*The ~~unmodified cells~~ initial cellular population, viral or non-viral vectors and any other nucleic acid and/or protein used in the genetic modification of the cells are considered starting material.*"	
244-246	5	**Comment:** This sentence needs to be rephrased to cover in cases where the initial cellular material has already been modified by other means, e.g. iPSCs used as starting material. **Proposed change (if any)**: The ~~unmodified cells~~ **initial cellular population**, viral or non-viral vectors and any other nucleic acid and/or protein used in the genetic modification of the cells are considered starting material**.**	Accepted.
244-246	15	**Comment**: In addition to this, further national provisions may apply. **Proposed change** (if any): add sentence The unmodified cells, the viral or non-viral vectors and any other nucleic acid and/or protein used in the genetic modification of the cells are considered starting material. Additionally, further national provisions may apply. The requirements for the gene/vector component should additionally be taken into consideration.	Accepted.
244-248	3	**Comment**: The classification of viral vectors used to produce ex vivo genetically modified human cells as starting material is not consistent with the USFDA approach. The viral vectors are to be described as DS in a US FDA filing. **Proposed change** (if any): Please consider harmonization the classification scheme.	Rejected. Where possible further alignment on concepts/terminology with FDA is sought, however in some cases this is not possible due to differences in legislation (e.g. definition of viral vector used to produce genetically modified cells as starting material vs. active substance)

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
244-248	12	**Comment**: The classification of viral vectors used to produce ex vivo genetically modified human cells as starting material is not consistent with the US FDA approach. The viral vectors are to be described as DS in a US FDA filing. Please consider harmonization of the classification scheme or, alternatively, would EMA work with the FDA to consider a harmonized approach in classifying viral vectors, plasmids, etc. as a critical starting material. Proposed change (if any):	Rejected. Where possible further alignment on concepts/terminology with FDA is sought, however in some cases this is not possible due to differences in legislation (e.g. definition of viral vector used to produce genetically modified cells as starting material vs. active substance)
247-249	1	**Comment**: The guideline states that for *ex vivo* use, viral vectors, plasmids, recombinant proteins and recombinant mRNA, the components to produce them (e.g. plasmids, cells) are considered starting materials. While it is agreeable that the viral vectors used for *ex vivo* gene modification should be considered starting materials, a risk-based approach should be taken to assess whether plasmids, cells used to produce vectors or the editing machinery for *ex vivo* use will not form part of the active substance and should be considered as raw materials, or whether they will be incorporated in the active substance and should be considered as starting materials. For example, residual amounts of the modifying enzyme protein or mRNA may still be found in the drug product but could nevertheless be considered as raw materials if the risk-based approach establishes that because of their nature, they are short-lived and do not form an essential part of the active substance. , **Proposed change:** *"In* ~~***this***~~ ***the*** *case of ex vivo use, viral vectors* ***are considered starting materials. A risk-based approach should be taken to determine whether*** *plasmids, recombinant proteins, recombinant mRNA,* ***and*** *the components to produce them (e.g. plasmids, cells)* ***will form part of the active substance and should be considered as starting materials.*** *"*	Rejected. Starting material and active substance are defined in the legislation and thus not accessible to a risk based approach. The wording is not changed.
247-249	5	**Comment**: While it is agreeable that the viral vectors used for ex vivo gene modification should be considered starting material, we do not agree that the plasmids, cells used to produce vectors for ex vivo	Rejected. Starting material and active substance are defined in the legislation and

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		use should be categorically specified as starting material. For example, it should be considered acceptable to use non-GMP plasmids to manufacture clinical trial material. Furthermore, the level of details required for Starting Materials for GTIMP, as outlined in lines 559-562, 571-575, 594-605, 613-618, 619-631, may not be mandatory for ex vivo use. Is there other guidance stating acceptability of 'HQ' plasmid for clinical trial materials? Language should be aligned between other sources and this Guideline. **Proposed change (if any)**: In this case of ex vivo use, viral vectors, plasmids, recombinant proteins and recombinant mRNA~~, the components to produce them (e.g. plasmids, cells)~~ are also considered starting materials.	linked to dedicated manufacturing requirements.
247-254	6	**Comment:** In case of *ex-vivo* use, several starting materials are considered in this paragraph, including starting materials (*e.g.* plasmids and cell bank used to produce the viral vector that is used to genetically modify target cells) of starting materials (*e.g.* viral vectors and cells to modify genetically). For clarity purposes, it is proposed here to differentiate them by using different terms such as "primary starting materials" (*e.g.* unmodified cells and vector) and "secondary starting materials" (*e.g.* plasmids and cell bank). The way it is understood in this guideline, the principles of GMP apply from the cell bank systems used to produce the secondary starting materials (*e.g.* Master cell bank used to produce the working cell bank used in production, and glycerol bank used to produce the plasmids used in the vector manufacturing process). This guideline being specific for investigational ATMPs, this does seem like a challenge, including financially, for products in early development phases such as the ones used in first in human studies. Alternative wording proposed. **Proposed change**: In this case of *ex vivo* use, viral vectors, plasmids, recombinant proteins and recombinant mRNA, the components to produce them (e.g. plasmids, cells) are ~~**also**~~ considered **secondary** starting materials. In this case, the principles of GMP, as provided in the General Principles in the Guidelines for GMP for ATMP, should be applied from the cell~~s~~ bank systems used to	Rejected. Wording in alignment with other guidance documents.

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		produce the **secondary** starting materials, when applicable (t**his may not be applicable at early phases of clinical trials (phases I and II))**.	
247-249	8	**Comment**: In the case of *ex vivo* genome editing, the editing machinery could be considered raw material because it will not end up in the final product, except for an eventual copy of the repair template. This should remains true even if residual amounts of the modifying enzyme protein or mRNA are still found in the final product, as these materials are necessarily short-lived because of their nature. Thus, manufacturing requirements could be appropriately adjusted to the risk assessment, choice and specific design of the reagent and stage of clinical development.	Rejected. Editing tools are considered as starting material.
247-248	15	**Comment**: Redundant to line 249. **Proposed change** (if any): delete<br ~~In this case of ex vivo use, viral vectors, plasmids, recombinant proteins and recombinant mRNA, the~~ The components to produce them (e.g. plasmids, cells) are also considered starting materials.	Accepted. Wording has been changed
248-253	9	**Comment**: During early clinical development, setting meaningful IPCs and acceptance criteria is challenging as this can related to experience of patient starting material (which can vary across clinical indications) as well as the overall manufacturing process. We would propose to clarify that as process knowledge and experience increases, these data should be leveraged for process characterisation studies and definition of a robust set of IPCs.	The comment is acknowledged

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
249-251	1	**Comment:** It would be helpful if more clarity (with examples) was provided about at which point the principles of GMP should apply. "*Principles of GMP*" is conceivably less stringent than full compliance with GMP. Examples would also contribute clarifying this. The following typo correction is also proposed: **Proposed change**: "*… should be applied from the cell~~s~~ bank systems used to produce the starting materials, when applicable*".	Accepted. Reference to the relevant Q&A has been added Accepted
249-251	5	**Comment**: The guideline states that the GMP principles should be applied for the cell bank system. It is not clear if the GMP principles should apply for the WCB or in addition for the MCB. We assume that GMP principles should apply for the WCB but not necessarily for the MCB. Also, we assume that requirements change with the phase of development. **Proposed change (if any)**: - Clarification that GMP principles should be applied to the WCB but not necessarily to the MCB - Differentiate the requirements for cell bank systems' quality for FIH trials and confirmatory trials.	Partially accepted. Wording has been modified. Reference to respective guidance has been inserted in the relevant section
249-251	8	**Comment:** It is appropriately stated that GMP principles should be applied from the cell banks used to produce starting materials. "Principles of GMP" is conceivably less stringent than full compliance with GMP.	Partially accepted. Wording has been modified. Reference to respective guidance has been inserted in the relevant section
252-254	12	**Comment**: When additional biological/biotechnological components are obtained from manufacturers detailed information may be considered proprietary and not available for inclusion in the CTD. Should an allowance or additional guidance be provided in cases of proprietary information? Proposed change (if any):	Rejected. This issue is not ATMP specific and not in scope of this guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
S.1 General information			
256-259	11	**Comment**: Some of our members will not know what INN stands for, please spell out or provide a glossary of terms and acronyms. **Proposed change** (if any): define INN	Accepted
259	3, 5	**Comment**: This sentence is unclear. Normally S.1 covers the current names of the product. The same name should be used throughout the IMPD, so naming history not needed. It is proposed that this is deleted. **Proposed change** (if any): ~~The naming history should be included.~~	Rejected. Name changes are a reality.
261-263	12	**Comment**: For gene modified CBIMP should the sequence description and diagrammatic representation of the construct of the gene also be provided? Proposed change (if any):	Noted. Wording has been changed, not required in section S.1.2.
264-267	1	**Comment:** Addition of exemplary language pertinent to *in vivo* genome editing products would be helpful.	Accepted; text reflects current experience.
264-265	5	**Comment**: It is proposed to add detail of the vector in S.1.2 as well as the construct. The active substance is the vector plus the genetic component, so it is strange to only list the construct part in S.1.2 structure of the active substance. **Proposed change (if any)**: For gene therapy investigational medicinal products (GTIMP), **a description of the vector and its structural features should be provided, and** a description and diagrammatic representation of the **genetic** construct should be given.	Partially accepted. Wording has been revised
264-267	11	**Comment**: For GT IMP we accept the sequence of the construct is the critical element for the mechanism of action. However, S.1.2	Noted. Wording has been changed, not required in section S.1.2.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		relates to the structure of the active substance, which for a GT vector product includes the structure of the vector particle itself, e.g. capsid, envelope. Our members note that this is a common omission in IMPD, so should be clarified here. Omission could also lead to misunderstanding of the comment in line 227 later. **Proposed change** (if any): Add to need to describe the structure of the vector particle itself for GT vector products.	
265	5	**Proposed change**: "[…] The ~~therapeutic~~ sequence(s) **of the therapeutic gene cassette, of the** junction regions and regulatory elements should be provided. […]"	Rejected. Wording is in line with other EMA guidance
268-336 (Section S.1.3.)	1	**Comment:** It would be helpful if section S.1. was consistent with the guidance provided in the FDA GT IND guideline – with advice to provide (annotated) sequence in Section S.3.1. This section speaks to biologic vectors and gene therapies. Additional considerations would have to be addressed to cover the different types and particular situations of in vivo gene editing products. It would be helpful to clarify throughout the guideline what is applicable or not applicable to such products.	Noted. Wording has been updated. Information not required in section S.1.2.
268-336	11	**Comment**: General comment: Considering ICH M4Q (intended for MA) states S.1.3. "*A list should be provided of physicochemical and other relevant properties of the drug substance, including biological activity for Biotech.* " S.1.3. is intended to be a brief (ICH M4Q suggests list) overview of the relevant general properties of the active substance, and as such is rarely more than a few paragraphs of an IMPD. However, the advice in this guidance suggests considerably more information and implies even data might be required. It appears the authors have lost sight of the dossier section and discussed some aspect to a detail not relevant for S.1.3. We recommend aligning the detail, of the discussion here to the detail required in dossier section S.1.3., and where necessary cite the dossier section where the main information	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		and data are normally presented and move the extended text to its correct place. For example, it is relevant to say in S.1.3 that the vector is designed to be replication incompetent; details beyond this would be described more fully in S.2.3 as that design is translated to the design of the plasmids (a starting material). But the text in the guideline goes out of scope to discuss the testing strategy (lines 296-303), those data belong in S22/S24 etc. Other topics such as insertional mutagenesis are not likely to be an intended mechanism, so their inclusion here seems off-topic. RCV testing should be discussed in the appropriate sections, e.g. S.4.1, S.4.5, S.2.4 etc. Overall, we endorse presenting the guideline in CTD, but ask that the detail and content of the discussion under each section is limited to the detail and scope of the CTD section as many ATMP developers have limited experience and may take the text too literally. We provide specific comments below. **Proposed change** (if any): Refine section to the level of detail required in the IMPD; ensure comments relate to the section heading.	
268-336	17	**Comment**: How does the information requested in this section differ from the info to be provided in S.2.3 Controls of Materials and S.2.6 Manufacturing Development (for example: the origin and the type of the initial cells for CBIMPs, rationale for the choice of vector system for GTIMP, the strategy taken to render the viral vector replication incompetent should be clearly documented and replication deficiency demonstrated for integrated vectors ..) **Proposed change** (if any): To provide only in this section "A list of physico-chemical and other relevant properties of the CBIMPs and GTIMP based on the proposed mechanism of action".	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		And to provide information related to a. Vector Design and b. Development Genetics in S.2.3 Controls of Materials and/or S.2.6 Manufacturing Development	
269-274	3, 5	**Comment**: The flow of information on starting materials is very confusing and hard to follow. As per other types of product (biologics/small molecules) and in line with ICH M4Q and ICH MQ4 Location issues – Quality Questions and Answers, it is proposed to move all information on starting materials (source, manufacturing overview, control) to be together under Section S.2.3 (see proposed edits S.2.3). Section S.1.3 should be limited to the general properties of the active substance itself e.g. for CBIMP this includes properties such as biological activity, adherence, differentiated status, ability to undergo mitosis/growth, etc. **Proposed change** (if any): Delete lines 272-274 and move to S.2.3. Add more text giving examples for properties for CBIMP and align wording more with biologics IMPD guideline. **S.1.3 General Properties** A list of physico-chemical and other relevant properties of the active substance should be provided including biological activity (i.e. the specific ability or capacity of a product to achieve a defined biological effect). The proposed mechanism of action should be presented and form the basis for the definition of the relevant biological properties of the active substance.~~, including biological activity (i.e. the specific ability or capacity of a product to achieve a defined biological effect)~~. For CBIMPs, this includes properties such as adherence, differentiated status, ability to undergo mitosis/proliferation, secretion/production of trophic factors or other proteins, binding to and/or activation of immune cells, and other biological activity.~~For CBIMPs where the cellular starting materials are obtained through specific technologies (e.g. reprogramming, genetic modification, activation), the origin and the type of the initial cells, information on the processing technique together with the target function need to be provided.~~	Partially accepted, wording has been revised

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
272-274	12	**Comment**: Clarification is being requested on how information on the processing technique differ from the description of the manufacturing process in section S.2.2. Proposed change (if any):	Noted, wording has been updated
272-274	15	**Comment**: Only little information is provided on the general principles for CBIMPs, which should be included here, e.g. cellular composition of the IMP, potential genetic modification, etc. **Proposed change** (if any): Add essential information for general properties of CBIMPs.	Accepted. Wording has been expanded.
274	3	**Comment**: How does information on the processing technique differ from the description of the manufacturing process S.2.2.?	Noted, wording has been modified
275-295	3, 5	**Comment**: Some of the information appears out of place here. Benefit-risk assessments and safety assessments are to be addressed under the clinical section 6.1.1 of the guideline. Information in S.1.3 should be limited to the biological properties of the molecules as defined by its structure (including those that may impact safety) but not a clinical risk assessment. Suggest deleting as this information is already covered in clinical section 6.1.1. Also propose streamlining the text to clearly cover all GTIMP, followed by guidance specific to microbial vector-based products. **Proposed change** (if any): ~~For GTIMP composed of viral vectors, the following aspects should be described:~~ ~~a. Vector Design~~ For GTIMP a list of physico-chemical and other relevant properties, such as biological activity of the GTIMP, should be provided. ~~In~~	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		~~particular the applicant should set out the rationale for the choice of vector system, in relation to the proposed clinical indication, mode of administration (*ex vivo* or *in vivo*), transfection/transduction efficiency on the target cell population, patient and user safety and the functional activity of the therapeutic sequence(s).~~ For products based on viral or bacterial vectors, this includes biological properties such as ~~considerations should be given to~~: i) Serotype or strain of the vector parental organism and its pathogenicity and virulence in man ~~and in other animal species of the parental organism~~; ii) Replication competency, and if relevant the tissue specificity of replication; ~~The engineering of viral vectors to render them, where necessary, replication defective~~; iii) ~~Steps taken to~~ Structural features that minimize the possibility of homologous recombination with any human pathogens or endogenous viruses; iv) Tissue tropism of the vector; v) Transduction efficiency in the target cell population and whether the target cells are dividing or terminally differentiated; vi) sequence(s) important for anti-viral chemotherapy of the wild type virus; ~~vii) The tissue specificity of replication;~~ ~~viii) Germline transmission.~~ ~~For integrating vectors, the risk of insertional mutagenesis should be addressed. Reference is given to the *Reflection paper on clinical risks deriving from insertional mutagenesis* (EMA/CAT/190186/2012).~~	
276-313	10	• Are there any specific requirements for vectors such as AAV that persist episomally though may, if the MOI is high enough, intregrate at low frequency? This is not discussed. **Proposed change:** Perhaps add a cross reference to the reflection paper for AAV	Partially accepted. Wording has been revised.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		• What is the EMA position on vectors that encode superfluous genetic sequences, for example β-gal that may have been introduced to help identify the virus when looking a biodistribution historically but does not have any influence on the MOA of the product. While they may not be detrimental to patient safety, should such genes be removed from the commercial vector? • Again, subheadings would improve readability	
277	15	**Comment**: Biological properties are most crucial and should be added. **Proposed change** (if any): A list of physico-chemical, biological and other relevant properties of the GTIMP should be provided.	Accepted
278-281	1, 5	**Comment**: The original wording of this sentence may sound misleading; transfection/transduction efficiency on the target cell *population* may improve during development; the transfection/transduction efficiency of a particular vector system on the intended cell *type* is part of the relevant properties of the GTIMP. **Proposed change:** "*In particular the applicant should set out the rationale for the choice of vector system, in relation to the proposed clinical indication, mode of administration (ex vivo or in vivo), transfection/transduction efficiency on the target cell* ~~***population***~~ ***type****, patient and user safety and the functional activity of the therapeutic sequence(s).*"	Noted. The wording has been modified
283	5	**Proposed change**: "Pathogenicity and virulence in ~~men~~ **human** and in other animal species"	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
285-286	15	Comments: Any human pathogen in this context is considered to be a fairly wide range for steps considered to be taken to minimise recombination. Possibility of plasmid conjugation in case of use of bacterial vectors should be considered. Proposed change (if any): iii) Steps taken to minimise the possibility of homologous recombination with parental virus family, endogenous viruses, and bacteria~~any human pathogens or endogenous viruses~~; Steps should be taken to minimize plasmid conjugation in case of bacterial vectors to be used;	Noted. The wording has been modified
288-289	1	**Comment:** A rewording of the bullet point is proposed, in line with the above comment. **Proposed change:** **"***Transduction efficiency in the target cell* ***~~population~~*** ***type*** *and whether the cells are dividing or terminally differentiated;"*	Information moved to another paragraph (2. Characterisation studies of gene-therapy investigational ATMPs) and reworded more in line with expectations.
290-291	1, 6	**Comment**: The term "chemotherapy" is widely used to designate cancer treatments. In the proposed sentence it is however understood that the risk of presence and persistence of the viral gene sequence(s) in patients should be considered and discussed in case of later use of an anti-viral treatment against the wild type parental virus. **Proposed change**: *"vi) The presence and persistence of the viral gene sequence(s)* ***(especially*** *important in case of later use of an anti-viral* ~~*chemotherapy*~~ *treatment targeting* ~~*of*~~ *the wild type* ***parental*** *virus****);"***	Accepted. Text reworded.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
292 and 313	1, 6	**Comment**: It is here understood that it is the vector replication specificity in the target tissue that should be considered (in case of replication competent vector). It is however not clear if this is the vector replication in the tissue, or the tissue cells' DNA replication and impact on inserted genes amount per tissue over time that is being considered. Slightly different wording proposed for clarity purposes. **Proposed change:** "*The* ***vector replication specificity in the target*** *tissue* ~~***specificity of replication***~~"	A partial rewording has been implemented (line 297-298).
293	1	**Comment:** It would be useful to include a statement clarifying that germline transmission assessment can be based on literature data for the vector. Additionally, if a vector is modified it would also be helpful to understand expectations for any additional evaluation of germline transmission.	Germline transmission aspects moved to other section.
294	5	**Comment**: Even for vectors considered to be non-integrating, such as AAV, the risk of insertional mutagenesis (IM) should be addressed. When introducing vector genome copies to cells, in vivo or ex vivo, there is a theoretical risk of IM. [As stated in EMA/CAT/190186/2012: "For vectors that do not efficiently integrate, such as adeno-associated vectors (AAV), plasmids or retroviral vectors modified to avoid integrations, insertions into the genome represent unintended and potentially rare events and therefore insertional oncogenesis remains, theoretically, at low risk."]. It is proposed that this sentence is rephrased to include all viral vectors, so that the sponsor addresses the referred to guideline within section S.1.3.	Rejected. Reference is maintained to integrating vectors.
296-297	15	**Comments**: First part of sentence is considered to be better suited in S.2.3 Second part of sentence is considered to be rather an issue to be addressed in the non-clinical part.	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Proposed change (if any): [For replication deficient viral vectors, the strategy taken to render the viral vector replication incompetent should be clearly documented …] → Move to S.2.3 [… and replication deficiency demonstrated.] → delete or move to Non-Clinic	
296-303	1	**Comment:** It is suggested to clarify that, for gene modified cells, RCV testing at the vector level or "virus starting material" should be implemented.	Partially accepted and reworded in line with expectations.
296-303	8	**Comment:** It may be difficult to "exclude" recombination in absolute scientific terms. We would rather add: "conceivably.." or say: be extremely unlikely...	Rejected as the text already mentions the "possibility" of any recombination events […].
296-303	1, 6	**Comment**: In this paragraph, activities do not seem to need detailed descriptions in section 3.2.S.1.3 General Properties, except for the "strategy taken to render the viral vector replication incompetent". Replication deficiency demonstration and details of the RDV control strategy seems more appropriate in the applicable section (depending on where the test is performed, in S.2.3, S.4, P.5). **Proposed change**: "*For replication deficient viral vectors, the strategy taken to render the viral vector replication incompetent should be clearly documented and replication deficiency demonstrated* ***in the appropriate CTD Module 3 section****. The drug substance and where appropriate intermediates, as well as any packaging/producer cell lines, should be screened for Replication Competent Viruses (RCV)* ***(RCV control strategy should be presented in appropriate section(s) such as, for example, S.2.3, S.2.4 and/or S.4 as well as in section***	Accepted. Structure and wording have been changed

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		A2 as applicable)*. The possibility of any recombination events leading to RCV or replication via trans regulation should be considered. In the case of genetically-modified cells, RCV testing at the Drug Substance or other intermediate levels is not deemed necessary provided that absence of RCVs has been demonstrated at the level of the virus starting material and RCV formation during manufacturing of the genetically modified cells can be excluded* ***(RCV control strategy should be presented in appropriate sections such as, for example, section(s) S.2.3, S.2.4, S.3, S.3.4 and/or S.4 as applicable)****."*	
296-313	3, 5	**Comment**: Information in lines 296-313 is general guidance already captured in "Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products" and is not captured in this guideline per CTD heading but is more an overview of development. Information on control strategy and product design/ characterization should not go in S.1.3, but rather ought to be divided across the dossier (e.g. S.1.2 for genetic construct, S.3.1 characterization for data showing replication deficiency or competency, cell line screening for RCV in A.2, tests for DS in S.4.1 and S.4.5). **Proposed change** (if any): It is proposed that this information is moved to S.3.1 and any information that is also addressed in other parts of the IMPD is deleted. Similarly, there was no guidance for viral vectors on what to include in S.3.1 so propose to include it as part of this edit. Move lines 296-313 to S.3.1, and merge. See proposed changes to S.3.1 under comment line 852.	Accepted. Structure and wording have been changed

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
299-313	15	**Comment**: Considered to be better suited in S.2.6 Process development. **Proposed change** (if any): [The possibility of any recombination events leading to RCV or replication via *trans* regulation should be considered. In the case of genetically- modified cells, RCV testing at the Drug Substance or other intermediate levels is not deemed necessary provided that absence of RCVs has been demonstrated at the level of the virus starting material and RCV formation during manufacturing of the genetically modified cells can be excluded. For replication competent viral vectors or replication-conditional viral vectors, a clear rationale for the construct and the individual genetic elements that control replication should be provided regarding to its safe use for the proposed clinical indications. Consideration should be given to the following factors: i) That replication competence is required for the efficacy of the medicinal product; ii) That the vector does not contain any element(s) known to induce oncogenicity/tumorigenicity in humans; iii) That if the parental viral strain is a known pathogen, the infectivity, virulence and pathogenicity of the RCV should be determined after the desired genetic manipulations and justified for the safety of its use; iv) The tissue specificity of replication.] → Move to S.2.6	Accepted. Structure and wording have been changed
300-303	5	**Comment**: In this sentence it is not very clear whether genetic modification is made in situ (in vivo) or ex vivo. **Proposed change (if any)**: "In the case of genetically modified cells **(both for in vivo and ex vivo genetically modified cells)**, RCV testing at the Drug Substance or other intermediate levels is not deemed necessary…"	Rejected. Meaning is implicit. Testing of cells modified in vivo is not part of the manufacturing process.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
301	5	**Comment**: We do not think that this text is clear: "*RCV testing at the Drug Substance or other intermediate levels is not deemed necessary provided that absence of RCVs has been demonstrated at the level of the virus starting material and RCV formation during manufacturing of the genetically modified cells can be excluded*" **Proposed change (if any)**: would it be better if it said – "**If absence of RCVs has been demonstrated at the level of the virus starting material, RCV formation during manufacturing of the genetically modified cells can be excluded and hence RCV testing at the Drug Substance or other intermediate levels is not deemed necessary.**"	This wording is found in S.2.3
304	5	**Comment**: Consider rephrasing "regarding to" to "specific to"	Accepted
304-313	5	**Comment**: In some cases, vectors may contain elements that might induce oncogenicity, however this can be managed and mitigated by taking a risk/based approach. It is proposed that this is reflected in the guidance. **Proposed change (if any)**: "For replication competent viral vectors or replication-conditional viral vectors, a clear rationale**, centred on a risk-based approach,** for the construct and the individual genetic elements that control replication should be provided regarding to its safe use for the proposed clinical indications. Consideration should be given to the following factors: i) That replication competence is required for the efficacy of the medicinal product; ii) **The risk that** the vector contain**s** any element(s) known to induce oncogenicity/tumorigenicity in humans **has been mitigated;** iii) That if the parental viral strain is a known pathogen, the infectivity, virulence and pathogenicity of the RCV should be determined after the desired genetic manipulations and justified for the safety of its use; iv) The tissue specificity of replication."	Rejected. As outlined in the introduction, the entire development of ATMPs may follow a risk-based approach.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
305 – 306	1	**Comment**: Rephrasing is suggested **Proposed change:** *"…the individual genetic elements that control replication should be provided regarding ~~**to**~~ **its** safe use…"*	Noted. Wording has been modified
314-329 334-336	3	**Comment**: The flow of information on starting materials is very confusing and hard to follow. **Proposed change** (if any): Propose to move all information on starting materials (source, manufacturing overview, control) to be together under Section S.2.3 (see proposed edits S.2.3). Section S.1.3 should be limited to the general properties of the active substance itself.	Accepted
314-329 334-336	5	**Comment**: The flow of information on starting materials is very confusing and hard to follow. As per other types of product (biologics/small molecules) and in line with ICH M4Q and ICHMQ4 Location issues– Quality Questions and Answers, propose to move all information on starting materials (source, manufacturing overview, control) to be together under Section S.2.3 (see proposed edits S.2.3). Section S.1.3 should be limited to the general properties of the active substance itself. **Proposed change (if any)**: ~~b. Development Genetics~~ ~~For all vectors, full documentation of the origin where applicable, history and biological characteristics of the parental virus or bacterium should be provided.~~ ~~All the genetic elements of the GTIMP should be described including those aimed at therapy, delivery, control and production and the rationale for their inclusion should be given. For helper virus, the same level of detail should be provided.~~ ~~For plasmid DNA, full sequence should be provided.~~	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		~~DNA elements used for selection should be justified. The presence of antibiotic resistance genes in a GTIMP finished product should be avoided given the burden of bacterial multi-resistance to antibiotics and the existence of alternatives methods for selection. If unavoidable a risk analysis should be made.~~ ~~Data on the control and stability of the vector and the therapeutic sequence(s) during development should be provided. The degree of fidelity of the replication systems should be ensured as far as possible and described.~~ ~~Evidence should be obtained to demonstrate that the therapeutic sequence remains unmodified and is stably maintained during any amplification.~~ ~~Cells used for the amplification of the genetic material should be 65haracterized.~~ ~~Details of the construction of any packaging/producer cell line or helper virus should be provided,~~ ~~Where, during development, changes to the design of the vector are made to obtain new improved product characteristics, the clinical impact of the change(s) should be evaluated (consult the Guideline on the quality, preclinical and clinical aspects of gene therapy medicinal pr 332 oducts) and comparability studies should be considered.~~ ~~When GTIMP consists of genetically modified cells, both the required information on the viral vector plus information on the modified cellular component should be provided following the recommendations above.~~	
314-336	10	Most of the information in *'b. development genetics'* would ordinarily be provided in S.2.3. While some information may be generically described in S.1.3. the level of detail as requested here seems excessive and will lead to significant duplication in S.2.3.	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Proposed change: Suggest the level of detail for development genetics is more minimized in S.1.3., including appropriate cross referencing to S.2.3 where relevant, leaving the details to be presented in S.2.3. Where changes are made to the vector during development, these should be discussed, and comparability data presented in S.2.6. Please include this reference in rows 330-333	
314-339	11	**Comment**: The heading may not be clear to many developers; a search of ~50 guidelines identified this term in 2 guidelines only from 1994 and 2001 (transgenic animals and GT). There also appears to be overlap with the section on vector design (starting line 276) so it is not clear if these aspects should be discussed together or separately and we see scope for unnecessary repetition as a result. Lines 315-316 might be better understood as 'provenance' of the parental vector. Lines 317-319 and 321-323 seems repetition of the section starting line 276. Line 329 seems to belong there also. Line 320 is not in scope of S13 and belongs in S23 (starting materials). The sentence starting line 324-327 refers to data that do not belong in S13, these data would be in S23 (starting material), so should be removed/moved. The producer cells are not a general characteristic of the active substance, at most the type of cell might be mentioned in S13, but their characterisation belongs in S23. Line 330-333 is out of scope of S13 and belongs in S26. **Proposed change** (if any): revise to be clear and precise what information is summarised in S13, remembering that the intent of this section is merely a high-level overview of the general characteristics of the active substance (ICH M4Q); and move or delete the off-topic text.	Accepted. Structure and wording have been changed

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
317	3	**Comment**: This is a general statement and would require describing genetic elements of a vector and/or genetically modified cells that are not relevant for the intended use.	Rejected, comprehensive information needs to be provided.
317-319	12	**Comment**: Additional clarification is requested as this generalized statement would require describing genetic elements of a vector and/or genetically modified cells that are not relevant for the intended use. Proposed change (if any):	Comprehensive information needs to be provided – see Guideline text.
320	3	**Comment**: Consider stating "plasmid DNA vector" or "plasmid DNA gene transfer vehicle" to differentiate plasmids that may be used as starting materials in S.3.	Section has been reworded.
320	5	**Comment**: "for plasmid DNA, full sequence should be provided" Suggestion to add a sentence that linear DNA template be regarded as a starting material for mRNA-based GTIMP. Alternatively, consider stating "plasmid DNA vector" or "plasmid DNA gene transfer vehicle" to differentiate different plasmid types that may be used as starting materials in S.3.	Section has been reworded and information is included.
320	10	Full plasmid sequencing is requested but not full viral vector sequencing – what is the rationale for the disparity in the approach? Referring to rows 614-616, this is not aligned, as only confirmation of the therapeutic sequence and regulatory sequences is required for RNA/DNA vectors and plasmids **Proposed change**: Ensure all relevant sections of the guideline are aligned in terms of expectations of the extent of sequencing required. Wording used in 614-616 for vectors regarding of viral or bacterial or plasmid origin seems reasonable	Section has been reworded and information is included.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
321	5	**Comment**: Please consider elaborating further here on what level of "justification" is required for inclusion of DNA elements for selection. It is currently unclear if this relates only to antibiotic resistance genes?	Rejected since it requires product-specific considerations that can only be addressed by the Applicants.
324	15	**Comment**: Assumed that rather vector genome instead of vector is meant. **Proposed change** (if any): Data on the control and stability of the vector genome and the therapeutic sequence(s) during development should be provided.	Accepted.
324-333	1, 6	**Comment**: It looks like some of the information mentioned in this paragraph under "b. Development Genetics" should be presented in other dossier sections as appropriate. For example: - Data on the control and stability of the vector and the therapeutic sequence(s) during development: these could be presented in the appropriate control and stability sections, or in the characterisation section as applicable, - Evidence that the therapeutic sequence remains unmodified and is stably maintained during any amplification: these could be presented in the appropriate control and/or control of intermediates sections as applicable, - Characterisation of the cells used for the amplification of the genetic material: these could be presented in starting material section, - Changes of the design of the vector and comparability studies: these could be presented in the manufacturing development section. **Proposed change**: *"Data on the control and stability of the vector and the therapeutic sequence(s) during development should be provided* ***in the appropriate section(s) (e.g. S.2.3, S.4, S.7).*** *The degree of fidelity*	Accepted. Structure and wording have been changed

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		*of the replication systems should be ensured as far as possible and described. Evidence should be obtained to demonstrate that the therapeutic sequence remains unmodified and is stably maintained during any amplification**, and should be presented in the appropriate section (e.g. S.2, S.3, S.4).*** *Cells used for the amplification of the genetic material should be 69haracterized.* ***Data should be provided in section S.2.3.*** *Details of the construction of any packaging/producer cell line or helper virus should be provided~~,~~**.** *Where, during development, changes to the design of the vector are made to obtain new improved product characteristics, the clinical impact of the change(s) should be evaluated (consult the Guideline on the quality, preclinical and clinical aspects of gene therapy medicinal products) and comparability studies should be considered.* ***Changes and comparability studies' data should be presented in appropriate section(s) (e.g. S.2.3, S.2.6, P.2.3 for CMC changes and comparability data).*** *"*	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
326-327	1	**Comment**: Stability and fidelity of replication of genetic sequences vary with the vector choice and are primarily determined by the intrinsic biological properties of the vector and also by sequence-specific features, which may be unique to each transgene design. Please note also that viral systems typically have a low fidelity of replication, with up to 1 mutation each 1,000 base pairs. Thus, it is theoretically and practically impossible to prove that the sequence remains unmodified in all of the product, while it would be appropriate to prove that the expected therapeutic sequence is found in the vast majority of the bulk cell product. Furthermore, one should not be requested to demonstrate the already known biological properties of the vector chosen (i.e. extent of fidelity of replication), rather to verify only that the chosen transgene / cassette design does not impact such intrinsic properties in terms of transfer and stability. **Proposed change:** *"Evidence should be obtained to demonstrate that the therapeutic sequence remains unmodified* ***in the vast majority of the genetically modified cells*** ~~***and is stably maintained during any amplification.***~~*"*	Rejected for the purpose of the GL; in exceptional cases more flexibility may be justified based on a risk-based approach

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
326-327	8	**Comment:** Stability and fidelity of replication of genetic sequences vary with the vector choice and are primarily determined by the intrinsic biological properties of the vector and also by sequence-specific features, which may be unique to each transgene design. Please note also that viral systems typically have a low fidelity of replication, with up to 1 mutation each 1,000 basepairs. Thus it is theoretically and practically impossible to prove that the sequence remains unmodified in all of the product, while it would be appropriate to prove that the expected therapeutic sequence is found in the vast majority of the bulk cell product. Furthermore, one should not be requested to demonstrate the already known biological properties of the vector chosen (i.e. extent of fidelity of replication), rather to verify only that the chosen transgene / cassette design does not impact such intrinsic properties in terms of transfer and stability.	Addressed above.
328	12	**Comment**: Additional clarification/guidance is requested for the minimum requirements for characterization of cells used for amplification of genetic material. Proposed change (if any):	Rejected as this may require cell type-specific considerations that only the Applicants' can address.
329	10	A rationale for the use of the packaging/producer cell line or helper virus should be included here. It is better placed here rather than in S.2.2 (row 383) **Proposed change**: Rational for the use, and details of the construction, of any packaging/producer cell line or helper virus should be provided	Section has been reworded.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
329	15	**Comment**: Considered to be better suited in S.2.3 **Proposed change** (if any): [Details of the construction of any packaging/producer cell line or helper virus should be provided.] → Move to S.2.3	Section has been reworded.
330-333	1	**Comment:** It would be helpful to add reference to the relevant Guidelines and clarify that it is up to the sponsor to justify the need for analytical and/or clinical comparability studies taken into consideration the extent and impact of the changes. **Proposed change:** *"Where, during development, changes to the design of the vector are made to obtain new improved product characteristics, the clinical impact of the change(s) should be evaluated (consult the Guideline on the quality, preclinical and clinical aspects of gene therapy medicinal products **(EMEA/CAT/80183/2014) and Quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells (CHMP/GTWP/671639/2008), as applicable)** and comparability studies should be considered. **The sponsor should justify the need for analytical and/or clinical comparability studies taking into consideration the extent and impact of the changes."***	Partially accepted. Relevant guidelines are listed under "References"
330-333	3	**Comment**: This text is general development guidance and not relevant to S.1.3. It is proposed to delete as it is covered in other guidance on ATMPs and biologics.	Accepted. Structure and wording have been modified.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
330-333	5	**Comment**: Suggest to clarify that it is up to the sponsor to justify the need for analytical and/or clinical comparability studies taken into consideration the extent and impact of the changes. **Proposed change (if any)**: "Where, during development, changes to the design of the vector are made to obtain new improved product characteristics, the clinical impact of the change(s) should be evaluated (consult the Guideline on the quality, preclinical and clinical aspects of gene therapy medicinal products (**EMEA/CAT/80183/2014**) and **Quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells (CHMP/GTWP/671639/2008**), as applicable) and comparability studies should be considered. **The sponsor should justify the need for analytical and/or clinical comparability studies taking into consideration the extent and impact of the changes**."	Partially accepted. Relevant guidelines are listed under "References"
334-336	10	Presumably the genetic stability of the vector / therapeutic sequences in the cell line should be demonstrated. This is not explicitly or implicitly stated in the recommendations above, but if the cell is for example an HSC that will engraft the patient, surely genetic stability of the transduced cell is of paramount importance, and should be called out specifically in this document, or reference made to alternative guidance on this topic.	Section has been reworded.
S.2 Manufacture			
339-341	3, 5	**Comment**: Proposed editorial change to simplify. **Proposed change** (if any): The name(s) and address(es) and responsibilities of each manufacturer or facility, including contractors, ~~and each proposed~~	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		~~production site or facility~~ involved in drug substance manufacture, testing and batch release should be provided.	
339-341	11	**Comment**: It would be useful if the text could clarify the situation of continuous manufacture, e.g. most CBMP. Should all manufacturers be in S21 with P31 empty or is another approach preferred? Another point some ATMP developers are uncertain about is whether the manufacturers and test labs etc for the plasmids, vector, or even other bespoke starting materials should be included here or not? Should the plasmid supplier be listed here (can't formally be GMP)? **Proposed change** (if any): revise and recommend changing 'contractors' to 'sub-contractors'	Partially accepted. Relevant wording has been added to section 4
341	15	**Proposed change** (if any): Add GMP certificates and/or Manufacturing authorisations should be provided.	Rejected. Text in line with other Guidelines for investigational products (Eudralex Volume 10)
342-400	11	Comment: This section is a simple description of the process and its controls with no data, explanation etc; yet the text provided in the draft guideline could be interpreted otherwise. Throughout, the text goes beyond the purpose of S22 and mentions aspects that belong most commonly in S24, but also other sections. These comments, if left as is, will lead to more confusion as to where certain details should be described. It is noted that compared to S22, S24 is short, we consider the focus is the wrong way around given S22 is a mere description, it is S24 where control of the process and intermediates is justified. Line 345-346 – the suitability of the process controls is discussed in S24 – please remove the last sentence. Line 348 – please clarify where the process flow diagram should start, e.g. receipt of the starting material at the GMP facility. This is important because the FDA guidance implies that the collection steps should be included, despite these being prior to the start of GMP (inconsistent with ICH principles). A related question is whether preparation of an allogeneic cell bank (CBMP) should be described as	Partially accepted. Structure and wording have been modified.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		part of the process in S22 (our assumption), or as for a cell substrate in S23. Line 351-353 – while process parameters are mentioned in the previous line, there is no mention in this sentence, yet unlike IPC etc, it's the process parameters that control the process. It therefore seems relevant to comment that an operational range should have been established for those likely to be critical. It has been noted by our members that these are often overlooked partly or wholly in S22. Line 354-356: this belongs in S24. 356-357 – belongs in S25 367-370: this doesn't relate to S22 (simple description of process) looks to belong in S26 and/or S3, please move. 371-372: ICH M4Q is not clear where transport of a DS, but as S22 is a description only (no data) most place this in S25, some in S24. Control of intermediates that are stored/held or transported belongs in S24. Transport of the starting material is S23. Please move this comment. 373-374: microbial control should be identified in S22; justification would be in S24, suggest move this comment. 378-379: clearly this is only described in S22, comment belongs in S24 where this would be justified. 380-382: The studies to establish this would be described in S26; either move this comment to S26 or edit the text to say based on studies described in S26…. 383 – this belongs in S23 (starting material) 384-388: this comment would be more appropriate in S24 as this is where you'd justify the testing. However, much of the testing described is unlikely to be tested in-process early in development (scope of guideline), e.g. HCP, HCDNA; so these points might be more appropriate in S44 (Justification of specs) and/or P54. The final sentence seems to relate to S26. 389-392: again, more relevant to S24, here it would only be described. 393-396 – S24 and S34 as relates to justifying specs 397-398 – S26 399-400 – s24, comment is repetitive.	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		For the most part if this text was moved to S24 it would be more appropriate. S22 should need rather little explanation as the section is a simple description of the process and its controls. Proposed change (if any): see above.	
344-357	5	**Comment**: Editorial changes are proposed to align with Biologics IMPD guideline which has much clearer wording and is easier to follow. It is also proposed to add new text to clarify where the manufacturing process starts as this is frequently a point of confusion for ATMP developers. Guidance to include storage and shipping conditions is also suggested **Proposed change (if any)**: ~~The manufacturing process of an ATIMP and process controls should be carefully designed and described concisely and step-by-step. The suitability of the controls for the intended purpose needs to be proven.~~ ~~A flow chart of all successive steps of the drug substance manufacturing process should be provided starting from biological fluid/tissue/organ or from cell banks/viral seeds. Critical steps and intermediate products should be indicated as well as relevant process parameters, in-process controls (IPCs) and acceptance criteria. IPC testing (for early phase developments) should focus at the minimum on safety aspects. Critical steps should already be identified for the manufacture of early clinical trial material and adequate acceptance criteria for these critical steps established, for other IPCs, monitoring might be appropriate.~~ ~~During development, as process knowledge is gained, further details of in-process testing should be provided and acceptance criteria reviewed. As development proceeds, manufacturing consistency needs to be demonstrated.~~ ~~For a marketing 76haracterized, the manufacturing process needs to be validated~~. The manufacturing process and process controls should be adequately described here. Storage and shipping conditions should be	Accepted. The section has been reworded

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		outlined. Manufacture and control of any starting materials should be included in Section S.2.3. The manufacturing process typically starts with one or more vials of the cell bank or bacterial/virus seed stock and can include cell culture, harvest(s) and purification operations. For CBIMP that do not use cell banks, the manufacturing process starts with the biological fluid/tissue/organ from which the cells are obtained, and typically includes cell separation and/or culture steps. **A flow chart of all successive manufacturing steps including relevant process parameters and in-process-testing should be given. The control strategy should focus on safety relevant in-process controls (IPCs), and acceptance criteria for these controls should be established for manufacture of phase I/II material.** **For other IPCs, monitoring might be appropriate and acceptance criteria or action limits do not need to be provided. Since early development control limits are normally based on a limited number of development batches, they are inherently preliminary. During development, as additional process knowledge is gained, further details of IPCs should be provided and acceptance criteria reviewed. *** *(based on Biological IMPD guideline)	
344-345	15	**Comment**: Relevant information on processing/holding times as well as location of IPCs is missing and is especially required for assessment of the overall microbiological safety strategy **Proposed change**: The manufacturing process of an ATIMP and process controls should be carefully designed and described concisely and step-by-step. All relevant processing and holding times should be specified and defined at which process stage controls have been exactly established.	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
345-346	10	It is unclear exactly what is meant by '*The suitability of the controls for the intended purpose needs to be proven.'* The control strategy around the process, including the testing methodology and decisions on which steps are critical and how those steps are controlled, are normally described in S.2.4, and the process taken to define the control strategy, including supporting data, are provided in S.2.6. The amount of information expected is of course going to depend on the stage of development. This statement seems out of the place in S.2.2. **Proposed change**: Suggest the sentence is removed.	Accepted. The section has been reworded
345	17	**Comment**: Discussion on suitability of the controls should be part of the S.2.6 Manufacturing Development. **Proposed change** (if any): to delete the sentence **~~"The suitability of the controls for the intended purpose needs to be proven."~~**	Accepted. Wording has been modified
348-353	1, 5	**Comment:** It is often not possible to define meaningful critical steps in early clinical development; therefore, it is proposed to clarify that initial IPCs can be used to accumulate process knowledge and to form basis for process characterisation studies, which will then enable the definition of IPCs.	Rejected. This is implicit
350	5	**Comment**: What safety tests are advised for in process testing?	Rejected. Answer is not generalizable.
351	17	**Comment**: To outline that information related to Critical steps have to be provided in the dedicated section S.2.4.	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Proposed change (if any): "Critical steps should already be identified for the manufacture of early clinical trial material and adequate acceptance criteria for these critical steps established **and described in S.2.4** , for other IPCs, monitoring might be appropriate"	
355-356	10	*As development proceeds, manufacturing consistency needs to be demonstrated.* This is not relevant to S.2.2., it is more useful to state this in batch analysis sections.	Accepted
356	15	**Comment**: It is not evident what this statement is meaning for clinical trials. **Proposed change** (if any): Only for a marketing authorisation, the manufacturing process needs to be fully validated.	Accepted. Reworded
356-357	10	*For a marketing authorization, the manufacturing process needs to be validated.* This is not relevant to the S.2.2 section of the dossier; it should be described in S.2.5	Accepted
359-362	3, 5	**Comment**: Changes are proposed to enhance clarity. Some cells start with a cell bank vial, so cell "sourcing" is misleading when talking about batch definition. Also, many cell processes are continuous through to DP, so the DS may not be in a final container; a note on continuous manufacture is suggested. Finally, size is often not relevant for cells (e.g if you have a monolayer). **Proposed change** (if any): For CBIMP the following aspects should be considered as applicable: A clear definition of a production batch of drug substance ~~from cell sourcing to labelling of final container~~ should be provided (i.e. ~~size, information on intermediate cell banking,~~ number of cell bank vials used per batch or amount of source tissue/blood per batch, number of cell passages/cell population doublings, pooling strategies, batch numbering system). The purpose of the batch definition is to ensure	Accepted. Wording has been revised

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		consistency and traceability. If a continuous manufacturing process is used through to final drug product (i.e. no isolated drug substance), the batch definition should include all steps through to final drug product in its container.	
361	17	**Comment**: Recommendation of the agency for the expected data on pooling strategy	Rejected. Answer not generalizable.
363-370	5	**Comment**: Clarifications and typographical corrections are proposed. **Proposed change (if any)**: - **For CBIMP that do not use cell banks,** the IMPD should contain information on the volume/number of cells collected and a description of the manipulation steps after sourcing. This should include a description of any selection/separation equipment used. - **For all CBIMPs,** the type of manipulation(s) required for cell processing **and the conditions and duration of cell culture** shall be described. **Any wash steps or other manipulations to remove impurities should be described.** - Manufacture of combined medicinal products consisting of cells and matrices/ devices/ scaffolds require additional consideration regarding cell-matrix/ scaffold interactions and associated quality issues. Attention should be given to biodegradable materials, which may ~~effect~~ **cause** environmental changes (e.g. raising pH) for the cells during ~~the~~ manufacture.	Accepted.
366	15	**Comment**: Wording proposed to be changed. **Proposed change** (if any): The type and steps of manipulation(s) required for cell processing shall be described.	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
371-372	3, 5	**Comment**: It is proposed that terminology is clarified to explain the need to identify process intermediate storage and shipping conditions and to align wording with S.2.4. **Proposed change** (if any): Information on ~~procedures used to transport material during the manufacturing process of the product, including transportation and~~ process intermediate storage temperatures and times, and shipping conditions (if relevant) ~~and holding times,~~ should be provided.	Accepted. Section has been modified
373-374	10	There is a strong reliance of aseptic processing for ATMP manufacture, but in our experience basic procedures commonly used in the biotech industry, even simple things like 0.2um filtering media/supplements into a culture vessel, are not routinely performed. Such standard good practice to ensure microbial safety of the products should be highlighted in guidance's of this nature. **Proposed change**: Microbiological control is a pivotal aspect of process control; the procedures implemented to minimize microbial ingress should be described and justified, such as 0.2 µm filtration of media and supplement into culture vessels, as well as routine IPC testing for microbial contamination during manufacture	Accepted. Section has been modified
375	1	**Comment:** This section speaks to biologically based GTIMP. This needs to include synthetic/non-viral derived APIs.	Rejected. The ATMP definition excludes synthetic/non-viral derived APIs
376-377	3, 5	**Comment**: It is proposed that this is aligned with CBIMP to include reference to batch numbering system. **Proposed change** (if any): For GTIMP the following aspects should be considered as applicable: • Batch(es) and scale should be defined (including information on any pooling of harvests or intermediates, and batch numbering system, if appropriate).	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
380-382	1	**Comment**: Vector sequence stability and max passage number in short term culture may not be necessary, when properly justified.	Noted. ATMP development is meant to follow a risk-based approach.
380-383	5	**Comment**: Some modifications are proposed, e.g., inclusion of a reference to S.2.3 (cell line stability EEPCB studies) this is the same CTD structure as for biotech products (see ICHM4Q). The rationale for the chosen cell substrate in Line 383 is also better placed in S.2.3 where choice of starting materials is normally justified (aligns with biologics and small molecule structure, see ICHMQ4 Location issues– Quality Questions and Answers). S.2.2 does not contain this type of information as per ICHM4Q. **Proposed change (if any)**: • The applicant should establish that the vector sequence remains stable throughout cell culture. Where sufficient manufacturing experience permits, a maximal passage number for the cells should be established **and reported here (supporting genetic stability data for End of Production Cells should be in S.2.3).** • ~~The rationale for the use of a particular cell substrate should be provided.~~ • Vector sequence stability and max passage number in short term culture may not be necessary, when properly justified.	Accepted. Section has been modified
380-383	10	Hasn't this already been covered in general properties? You should specify the passage history limits of the vector and population doublings of the cells as part of the process control strategy of course, but demonstration of genetic stability would not be provided in this section. Furthermore, this a perfect example of where more firm guidance could be provided on regulatory expectation during product development: '*where sufficient manufacturing experience permits, a maximal passage number for the cells should be established.*' Are you suggesting such information should be included for phase 2 submissions, after 10 batches have been manufactured, or will you	Accepted. Section has been modified

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		approve confirmatory studies without this information, making it only needed for MAA?	
383	10	Rationales should be provided in general information. S.2.2 provides a description of the process, not a justification for the process or cell substrates used. See comment for row 329	Accepted
383	17	**Comment**: "The rationale for the use of a particular cell substrate should be provided". Discussion around this topic to be provided in S.2.6 Manufacturing Development section. **Proposed change** (if any): To remove the sentence **~~"The rationale for the use of a particular cell substrate should be provided"~~** from the S.2.2 section.	Accepted
384	1	**Comment:** A clarification of what is meant by hybrid virus is needed.	Accepted. Wording has been modified
384	5	**Comment**: "Impurities include **hybrid viruses** in the case of virus vector production, host cell-DNA and protein, residual plasmid DNA, lipids" **Proposed change (if any)**: Please, clarify what hybrid viruses means. Is it replication competent recombinant virus?	Accepted. Wording has been modified
384-388	1	**Comment:** It is suggested to include empty viral particles in the list of impurities in the case of viral vector production if these can impact the purity of the DP. Additionally, it is suggested to include an assessment of the ratio of infectious to physical particles in the case of viral vectors and a similar assessment of specific transduction efficiency (potency) for non-viral particles, if available.	Accepted. Wording has been modified

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
384-388	1, 6	**Comment**: The list of impurities does not seem complete, as for example in the case of viral vector production viral proteins that did not form capsids are considered as impurities as well; plasmid DNA is mentioned but any residual DNA not encapsidated is considered as an impurity (and can come from a virus as well or from a bacmid in the case of a manufacturing process involving the use of baculovirus, therefore not necessarily a plasmid DNA). Finally gene editing tools used in GTMPs such as CRISPR-Cas9 are not considered in this list of impurities. The list of impurities can either be completed trying to list all impurities depending on the manufacturing process and on the starting materials, or examples can be provided instead. As the list of impurities may evolve over time while new GTMPs are developed, it is proposed here to complete it while clarifying that this list is not exhaustive. In addition, in this paragraph the meaning of the sentence "Ideally steps should be taken over time, in design, construction and production to 84haracte or eliminate these "may require further clarification. **Proposed change:** ***"A purification process should be in place to*** *minimise or eliminate* ~~***reduce***~~ *product and process* ***impurities****. Impurities vary depending on the product and its manufacturing process. GTMP* ***impurities*** *can* ***include*** *(but are not limited to)* ***hybrid viruses****, empty viral particles, viral proteins, vector aggregates* ***in the case of virus vector production****; residual starting material (e.g. residual virus in the case of a manufacturing process using a virus (e.g. baculovirus) as one of the starting materials, residual gRNA or proteins in case of a manufacturing process which involves a CRISPR-Cas9 gene editing system)****;*** *residual DNA and proteins from the starting material (e.g.* ***host cell-DNA and protein, residual plasmid DNA****, residual viral DNA and proteins in the case of a manufacturing process using a virus as one of the starting materials,* ***lipids and polysaccharides in the case of production systems which involve bacterial fermentations****);* ~~***and***~~ ***RNA and***	Accepted. Wording has been added in S.3.2

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		chromosomal DNA in the case of plasmid ~~purification~~ *production**. ~~Ideally steps should be taken over time, in design, construction and production to minimise or eliminate these."~~***	
384-388	8	**Comment:** It is suggested to include an assessment of the ratio of infectious to physical particles in the case of viral vectors and a similar assessment of specific transduction efficiency (potency) for non-viral particles, if available.	Accepted. Wording added to S.4.1.
384-388	10	'*hybrid viruses in the case of virus vector production'*; the genetic engineering of the vector should minimise the production of such impurities as discussed in rows 285-6; it is difficult to envision how you could purify such hybrid viruses from the actual vector that is the product unless you resort to density gradients, as the composition of the hybrid vector is not going to be that significantly different to the product. We would consider it is preferable to minimise the possibility of such impurities being generated in the first place by genetic engineering and to ensure there is an appropriate control strategy around them as IPC where relevant but specifically in release testing of DS/DP. In early development, IPC testing to determine whether such impurities are being generated should be implemented and the contaminating levels quantified. Release testing for such impurities should also be implemented. Specific guidance on tackling such impurities should be added to this document.	Text has been moved and reworded.
384-388	10	The process description should identify which steps have been introduced to specifically remove impurities whether it is host cellular DNA, residual plasmid, DI particles or other supplements added. During process development/minimized the control strategy around that step should be defined, with data presented in S.2.6 as it becomes available and is relevant. Eventually it should be demonstrated that it is effective in removing that impurity, which may ultimately justify removing IPCs during manufacture or release	Accepted. Wording has been added.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		testing of the product for that impurity in the final specification at the time of MAA. **Proposed change:** A purification process should be in place to reduce process and product related impurities. Purification steps that have been implemented for the purpose of removing one or more process or product related impurity should be clearly identified. The control strategy around such steps should be defined as the process develops, and ultimately the effectiveness of that step to remove impurities demonstrated, ideally prior to confirmatory trials, but certainly prior to MAA.	
385-386	15	**Comment**: Unclear for which products lipid and polysaccharide impurities should be considered. **Proposed change** (if any): Please provide examples when lipids and polysaccharide impurities should be considered as impurities or delete.	Accepted. Wording has been revised
387-388	15	**Comment**: Unclear what is meant by construction. Construction of the process or the active substance? In case of the latter more information is required on the impact of changes to the IMP. Moreover, this statement may be read to encourage major process changes irrespective of comparability issues. **Proposed change** (if any): Please provide clarification.	Accepted. Wording has been revised
388 390	5	**Comment**: It is proposed that this information is deleted to simplify. Methods to prevent contamination and environmental control are not covered in S.2.2, which focuses on process controls to test for contamination so "assess" (rather than "prevent") seems more appropriate.	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Proposed change (if any): • A purification process should be in place to reduce impurities. Impurities include hybrid viruses in the case of virus vector production, host cell-DNA and protein, residual plasmid DNA, lipids and polysaccharides in the case of production systems which involve bacterial fermentations, and RNA and chromosomal DNA in the case of plasmid purification. Ideally steps should be taken ~~over time, in design, construction and production~~ to characterize or eliminate these. • For non-replication competent viral vectors and conditionally replicating viral vectors, information should be provided on process parameters, and controls conducted to ~~prevent~~ **assess the potential** contamination of the packaging cell line by wild-type, helper or hybrid viruses which might lead to the formation of replication-competent recombinant viruses during production.	
389-392	15	Comments: Suggest to replace "non-replication competent" by "replication-deficient". Second part of sentence is considered to be a GMP issue and also covered by RCV testing. Suggest to delete. **Proposed change** (if any): - For replication-deficient ~~non-replication competent~~ viral vectors and conditionally replicating viral vectors, information should be provided on process parameters~~, and controls conducted to prevent contamination of the packaging cell line by wild-type, helper or hybrid viruses which might lead to the formation of replication-competent recombinant viruses during production~~.	Accepted
393-396	10	The comments are here more relevant to S.4.2/4.3 and P.5.2/5.3 than the manufacturing description, as you are describing assay performance rather than process control. More detail on what constitutes an acceptable IPC test should be given in the method section.	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		What would be helpful in addition is to give guidance as to where IPC tests (that are not used for release purposes) should be describe, in relation to their qualification status. Should this be described in a subsection in S.2.2 or is it better placed as a subsection in S.4.2.? **Proposed change:** For conditionally replicating virus vectors, a suitably qualified in process test is essential to show that replication competent viruses are controlled within acceptable limits. For non-replication competent viral vectors, the absence of RCV should be demonstrated using a suitably qualified assay.	
395	3	**Comment**: What is an appropriate level of sensitivity for detecting RCV?	RCV wording has been updated; a specific statement on assay sensitivity is not feasible.
395	15	**Comments**: Suggest to replace "non-replication competent" by "replication-deficient". Absence of RCV might not be feasible for all viral vector types. **Proposed change** (if any): For replication-deficient ~~non-replication competent~~ viral vectors, the absence or level of RCV should be controlled with an assay of appropriate sensitivity.	Partially accepted, reworded.
395-396	12	**Comment**: Clarification/guidance is requested for the appropriate level of sensitivity for detecting RCV. Proposed change (if any):	RCV wording has been updated; a specific statement on assay sensitivity is not feasible.
397-398	10	*Manufacturers should seek to control unintended variability as far as possible, for example in culture conditions or inoculation steps during production.*	Accepted. Wording has been revised

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		We do not really follow what the intention is with this sentence. Surely as a minimum incubation conditions should be clearly described with defined ranges around temperature, CO_2 etc, even for FIM studies; furthermore, batch manufacturing records would be written so inoculation procedures should, in theory be minimized, so we are wondering if you inferring to operator induced variability? If so, perhaps this can be more clearly written making it clear that appropriate training and qualification of operators, where processes are heavily reliant on manual procedures, is needed to 89inimize this.	
399-400	10	See comment for row 373-374	
399-400	15	**Comment**: Clear distinction between different microbiological quality requirements depending on the IMP/process characteristics **Proposed change**: The manufacturing process must be set up to minimise the risk of microbiological contamination. However, IMPs required to be sterile have to be processed aseptically.	Accepted. Wording has been revised
400	13	**Comment**: Consider if applicable to include the interval of manufacturing process in number of days. This is crucial when working with cell therapy for instance. If this is ok, then should be included in the document (adding its section) Proposed change (if any):	Accepted.
401	11	**General comment on S.2.3**: This section would benefit from some re-organisation. Some text could be shortened by reference to e.g. Ph.Eur. 5.2.12 because that and other guidance cover much of what is said here. We also urge that comments under this main heading are limited to the information that is presented in S23, or where necessary the text could direct the reader to other sections.	Accepted. The section has been restructured and rewritten

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Sub-heading line 402, this heading might be useful if changed to something like 'materials specifications' and address common concepts of materials control, adventitious agents etc., with the next sections addressing specific comments. We would appreciate clarity that GMP is not a grade, and the possible grades are limited to pharmacopoeia, licensed medicine or in-house (defined by the developer, not the supplier (the term manufacturer is ambiguous). Comments could be useful on the use of CE marked ancillary materials for medical devices, and whether these require further justification (as they are used outside the medical device approval).	
402-416	5	**Comment**: In the subsection on Raw and starting materials, suggestion to add the following: "Describe the definitions of starting materials and the principle of risk-based approach that may be applied to determine the extent of quality, non-clinical and clinical data to be included in the IMPD and afterward in the MAA."	Partially accepted. Wording modified
403-405	12	**Comment**: Clarification/guidance on qualification requirements for raw materials versus starting materials would be helpful. Proposed change (if any):	Rejected. Requirements need to be justified with respect to context of use
406-408	3, 5	**Proposed change** (if any): It is proposed that this information be deleted as it is a copy of lines 421-423. ~~Reference to quality standards (e.g. compendial monographs or manufacturer's in-house specifications) should be made where possible. If non-compendial materials are used, information on the quality and control thereof should be provided.~~	Accepted.
407-408	1	**Comment**: Regarding acceptance criteria for raw and starting materials, it would be helpful to provide additional guidance on what kind of information would be acceptable for non-compendial materials.	Rejected. Requirements need to be justified with respect to context of use

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
409-410	10	*'minimising variability'* is not always feasible, particularly where you have an allogeneic product, given there is considerable donor to donor variability, rather understanding which QA of the starting material influences significantly product quality, and implementing procedures to ensure those CQA of the starting material are met, will hopeful act to improve product consistency. QA that may be important will include microbial and viral safety attributes as well as defined cell populations for cell therapies if the starting materials is donor APH for example, and P:I ratio's of vectors. **Proposed change:** The quality of starting and raw materials is a key factor in the production of ATMPs. During product and process development effort should be made to identify those quality attributes that may affect product quality and patient safety, and implement control measures where feasible, to minimise quality impact and improve final product consistency. Criticality assessments of raw materials with respect to their impact on product quality should be undertaken, with appropriate raw material release testing implemented to ensure consistent quality of the raw materials.	Acknowledged. General statement, but different approaches may be justifiedin the context of the risk based approach.
412	10	Adequate precautions need to be set to ensure proper handling **Proposed change:** Suggest revising to 'Adequate procedures and training need to be implemented to ensure proper and consistent handling.	Acknowledged. The section has been reworded
415-416	12	**Comment**: Specific reference of the applicable legislation and guidelines would be helpful. Proposed change (if any):	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
417-461	11	General comment on S.2.3: This section would benefit from some re-organisation. Some text could be shortened by reference to e.g. Ph.Eur. 5.2.12 because that and other guidance cover much of what is said here. We also urge that comments under this main heading are limited to the information that is presented in S23, or where necessary the text could direct the reader to other sections. Sub-heading line 402, this heading might be useful if changed to something like 'materials specifications' and address common concepts of materials control, adventitious agents etc., with the next sections addressing specific comments. We would appreciate clarity that GMP is not a grade, and the possible grades are limited to pharmacopoeia, licensed medicine or in-house (defined by the developer, not the supplier (the term manufacturer is ambiguous). Comments could be useful on the use of CE marked ancillary materials for medical devices, and whether these require further justification (as they are used outside the medical device approval).	
419	15	**Comment**: Human serum and human platelet lysate are widely used **Proposed change** (if any): Raw materials are the reagents that are used during the manufacturing process but are not part of the final product. Examples include foetal bovine serum, human serum or platelet lysates, trypsin, digestion enzymes……	Accepted
420	3, 5	**Proposed change** (if any): It is proposed that the reference to cell separation devices is deleted, as this is process equipment, not raw material, and so goes in S.2.2. Usually cell separation devices use reagents that are classed as raw materials (e.g. antibodies, beads etc). Examples include foetal bovine serum, trypsin, digestion enzymes (e.g., collagenase, DNAse), growth factors, cytokines, monoclonal antibodies, antibiotics, resins, ~~cell separation devices,~~ and media and media components.	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
423-425	1	**Comment:** It is suggested not to have this level of details in the IMPD. The amount of details to be provided should be based on the risk assessment. A statement that the raw materials have been found to be suitable for their use should suffice.	Rejected. This is part of regulatory review
425	15	**Comment**: As a principle , risky media additives should be avoided as early as possible during development **Proposed change** (if any): …suitable for their intended use should be provided. The necessity for media additives with risk of adventitious agent contamination (e.g. bovine or human serum, platelet lysates) for the culture of CBIMP with specific cell types should be carefully considered. For example, T cell cultures may be able to grow in the absence of animal or human serum. Where such materials are used, their use should be justified e.g. by supporting data.	Agreed, this is implicit from other text passages.
425-426	15	**Comment**: This request rather has the perspective of a MAA. Especially for explorative trials, raw materials with an adequate quality may be acceptable, even when not of pharmaceutical grade. Reference to Ph.Eur 5.2.12 may be given. **Proposed change** (if any): ~~While~~ raw materials should preferably be of pharmaceutical grade. However, it is acknowledged that, in some cases, other raw materials of adequate quality may be used, especially when only materials of research grade are available.	Accepted. Reworded.
427	5	**Comment**: Risks of using research grade materials should be assessed and documented, in addition to being understood. **Proposed change (if any)**: The risks of using research grade materials should be assessed, understood and documented in the	Comment noted. Required information is covered by standard GMP and IMPD requirements.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		IMPD (including the risks to the continuity of supply when larger amounts of product are manufactured).	
429-430	12	**Comment**: Clarification/guidance on whether considerations of raw material suitability should also include assessment of purity and stability in respect of the material's intended use in the manufacturing process. Proposed change (if any):	Rejected. Requirements need to be justified with respect to context of use
431-432	3	**Comment**: irradiated reagents tested for adventitious agents pose minimal risk. **Proposed change** (if any): Refer to EMA/410/01 rev 3 document within the text. (added on 15/7/2019)	Agreed and relevant text can be found in other sections.
431-434	1	**Comment:** It is suggested that one should also aim to reduce human derived materials (i.e. transferrin, albumin) due to viral safety. As it is not always possible to replace animal/human reagents with non-animal/human reagents, a risk-based approach should be taken and referred to in the guideline. **Proposed change:** Consider replacing the 2 last sentences in this paragraph as follows: *"Where possible, the use of human or animal raw materials should be avoided and replaced by non**-human/**animal derived raw materials of defined composition**~~. This is~~** **,** *due to their potential to introduce adventitious agents **~~and resulting additional requirements~~.*** ***Where necessary, manufacturers should justify the use of human and animal starting materials and should perform a risk assessment with additional testing to reduce contamination by adventitious agents."***	Accepted. Reworded
431-434	8	**Comment:** It is suggested that one should also aim to reduce human derived materials (i.e. transferrin, albumin) due to viral safety. As it is not always possible to replace animal/human reagents with non-	Accepted. Reworded

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		animal/human reagents, a risk based approach should be taken and referred to in the guideline. **Proposed change:** Consider replacing the 2 last sentences in this paragraph as follows: *"Where possible, the use of human or animal raw materials should be avoided and replaced by non-human/animal derived raw materials of defined composition, due to their potential to introduce adventitious agents. Where necessary, manufacturers should justify the use of human and animal starting materials and should perform a risk assessment with additional testing to reduce contamination by adventitious agents."*	
431-434	15	**Comment**: The statement for avoidance of animal reagents is endorsed. However, such statements are considered dangerous with respect to viral or prion safety as it might provoke a switch from animal-derived reagent (sera) to human-derived reagents. There is no species barrier for human viruses and there may be also a risk for transmission of human prion diseases with some raw materials. **Proposed change** (if any): Where possible, the use of animal and human reagents should be avoided and replaced by non-animal/non-human-derived reagents of defined composition (e.g. synthetic or from microbial or plant sources). This is due to their potential to introduce adventitious agents and resulting additional testing requirements.	Partially accepted. Reworded
435	17	**Comment**: Typically information on suppliers is only provided for starting materials (cell bank system …) Please clarify if supplier information is intended for other materials.	Accepted
435-436	17	**Comment**: For all raw materials of biological origin, information on stage of the manufacturing process where the material is used and risk assessment are part of the A.2 section	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
439	3, 5	**Comment**: It is proposed to clarify that helper viruses are raw materials and not starting materials and the level of detail expected. **Proposed change** (if any): add after Line 439 **Helper viruses are also classed as raw materials, however detailed descriptions of their design, construction, production and the banking system used should be provided with the same level of detail as is required for the starting materials.**	Accepted
445-448	15	**Comment**: Human sera and platelet lysates are frequently used as media additives but are made from blood or platelet donations rather than from plasma donations and a PMF will not be always applicable. PMFs may include whole blood donations as well as plasma donations. Reference to Ph. Eur. 5.2.12 and Ph. Eur. 5.1.7 is considered in principle adequate. However, experience from assessment of clinical trial applications, showed that it is necessary to give additional guidance with respect to the use of virus-inactivated human blood-derived raw materials. **Proposed change** (if any): Raw materials derived from human plasma or from blood components (e.g. platelet lysates) should be sourced from blood/plasma collected under an EU approved Plasma Master File (PMF). Otherwise, if the collection and testing has no EU authorisation and no PMF reference it should be confirmed that the recommendations provided in Ph. Eur. 5.2.12 and Ph. Eur. 5.1.7 are followed. In line with Ph. Eur. 5.1.7 and Guideline of plasma-derived products (EMA/CHMP/BWP/353632/2010) consideration is given to adequate virus inactivation/removal and human TSE-safety as outlined in CHMP/CAT position statement on Creutzfeldt-Jakob disease and advanced therapy medicinal products (EMA/CHMP/BWP/353632/2010) and CHMP Position Statement on Creutzfeldt-Jakob disease and plasma-derived and urine-derived medicinal products. (EMEA/CHMP/BWP/303353/2010.	Accepted, reworded.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
452	1	**Comment:** It is not clear what microbial purity means, no bioburden or low level bioburden? It is not always possible to source raw materials with demonstrated microbial purity. Therefore, options such as the sterile filtration of solutions before use should be acceptable. Overall, lack of impact on the active substance would need to be demonstrated. **Proposed change:** "*Microbial purity and low endotoxin level of raw materials should be ensured**, as far as possible***." Consider adding clarifications when bioburden free ingredients are not available.	Accepted, reworded.
452	5	**Comment**: Suggest adding 'as appropriate' to take into account specific circumstances for unusual processes or raw materials. Holding very high standards for raw materials used in ATIMP production can be inhibitory. While safety should always be ensured for patients, it should be possible to take into account circumstances that are different for ATIMPs than for conventional IMPs. **Proposed change**: "Microbial purity and low endotoxin level of raw materials should be ensured**, as appropriate."**	Accepted, reworded.
452	15	**Comment**: Clarification required that there may be different expectations on the microbiological quality of raw materials depending on the process/IMP characteristics (sterile, bioburden, spec. micro-organisms, endotoxin level irrelevant, etc.) **Proposed change**: ~~Microbial purity and low endotoxin level of raw materials should be ensured.~~ For all raw materials confirmatory documentation is required demonstrating their adequate quality with respect to microbiological safety in context of the special process/product characteristics of the IMP.	Accepted, reworded.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
453	3, 5	**Comment**: Rewording of 453 is suggested to make applicable to all ATIMP. **Proposed change** (if any): The manufacturing process of ATIMP~~CBIMP~~ usually does not include terminal sterilization, ~~purification steps,~~ viral removal and/or inactivation steps.	Accepted
455	5	**Comment:** "[…] acceptance criteria for all materials derived from human or animal origin should be adequately defined […]" Suggest flexibility with regards to tissue requirements and how to balance sample acceptance criteria, manufacturability and sequence quality.	Rejected. Legal requirements apply.
456 – 457	1	**Comment**: We recommend adding the appropriate guidance reference number for clarity following the instruction **Proposed change**: "*Sterilisation conditions applied to all materials can be found in the Guideline on the 98haracterized of the medicinal product, active substance, excipient and primary container* ***(EMA/CHMP/CVMP/QWP/850374/2015).***"	Accepted
456-457	5	**Comment**: Relocation of information on sterilisation guideline to S.6 and P.7 where it will be of more relevance is suggested. **Proposed change (if any)**: …to their intended use. ~~Sterilisation conditions applied to all materials can be found in the *Guideline on the 98haracterized of the medicinal product, active substance, excipient and primary container.*~~	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
458-461	15	**Comment**: Considered to be a GMP issue. **Proposed change** (if any): delete ~~In accordance with Article 15 of Regulation 1394/2007, traceability information should also cover raw materials and all substances coming into contact with the cells or tissues. Details on the implementation of this obligation have been developed in the Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products.~~	Accepted
485-461	17	**Comment**: GMP consideration is out of the scope of the data requirements for clinical trial application. Details around GMP compliance should not be required in CTA submissions	Accepted
462 (section on starting materials for CBIMP)	1	**Comment:** "*Primary cells cultured for a few passages before being used for the CBMP (cell stocks)*": considering this sentence, the *primary cells* can be considered the starting material. And regarding line 469 and 507-509 and 539, culturing/expanding this "starting material" (primary cells) might allow to establish a cell stock. However, this is confusing when considering lines 538-546, whether the cell stock is also considered as the starting material. Additional clarification is being sought and it would be helpful to detail where primary cells and cell stocks should be described in the IMPD. An approach to consider is that: - the primary cells (e.g. a bone marrow sample) are the starting material (which can be controlled, characterized,...) and are described in the section S.2.3. - the issued cell stock (after expansion and/or other processing) is an intermediate in the manufacturing process (this cell stock (limited number of vials) can be then stored and further used to manufacture CBIMP according to line 540) and is described in section S.2.4.	Accepted. The section has been restructured and reworded**.**

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
462-486	11	Comment: First sentence isn't aligned with the ICH definition of a starting material – they are partially or wholly incorporated into the active substance. line 466 – once processed means after manufacturing has started, yet this is S23. However, we appreciate this may be useful, but as written it needs to be amended to avoid confusion: General: unclear (given heading on line 487) if this sub-section applies to primary cells only, or cell lines (e.g. producer cells for vector, feeder cells) which is important because the approach will differ. Line 469 – the cell stock (intermediate) would be described in S24, please acknowledge this. 470-471: if the cell banking system is made once for the whole product lifecycle (unlikely for CBMP), it would be described here in s23 similarly to a cell substrate for biotech. However, if it was an allogeneic cell bank system with a limited lifetime, its preparation would be included in S22, and the control of the banking system described and justified in S24. Please clarify this in the text. If the cell bank system is a cell substrate, producer cell for vector manufacture, or feeder cell, this would follow the biotech convention and preparation and control of the cell bank would be described here in S23. 473-474: isolation of the cells would be described in S22 and justified in S24 – not here in s23, please clarify this in the text. 475-476: for CBMP this would be described in S22/S24 (unless the cell bank lasts the product lifecycle). 477-486: Pooling would occur after initial isolation, therefore an intermediate stage of manufacturing; consequently, this comment belongs in S22 and S24. It is also noted that the recommendation on pooling differs a little from the previous CBMP guideline, it might be helpful to expand on this. It is assumed the last statement on identity testing relates to banked cells; in which case what aspect/s of identity are meant? Identity of the cell type is generally understood, but there is also the question of traceability if the donor where multiple cell banks of the same cell type will be present in a single manufacturing facility. Please add recommendations on this	Accepted. The section has been restructured and reworded**.**

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		aspect, e.g. is DNA fingerprinting or similar expected, should isoenzymes be used, would HLA be sufficient etc. Otherwise the statement says identity, but indirectly asks also for evaluation of purity (quantification of positive cells). It would be helpful if this can be clarified. Proposed change (if any): See above.	
464	5	**Comment**: The flow of information on starting materials is very confusing and hard to follow. As per other types of product (biologics/small molecules) and in line with ICH M4Q and ICHMQ4 Location issues– Quality Questions and Answers, it is proposed to move all information on starting materials (definition, source, manufacturing overview, control) to be together under Section S.2.3. Text has been deleted from other sections of the guideline and merged into S.2.3 as proposed below (see line numbers to show where merged information is taken from). **Proposed change (if any)**: add lines 233-237 below line 464. ***Starting materials for CBIMP*** This section applies to all materials that will be part of the active substance and is not limited to cells or tissues. **Additional substances (e.g. scaffolds, matrices, devices, biomaterials, biomolecules and/or other components) when combined as an integral part with the ~~manipulated~~ cells are considered part of the active substance and are therefore considered as starting materials, even if not of biological origin. Information on~~ relevant~~ manufacturing and control and viral safety aspect of these additional substances needs to be provided.**	Accepted. The section has been restructured and reworded**.**

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
466 474	5	**Comment**: The flow of information on starting materials is very confusing and hard to follow. As per other types of product (biologics/small molecules) and in line with ICH M4Q and ICHMQ4 Location issues– Quality Questions and Answers, it is proposed to move all information on starting materials (definition, source, manufacturing overview, control) to be together under Section S.2.3. Text has been deleted from other sections of the guideline and merged into S.2.3 as proposed below (see line numbers to show where merged information is taken from). Edits are proposed to clarify what is the starting material as this is frequently a point of confusion for ATMP developers. **Proposed change (if any)**: ***Cells*** **The following types of starting materials are obtained from processing** donated cellular material (cells or tissues) from single or multiple donors~~, once processed may be~~: • A single primary cell isolates or cell suspensions containing various naturally occurring cell types used directly for the CBMP; • Primary cells cultured for a few passages before being used for the CBMP (cell stocks); • Cells based on a well-defined cell bank system consisting of a master cell bank and a working cell bank. The cell source should be documented, as well as tissue and cell type, and any patient pre-treatment required prior to donation. The procedure to obtain the cells from their source has to be described (with respect to the type of enzyme, media, etc.) and the purpose of respective steps explained. **For CBIMPs where the cellular starting materials are obtained through specific technologies (e.g. reprogramming, genetic modification, activation), the origin and the type of the initial cells, information on the processing technique together with the target function need to be provided.** Establishment and testing ……	Accepted. The section has been restructured and reworded**.**

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
472	10	Donors of materials may not always be patients. **Proposed change:** …, and any donor/patient pre-treatment …..	Accepted, wording has been changed.
472-474	1	**Comment:** More clarity is needed in case of multiple methods used for donation. For example, some patients are mobilised and some not for getting peripheral blood for an autologous process.	Accepted, information has been included.
475-476	15	**Comment**: Add Guideline-number **Proposed change** (if any): Establishment and testing of cell stocks or cell banks should be conducted according to the Guideline on human cell-based medicinal products (EMEA/CHMP/410869/2006).	Accepted, included in reference list.
477	15	**Comment**: Too general statement taking into account that products based cell pooling are undue development and in clinical trials. **Proposed change** (if any): suggest to rephrase ~~In general, cell pooling should be avoided as it raises questions if the clinical outcome is affected~~ In general, cell pooling may raise the question whether the clinical outcome may be affected by the variation of the starting materials from different donors.	Accepted, the wording has been changed.
477-478	1	**Comment:** This statement is unclear as pooling cells reduces variability rather than increasing it. In general, cell pooling should be avoided for safety reasons rather than for variability of the starting materials from donors. Please consider rephrasing this sentence.	Accepted, the wording has been changed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
484-486	15	Comment: As the focus of the GL is on exploratory trials this seems to be a too stringent requirement for all kind of products, e.g. in case of complex mixtures of cell types. Proposed change (if any): delete The identity of the cells used as starting material should be verified by relevant genotypic and/or phenotypic markers. ~~and t~~The proportion of cells bearing these identity markers may be evaluated as an indicator of the intended cell population.	Rejected. Knowledge on the nature of the starting material is essential. The risk based approach may be leveraged in justified cases.
487-509	11	**Comment**: 491-495: this is already explained on lines 477-486; suggest remove or reference backwards. 497-502: this statement relates to S22/S24 and should be moved. The question of whether is considered necessary to test sterility of the starting material is not addressed as a result, please add a statement as to this effect instead. Antibiotics are mentioned here, yet this is not discouraged (we think it should be) nor is there mention of which types of antibiotics should be favoured or avoided (e.g. beta lactams). 507-509: in this situation those data would be in S24; please move comment. **Proposed change** (if any): modify as outlined above.	Accepted, reworded.
491-494	15	**Comment**: Redundant to lines 480/481. **Proposed change** (if any): suggest to delete ~~If it is necessary to pool cells from different donors, the risk analysis should address the possibility that pooling of allogeneic cell populations may increase the risk of undesired immunological responses in the recipient and compromise its therapeutic activity.~~	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
491-495	3, 5	**Comment**: Information in Lines 491-494 is duplicated in Lines 479-481. **Proposed change** (if any): It is proposed to delete Lines 491-494 and merge Line 495 to below Line 481. In general, cell pooling should be avoided as it raises questions if the clinical outcome is affected by the variation of the starting materials from different donors. In case of pooling of similar allogeneic cell populations, the pooling strategies, pool size and measures to ensure traceability shall be described. A risk analysis should be conducted addressing the possibility of undesired (immunological) responses and disease transmission due to the pooling. ~~If it is necessary to pool cells from different donors, the risk analysis should address the possibility that pooling of allogeneic cell populations may increase the risk of undesired immunological responses in the recipient and compromise its therapeutic activity. In addition, pooling of cells may increase the risk of disease transmission~~. Depending on the nature of the source of the cells and tissues, other risk factors, e.g. previous radiation exposure, should be also considered and addressed. An adequately controlled cell storage system should be established ….	Accepted
497-500	15	**Comment**: In specific cases a screening approach may be justified. However as a general requirement it is not regarded adequate. **Proposed change** (if any): Microbiological quality of the procured cells should be tested, by compendial/validated methods. ~~A specific microbiological screening programme should be in place, adapted to the type of cells, at the most suitable or relevant step of the manufacturing process, with validated assays capable of detecting human infectious agents with appropriate sensitivity and taking into consideration the m~~Medium components that might interfere with the assays (e.g. antibiotics) should be taken into consideration for ensuring test sensitivity.	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
501-502	15	**Comment**: Product specific acceptance criteria according to intended use should be defined in any way, not only in case of procurement from non-healthy tissue **Proposed change** (if any): ~~When cells originate from non- healthy tissues, the~~ product specific acceptance criteria should be defined according to the intended use.	Partially accepted, reworded
508-509	15	**Comment**: Unclear which characterisation attributes should be considered. **Proposed change** (if any): More information on suitable attributes for characterisation should be added.	Rejected. This requires product-specific discussion.
510-537	11	**Comment**: Cell lines clearly follow the biotech approach and as such this text could simply cite those biotech guidance's (e.g. FIH for biotech guideline); additional text seems unnecessary. The situation for hESC and iPSC should be under a separate heading, we also refer to comments we made on lines 462-486 about cells that might supply the product lifecycle. It may make more sense to integrate in that section. The text clarifies it is the primary cells that are the starting material for iPSC, therefore the manufacturing steps that lead to iPSC generation would be described in S22/S24; this text should be moved there. For hESC it is assumed the isolation steps would be described here in S23, e.g. akin to biotech approach for a cell substrate. In which case this makes sense here (stablished cell lines). Line 534-537: this relates to characterisation (S3) and manufacture (isolation step, S22/S24). Please move these, or reference where such data would be located.	Partially accepted, text reworded.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Proposed change (if any): Simplify, either have a separate heading for hESC/iPSC or address them under primary cells.	
514-518	5	**Comment**: Simplifying edits are proposed: line 516 is a repeat of line 514. **Proposed change (if any)**: Information on the cell banking **process**, and characterisation and testing of the established cell banks should be provided, as well as available information on cell substrate stability. ~~The MCB and/or WCB (if used) should be characterised and results of tests performed should be provided.~~ The generation and characterisation of the cell banks should be performed in accordance with principles of CPMP/ICH guideline Q5D.	Accepted
516-518	15	**Comment**: Ph Eur 5.1.14 (Gene transfer medicinal products for human use) makes reference to Ph. Eur. 5.2.3 with respect to testing of cell substrates. **Proposed change** (if any): The generation and characterisation of the cell banks should be performed in accordance with principles of CPMP/ICH guideline Q5D and Ph. Eur. 5.2.3.	Partially accepted. Due to Ph.Eur revisions only general references are made
522	1	**Comment:** "*extensive viral safety*". It would be helpful to clarify what "*extensive*" means and if bacterial safety testing in the case of missing bacterial donor screening is also possible (only viral testing is mentioned). Limits of levels to exclude donors should be provided if possible.	Accepted, reworded.
527-530	12	**Comment**: Clarification is requested on what is considered initial manufacturing steps. Proposed change (if any):	Reference is made to the Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products
527-530	15	**Comment**:	Accepted, reworded.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Cell banks are considered to be starting material. Thus their manufacture is not needed to be performed under GMP compliance anyway. **Proposed change** (if any): delete this sentence ~~It is understood that in cases where the early steps for the generation of ESC or iPSC banks are conducted before a clear product concept is present, the initial manufacturing steps might not have been conducted under full GMP compliance.~~	
531	1	**Comment:** (i) correct minor typo, and (ii) section 7.35 in the GMP for ATMP guidelines does not appear to exist, please clarify or correct. **Proposed change**: "*…as describe**d** in the GMP…*"	Partially accepted. Typo corrected. 7.35 does exist
531	3, 5	**Comment**: The full reference should be provided. Proposed change (if any): At the minimum, the GMP principles should be followed in this exceptional situation, as described in ~~the GMP for ATMP guidelines~~ section 7.35 of Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products.	Accepted
532-533	12	**Comment**: Specific reference to applicable guidelines would be helpful. Proposed change (if any):	A non-exhaustive list of references is provided

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
534-537	3, 5	**Comment**: This information is confusing and seems out of context here. Deletion is therefore proposed. Control of starting materials is already addressed elsewhere. Alternatively, if this text is supposed to be specific to the IPSC two paragraphs above, merging with that paragraph is suggested. **Proposed change** (if any): ~~The origin and procurement of the starting material to isolate the stem cells is considered critical for the yield and identity/purity of the final cell population.~~ ~~The selection of appropriate markers is fundamental to the characterized109n of isolation conditions and to control cell populations, heterogeneity and yield.~~	Accepted
534-537	10	This paragraph appears to be addressing specifically the starting materials for isolation of stem cells, which implies they are being isolated from adipose tissues or bone marrow or other tissue, but it is discussed in the section titled 'Banking system for established cell lines. Surely this fits better in the Cells of primary origin section? The same principles could apply to other defined cell populations being specifically isolated; for example in our case we isolate monocytes from donor apheresis, however while we use cell markers for identity purposes and to quantify the number of target cells in the starting material, we do not use cell markers for isolation procedures i.e. if using clinimax. This paragraph should perhaps be written more generically to address different types of cell isolation procedures. *'The selection of appropriate markers is fundamental to the standardisation of isolation conditions and to control cell populations, heterogeneity and yield'* this does not seem to be necessarily relevant to the control of starting materials, as such it does not seem to be discussed in the correct section unless you are considering the isolated cell population as a starting material also? We consider the first step of the manufacturing process is the isolation of the required	Accepted, reworded

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		cell population from the starting material. This enriched cell fraction is a process intermediate, and it is well characterised using cell markers. **Proposed change:** Suggest moving this paragraph to the Cells of primary origin section. Revise to be written more generically rather than specifically for stem cells. Remove reference to the markers for isolation of the required cell populations, this is better discussed in S.2.2. as part of the process description instead.	
538-546	11	**Comment**: Cell lines clearly follow the biotech approach and as such this text could simply cite those biotech guidance's (e.g. FIH for biotech guideline); additional text seems unnecessary. The situation for hESC and iPSC should be under a separate heading, we also refer to comments we made on lines 462-486 about cells that might supply the product lifecycle. It may make more sense to integrate in that section. The text clarifies it is the primary cells that are the starting material for iPSC, therefore the manufacturing steps that lead to iPSC generation would be described in S22/S24; this text should be moved there. For hESC it is assumed the isolation steps would be described here in S23, e.g. akin to biotech approach for a cell substrate. In which case this makes sense here (stablished cell lines). Line 534-537: this relates to characterisation (S3) and manufacture (isolation step, S22/S24). Please move these, or reference where such data would be located. **Proposed change** (if any): Simplify, either have a separate heading for hESC/iPSC or address them under primary cells.	Rejected. The guideline is intended as stand-alone document to the extent possible.
547-557	11	**Comment**: Suggest a standalone heading, not within C. cell stocks. It is not clear if these comments actually relate to early clinical studies; there is much confusion as to how to address medical devices that might themselves be investigation into an ATIMP, for example. When would it be necessary to engage the NB, before FIH,	Separate heading accepted, reworded.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		or after? Most importantly, it isn't clear what information should be provided in S23 – the purpose of this guideline. Are details of any medical device expected here in S23 or in e.g. R? **Proposed change** (if any): Separate heading, e.g. D. Structural components. Address comments above in revised text as far as possible.	
548-549	12	**Comment**: Clarification using examples or reference to appropriate guidances is requested for structural components as starting materials that may be considered medical devices. Proposed change (if any):	Accepted, reworded.
550	1	**Comment**: Correct minor typo **Proposed change:** *`…laid down ~~**in**~~ **under** EU legislation''*	Accepted
554	1	**Comment:** It is suggested to include guidance on CE marked devices being used for a different use than the approved one.	Accepted, reworded.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
558-570	1, 6	**Comment**: The list of possible starting materials for GTIMP includes *ex-vivo* genome editing tools but not cells. It is not clear if the term "viral vectors" here only covers viruses used for *ex-vivo* cells transduction (*e.g.* excluding baculovirus, or phages in case of a bacterial GTMP) or not. In addition, clarity could be increase concerning the sentence "*The same level of information that is needed for the vector as active substance should be provided in this situation*". It is understood that for viral and non-viral vectors used to transduce patients' cells *ex-vivo*, the same level of information as for an active substance should be provided in the starting materials section. As this precision is only provided in the "viral vectors" paragraph, it is not clear if this requirement applies for all *ex-vivo* genome editing tools or for viral vectors only. Therefore, a different wording is proposed hereafter, based on the above understanding. In addition, as stated as comments on lines 247-249 for *ex vivo* gene therapies, we believe a risk-based approach should be applied to determine whether genome editing tools used to generate genetically modified cells, plasmids, or cells used to produce vectors will form part of the active substance and should be considered starting materials. It is recommended to adapt the text in this sub-section to address the above considerations and clarify requirements. **Proposed change**: ***Ex-vivo* transduced cells are starting materials. The genome editing tools (viral or non-viral vector) used to transduce those cells are starting materials as well, even when not remaining in the active substance.** ~~Information on the vector should be provided in the starting material section~~ **The level of information provided on the vector (viral or non-viral) used for *ex-vivo* cell transduction should be the same as for the active substance, and should be provided in the starting material section**. ~~The same level of information that is needed for the vector as active substance should be provided in this situation.~~	Accepted, reworded.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		~~Viral vectors are starting materials, also when used to transduce cells and not remaining in the active substance . Genome editing tools used ex vivo to generate genetically modified cells are by analogy also 563 considered as starting materials.~~ Also, for *in vitro*-transcribed (m)RNAs used as active substances, the linearized template plasmid DNA should be considered as a starting material. Complexing materials[6] for formulating the drug substance are considered as starting materials and have to be qualified for their intended purpose. The level of information to be provided will depend on nature of the complexing material and resulting DS. **Information on all starting materials should be provided in the starting materials section.** For further requirements refer to S.3.1.	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
558-563	3, 5	Comment: The flow of information on starting materials is very confusing and hard to follow. As per other types of product (biologics/small molecules) and in line with ICH M4Q and ICHMQ4 Location issues– Quality Questions and Answers, it is proposed to move all information on starting materials (definition, source, manufacturing overview, control) to be together under Section S.2.3. Text has been deleted from other sections of the guideline and merged into S.2.3 as proposed below (see line numbers to show where merged information is taken from). There is also no clear overview of starting materials for GTIMP here, so addition is proposed. In addition, for vector-based products using Packaging/Producer Cell Lines, the plasmid is also a starting material. This is not clear in the current draft. It is also proposed to delete the draft text on viral vectors and genetically modified cells and in vitro mRNA (line 559-566) as it is currently unclear and is covered by proposed new wording taken from other parts of the IMPD draft document. Proposed change (if any): ***Starting materials for GTIMP*** ~~Viral vectors are starting materials, also when used to transduce cells and not remaining in the active substance. Information on the vector should be provided in the starting material section. The same level of information that is needed for the vector as active substance should be provided in this situation.~~ ~~Genome editing tools used ex-vivo to generate genetically modified cells are by analogy also considered as starting materials.~~ ~~Also, for in-vitro-transcribed (m)RNAs used as active substances, the linearized template plasmid DNA should be considered as a starting material.~~	Accepted, restructured and reworded.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		In the case of GTIMP, the starting materials will depend on the type of product, and include things such as the master bacterial/virus seed or master cell bank(s), and the plasmids used to transfect the packaging or producer cells. **In the case of gene therapy *ex vivo* (i.e. genetically modified cells), the unmodified cells, the viral or non-viral vectors and any other nucleic acid and/or protein used in the genetic modification of the cells are considered starting material.** ~~**The requirements for the gene/vector component should additionally be taken into consideration. In this case of *ex vivo* use, viral vectors, plasmids, recombinant proteins and recombinant mRNA, the components to produce them (e.g. plasmids, cells) are also considered starting materials**~~**.** ~~**In this case.**~~ **The principles of GMP, as provided in the General Principles in the Guidelines for GMP for ATMP, should be applied from the cells bank systems used to produce the starting materials, when applicable.** **For genome editing approaches, the starting materials shall be, as appropriate, the vector (viral or non-viral vector) carrying the nucleic acid sequences encoding the modifying enzyme, the mRNA expressing the modifying enzyme, the modifying enzyme itself, the genetic sequence for modification of the cell genome (e.g. a regulatory guide RNA) or a ribonucleoprotein (e.g. Cas9 protein pre580 complexed with gRNA), the template (e.g. linear DNA fragment or a plasmid) <u>for mRNAs</u>, and the components to produce them.** **When mRNA or proteins are used to generate genetically modified cells, the principles of good manufacturing practice shall apply from the bank system used to produce these materials onwards.**	
558-570	11	**Comment**: The point on line 560-561 is understood, for some of our members the confusion is how to do this. The simplest approach, and one that appears to have been used at MA (and BLA) is to	Accepted, reworded.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		provide details of the vector manufacturing in a separate s-section (belonging in S.2.3). It would be helpful if this was mentioned as an option or even preference. It is made clear that the level of detail for the vector should be the same as an active substance – what is not clear is how this deviates from that expected at MAA (e.g. EMA/CAT/GTWP/671639). Proposed change (if any): address above if possible.	
559-562	10	No coherently phrased, please see suggested replacement text. **Proposed change:** Viral vectors may be defined as starting materials when used to transduce cells, generating a genetically modified cell product. In this case the viral vector per se does not constitute the active substance, nonetheless all quality information relating to the manufacture of the vector (equivalent to that if it were being manufactured as an active substance) should be provided in the starting material section.	Accepted, reworded.
559	5	**Comment**: This text is confusing: "*Viral vectors are starting materials, also when used to transduce cells and not remaining in the active substance.* *Information on the vector should be provided in the starting material section. The same level of information that is needed for the vector as active substance should be provided in this situation*. " **Proposed change (if any)**: Would be better written such as: "**Viral vectors, when used to transduce cells, are starting materials, regardless of whether they are removed from the active substance as part of the process and therefore information on the vector should be provided in the starting material section.** **The same level of information needed for the active substance should be provided for the viral vector in this situation."**	Accepted, reworded.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
560-562	5	**Comment**: risk-based considerations should be applied to define the dossier content in the case of a vector as starting material when compared to a vector as drug substance, e.g. different/appropriate control strategy, process steps validation, etc The same applies when comparing mRNA and plasmid DNA as a starting material to modify cells or as a drug substance. **Proposed change**: "The same level of information that is needed for the vector as active substance should be provided ~~in this situation~~ **(in case viral vectors are starting materials)"**	Rejected. However, the risk-based approach may be leveraged in a product-specific manner in all cases.
560-562	5	**Comment**: Is it acceptable to have a separate DS section for the vector if the vector is used for ex vivo modification of cells? **Proposed change (if any)**: "~~The same level of information that is needed for vector as active substance should be provided in this situation~~ **A separate DS section for vector can be used to provide necessary information.**"	Accepted
563-564	1, 8	**Comment:** See comment on lines 247-249.	Rejected. Editing tools are considered starting materials.
566	5	**Comment**: The draft guidance specifically states for active starting materials (for GTIMP) that: "for in vitro-transcribed (m)RNAs used as active substances, the linearized template plasmid DNA should be considered as a starting material". Suggest removing "plasmid" here since it is not necessarily a plasmid, but instead can be a linear product of polymerase chain reaction. Suggest that the Agency considers expanding its description of starting material of transcribed mRNA as an API. It is acknowledged that linearized DNA facilitates transcription for its lack of the tension and topological restrains of supercoiled DNA, however, the Agency may consider to align to ICH guidelines (i.e., ICHQ7) and provide the possibility for the sponsor on a case by case basis to designate	Accepted, reworded.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		starting materials (e.g., plasmid DNA and/or linearized plasmid DNA) and document the rationale for the production of the API (mRNA) by a continuous manufacturing process. **Proposed change (if any)**: To clarify and consider starting material terms such as linearized plasmid DNA or plasmid DNA (supercoil or circular) for RNA production. **Proposed change**: "Also, for in vitro-transcribed (m)RNAs used as active substances, the linearized template plasmid DNA should be considered as a starting material."	
567	1	**Comment:** Complexing materials: Do these also apply to RNA complexes? Please clarify.	Accepted, reworded.
567-568	15	**Comment**: The term "formulation" remains unclear in context of drug substance. **Proposed change** (if any): Please clarify	Accepted, reworded.
567-569	17	**Comment**: Clarification is required regarding the level of information to be provided on Complexing materials which "depends on nature of the complexing material and resulting DS." It is suggested to provide examples.	Rejected. Information required needs to be justified in a product-specific context following the risk based approach
570	17	**Comment**: To elaborate or remove the reference to S.3.1	Accepted, reworded.
571-631	11	**Comment**: Given there is a guideline (EMA/CAT/GTWP/671639) already for MA-level, and that aspects of cell banking have already been mentioned, we feel this section could be greatly shortened by reference to those. Consideration should also be given to whether the biotech guideline for FIH can be cited since viral vectors follow a similar approach. How the requirements vary for early CT versus MA is not at all clear.	This guideline is intended as a mostly self-standing guideline for developers. A non-exhaustive list of references is provided.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Some of this section could refer to Ph.Eur. general chapter on gene transfer medicinal products, then here focus on whether all the requirements of Ph.Eur. need to be implemented for early clinical studies. Otherwise there is no obvious value to repeating what is already in Ph.Eur. A common question from developers of GM-cell products is whether the plasmids need to be manufactured under GMP; addressing this for early studies at least would be helpful. **Proposed change** (if any): consider whether this section could be greatly reduced by reference to existing guidance and Ph.Eur. It is suggested to reconsider the structure to avoid repetition, e.g. why is it necessary to repeat sub-heading for cell banking etc? Any intended message on how the requirements for early clinical studies differ from MA is absent; please focus on this as otherwise this section is merely repetition of existing guidance in a more confusing structure.	Ph.Eur is under revision Accepted, reworded.
575-576	5	**Comment**: The flow of information on starting materials is very confusing and hard to follow. As per other types of product (biologics/small molecules) and in line with ICH M4Q and ICHMQ4 Location issues– Quality Questions and Answers, it is proposed to move all information on starting materials (definition, source, manufacturing overview, control) to be together under Section S.2.3. Text has been deleted from other sections of the guideline and merged into S.2.3 as proposed below (see line numbers to show where merged information is taken from). This includes text on vector sourcing and characterisation which was missing and was elsewhere in the draft guidance so relocation is proposed here. **Proposed change (if any)**: ***Source, history and generation*** A summarised description of the source and generation (flow chart of the successive steps) of the cell substrate/ viral seed should be provided.	Accepted, restructured and reworded.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Where cells or tissues of human origin are used, the procurement and testing should comply with conditions provided ~~for primary cells~~ above in the section on starting materials for CBIMP. **~~b. Development Genetics~~** **For all vectors, full documentation of the origin ~~where applicable~~, history and biological characteristics of the parental virus or bacterium should be provided.** **All the genetic elements of the GTIMP should be described including those aimed at therapy, delivery, control and production and the rationale for their inclusion should be given.** **For helper virus, the same level of detail should be provided.** **For plasmid DNA, full sequence should be provided.** **DNA elements used for selection should be justified. The presence of antibiotic resistance genes in a GTIMP finished product should be avoided given the burden of bacterial multi-resistance to antibiotics and the existence of alternatives methods for selection. If unavoidable a risk analysis should be made.** **Data on the control and stability of the vector and the therapeutic sequence(s) during development should be provided.** **The degree of fidelity of the replication systems should be ensured as far as possible and described. Evidence should be obtained to demonstrate that the therapeutic sequence remains unmodified and is stably maintained during any amplification.** **Cells used for the amplification of the genetic material should be 120haracterized.** **Details of the construction of any packaging/producer cell line or helper virus should be provided.**	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		When GTIMP consists of genetically modified cells, both the required information on the viral vector plus information on the modified cellular component should be provided following the recommendations above. For genome editing…	
576	15	**Comment**: This applies to ex vivo GE. **Proposed change** (if any): For ex vivo gene editing~~genome editing~~ approaches, the starting materials shall be, as appropriate, …	Accepted, reworded.
576-569	5	**Comment**:" Complexing materials for formulating the drug substance are considered as starting materials and have to be qualified for their intended purpose. The level of information to be provided will depend on nature of the complexing material and resulting DS." Under footnote 6, calcium phosphate, lipids, and proteins are given as examples of "complexing materials". Provide more guidance on when something should be classified as a complexing material, and what information is expected to be provided about these materials.	Rejected, this needs to be justified in a product-specific manner.
576-583	1	**Comment:** "For g*enome editing approaches, the starting materials shall be.."* See comment above for non-viral vectors, which conceivably includes lipid nanoparticles and should be considered more akin to drug product (see comment on lines 239-239).	Partially accepted, reworded
576-583	1, 6	**Comment:** When the principles of GMP apply for starting materials other than mRNA or proteins used to generate genetically modified cells is not mentioned. It is therefore proposed to include this notion. **Proposed change**:	Accepted, reworded.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		"*For genome editing approaches, the starting materials shall be, as appropriate, the vector (viral or non-viral vector) carrying the nucleic acid sequences encoding the modifying enzyme, the mRNA expressing the modifying enzyme, the modifying enzyme itself, the genetic sequence for modification of the cell genome (e.g. a regulatory guide RNA) or a ribonucleoprotein (e.g. Cas9 protein pre-complexed with gRNA), the template (e.g. linear DNA fragment or a plasmid), and the components to produce them.* ***The principles of good manufacturing practice apply for all starting materials.*** *When mRNA or proteins are used to generate genetically modified cells, the principles of good manufacturing practice shall apply from the bank system used to produce these materials onwards.*"	
576-586	5	**Comment**: The flow of information on starting materials is very confusing and hard to follow. It is proposed to move Lines 576-583 to be together with the other text defining starting materials and replace Lines 563-566 with Lines 576-583. (See above).	Accepted, restructured and reworded.
581	15	When mRNA or proteins are used to generate genetically modified cells, the principles of good manufacturing practice shall apply from the bank system used to produce these materials onwards. **Comment**: Probably should read "gene edited cells". **Proposed change** (if any): please clarify	Rejected. Refers to mRNA and proteins. Gene edited cells would not be "materials".
581-583	8	**Comment:** Unclear how one could generate a bank system for the production of such mRNA or protein. We can conceive generating a banked supply of each mRNA or protein, which would then be used in the editing process according to GMP principles but it may not be feasible to establish bank systems for the generation of these reagents under GMP principles. Again, as mentioned above, these reagents could be	Text has been reworded.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		considered raw materials and their production and purification might currently be challenging to perform under GMP principles.	
581-583	17	**Comment**: GMP requirements are contradictory to the statement in line 565 which defines the linearized template plasmid DNA as starting material. GMP is usually only required downstream of the starting materials. **Proposed change** (if any): To delete lines 581 – 583 ~~When mRNA or proteins are used to generate genetically modified cells, the principles of good manufacturing practice shall apply from the bank system used to produce these materials onwards.~~	Reworded
584-590	15	**Comment**: Redundant to line 524. **Proposed change** (if any): suggest to delete ~~For medicinal products based on induced pluripotent stem (iPS) cells generated by genetic modification, the principles of good manufacturing practice and the scientific recommendations given in this guideline should apply after procurement of the cells including the generation of iPS cells and the subsequent selection process. It is acknowledged that at the early steps in iPS cells generation, cell material may be limited and availability of samples may impact on the extent of testing and process qualification. The Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products should be considered.~~	Accepted, reworded.
584-593	5	**Comment**: This information is specific to GMP and should be covered in Annex 4 GMP for ATMPs. Deletion is proposed. **Proposed change (if any)**: ~~For medicinal products based on induced pluripotent stem~~ (~~iPS) cells generated by genetic modification, the principles of good manufacturing practice and the scientific recommendations given in this guideline should apply after procurement of the cells including~~	Rejected. Considered relevant information.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		~~the generation of iPS cells and the subsequent selection process. It is acknowledged that at the early steps in iPS cells generation, cell material may be limited and availability of samples may impact on the extent of testing and process qualification. The Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products should be considered.~~ ~~For the manufacture of active substances consisting of genetically modified cells derived from genetically modified animals, good manufacturing practice shall apply after their procurement and testing according to the *Guideline on xenogeneic cell-based medicinal products.*~~	
593	1	**Comment**: We suggest adding the appropriate guidance reference number for clarity. **Proposed change:** "*…testing according to the Guideline on xenogeneic cell-based medicinal products* ***(EMEA/CHMP/CPWP/83508/2009)***"	Accepted
595-605	1	**Comment:** This paragraph refers to bacterial/cell/virus seed or bank(s); however, line 601 only refers to cell banks. **Proposed change:** Please clarify what is expected for all types of banks.	Accepted, restructured and reworded.
601	17	**Comment**: Viability is not relevant for some banks (i.e. plasmids used as mRNA templates) **Proposed change** (if any): "Banks should be characterised for relevant phenotypic and genotypic markers so that the identity, viability (**if relevant for production**), and purity of cells used for the production are ensured"	Accepted, restructured and reworded.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
604-605	7	Please could the particular guideline recommended to be consulted as stated in this section be referenced, so it is clear which Guideline should be consulted.	Accepted
606-612	1, 6	**Comment**: Whether genetically modified phages or phage-like particles designed to transduce bacteria *in* or *ex-vivo* are part of the bank requirements described under "A. Virus seed bank" is unclear. **Proposed change**: "*Control of virus seed banks* ***(including genetically modified phages or phage-like particles designed to transduce therapeutic sequence in bacteria in- or ex-vivo)*** *should include …"*	Accepted, restructured and reworded.
608-609	3, 5	**Comment**: In most viral banks used for gene therapy it may not be possible or practical to demonstrate transcription/expression of the therapeutic sequences or biological activity of the therapeutic sequence.	Acknowledged. The risk-based approach may be leveraged for the control strategy in a product-specific manner.
617-618	15	The presence/absence of other genetic features such as immunomodulatory CpG sequences should be determined, unless otherwise justified. **Comment**: Questioned if needed on the level of the bank system.	Accepted; moved to section S.3.1
620-623	15	**Comment**: A more staggered approach should be employed, indicating need for requirements for the different clinical development stages. E.g. could be probably omitted at early clinical stages.	Rejected. The risk-based approach principally allows for flexibility, however patient safety needs to be equally ensured at all stages.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
631	10	The sentence seems to end prematurely. **Proposed change:** Revise to '…, with the same level of detail as described in section xxx.'	Accepted, reworded.
632-641	11	**Comment**: As with the previous section, this is covered by Ph.Eur. general chapter and other guidance. A clear message as to how this can differ from what is expected at MA would be appreciated, otherwise the text could merely cite other guidance. **Proposed change** (if any): section not useful, please revise to address early clinical studies.	Rejected. No changes. Ph.Eur texts are under revision
639-640	15	**Comment**: A more staggered approach should be employed, indicating need for requirements for the different clinical development stages. E.g. plasmid copy number and cell ration with and without plasmid could be probably omitted at early clinical stages.	Rejected. Risk-based approach to be leveraged however, failure to collect data is problematic for leveraging results in later development
642-654	11	**Comment**: S.2.2 and S.2.3 both contain discussion that belongs here. The current text is short compared to S.2.2, yet S.2.2 is ONLY a description, it is this section where the control of the process is justified, suggestive there is more to say here than S.2.2. 643-644: isn't the purpose of this guideline to address the stage of development, and what is needed? 646-649: some may not understand that a cell stock (term used in this guideline) or even 2-tier donor bank that will change from time to time are intermediates; please address the comments in S.2.2 and S.2.3 related to this by moving those comments here. 649-651: specifications should also be described in S.2.2, and many developers do not understand the purpose of S.2.4 for this reason. Please revise the text to clarify that this section should justify those specifications; acknowledging that studies to confirm e.g. operational ranges etc may not yet be initiated. It would help if the text clarified	Accepted. Reworded and restructured.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		that the studies to e.g. explore process parameters are described in S26 and referenced as justification for the ranges set here in S24. 652-654: seems a random statement given how short the text is. It is also mentioned elsewhere, although it is more appropriate here (move here). 665-669: relates to process control, yet not said in S.2.4 (data from S.2.6 mostly) – how then should this be used in S.2.5 of the IMPD? Please clarify 670-672: these seem to be MA-level guidelines; this guideline relates to early CT. Please clarify in the text, what is expected here is not clear. **Proposed change** (if any): Please consolidate comments related to S.2.4 found in other sections to this section. Many developers do not understand the purpose of S.2.4, or its relation to S.2.2; the heading itself adding to their uncertainty. It is therefore disappointing that this guideline does nothing to address this and perpetuates the idea this section merely lists process specifications, whereas it should provide the justification for those set. It would be highly appreciated if this point could be clarified.	
643-644	1	**Comment:** This sentence is not consistent with Line 348-350 above. Overall the wording in Sections S.2.5 and S.2.6 seems more restrictive than that in Section S.4.3. where there is an acknowledgement that the validation of analytical procedures during clinical development is an evolving process. An appropriate degree of method qualification should be applied at each stage to demonstrate the methods are suitable for their intended use at that time.	Accepted, reworded

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
643-644	5	**Comment**: *"Critical steps in the manufacturing process should be identified as appropriate for the stage of development", n*ot consistent with Line 348-350 above. Overall the wording in Sections S.2.5 and S.2.6 seem more restrictive that in Section S.4.3. where there is an acknowledgement that the validation of analytical procedures during clinical development is an evolving process. Method qualification appropriate for the stage of development should be applied to demonstrate the methods are suitable for their intended use at that time.	Accepted, reworded
643-644	17	**Comment**: Reference should be made in this section to "Description of Manufacturing Process and Process Controls" 3.2.S.2.2	The section has been reworded.
643-657	10	'*Critical steps in the manufacturing process should be identified as appropriate for the stage of development and all available data and acceptance criteria should be provided.'* If it is the regulatory expectation that all manufacturing processes should be validated prior to confirmatory studies (which we do not agree with, see comments below) this section needs to be revised such that it is consistent with that concept. For example if you are validating a process then it would be expected that the company has sufficient process understanding and characterisation to be able to identify which steps are critical to their product, and which parameters are critical to that step to ensure product quality is unaffected, thus they should be in a position to have a fully defined control strategy of those critical steps and critical intermediates prior to the confirmatory study. Please note this does not mean we are endorsing this a strategy, we are just making that point that it logistically follows that this should be case. **Proposed change:**	Accepted, reworded

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Ensure that the requirements for manufacturing strategy are aligned with respect to the extent of data required at early vs confirmatory vs MAA stages of development. As a company we do not endorse the expectation that the process be should be fully validated prior to confirmatory studies.	
647-649	5	**Comment**: Due to limited process knowledge, setting acceptance criteria for in process controls can be challenging. Is it acceptable to set wider acceptance criteria during exploratory clinical trials? **Proposed change (if any)**: "Intermediate cell products are products that can be isolated during the process; specifications of these products should be established in order to assure the reproducibility of the process and the consistency of the final product. **During early phases of the development, a wider specification limit can be justified due to limited numbers of batches manufactured.**"	Rejected. The section has been reworded, however, this is a general concept reflected in the guidance text already and does not need to be specifically highlighted here.
655-696	11	**Comment**: The first statement starts with 'process validation'; yet no one would validate a process for early exploratory trials (few do before confirmatory trials). It seems more appropriate to discuss how the process should be qualified/evaluated for early CT. Suggest remove first sentence. Line 659-662: other guidance covers MA, this comment of off topic; remove. 663-672: such data would be in S.2.6 the reference to setting process specifications relates to S.2.4; it would help to say this. EMA/CHMP/BWP/187338/2014 is an MAA level guideline, we suggest this could be in a list of guidelines and identified as MAA. The idea of this draft guideline is to help developers understand what is required for early clinical trials. There is a single ATMP for GMP guideline, and it also states validation isn't expected for ATIMP, but reiterates collection of data over development. Rather than re-iterate that, it would be helpful if some idea of the amount of qualification data expected for clinical trials is described, e.g. consistency batches. To what extend can this be presented in S.4.4 versus repeating in S.2.5,	Accepted. The section has been reworded in line with other investigational guidance.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		given characterisation likely doesn't go beyond release tests for early clinical trials. 678-682 – we sort of understand what is meant but this isn't clearly stated. Recommend rewording. Proposed change (if any): see above.	
656-660	1, 8	**Comment:** While it is feasible for standard drug development, for ATMPs it can be a challenge to have the process validated before the initiation of the confirmatory study, particularly in oncology/orphan diseases and for ATMPs with an iterative manufacturing process optimisation, for adaptive study designs and with limited clinical data package or in cases of expedited development. Process validation will be conducted after the commercial process is defined and before the MAA, typically while the confirmatory clinical trial is in progress, consistent to the expectations set forth in the Guideline on Process validation for finished products (EMA/CHMP/CVMP/QWP/BWP/70278/2012). It is also noted that process validation is generally not an FDA IND requirement. The language in this guideline should be adapted to take account of these considerations. Reference to leveraging prior knowledge/validation would be helpful for instances where similar manufacturing process is utilised for multiple products.	Accepted. The section has been reworded in line with other investigational guidance.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
656-662	3, 5	**Comment**: While it is feasible for standard drug development, for ATMPs it can be a challenge to have the process validated before initiation of the confirmatory study, particularly in oncology/orphan diseases and for ATMPs with an iterative manufacturing process optimisation, for adaptive study designs and with limited clinical data package. Process validation will be conducted after the commercial process is defined and before the MAA, typically while the confirmatory clinical trial is in progress, consistent to the expectations set forth in the Guideline on Process validation for finished products (EMA/CHMP/CVMP/QWP/BWP/70278/2012). It is proposed to align with biologics IMPD guideline which states "Process validation data should be collected throughout development, although they are not required to be submitted in the IMPD" and revise wording to be clear that process validation is not required to support a confirmatory clinical trial application. **Proposed change** (if any): Process validation is the documented evidence that the manufacturing process can consistently produce a result within specific parameters. Process validation data should be collected, although they are not required to be submitted in the IMPD. The manufacturing process for ATIMPs is not expected to be validated for ~~early~~ clinical trials but appropriate monitoring and control measures should be implemented to ensure compliance with the requirements in the clinical trial 131haracterizat. It is noted that for the confirmatory clinical trial to be used in support of a marketing 131haracterizat, ~~process validation~~ there should be sufficient process controls ~~required~~ to demonstrate that the manufacturing process of the ATIMP ensures consistent production.	Accepted. The section has been reworded in line with other investigational guidance.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
657-659	15	**Comment**: Manufacturing of an iATMP in compliance with the authorisation is already a legal/GMP requirement and there is no need to repeat. **Proposed change** (if any): The manufacturing process for ATIMPs is not expected to be validated for early clinical trials but appropriate monitoring and control measures should be implemented ~~to ensure compliance with the requirements in the clinical trial authorisation.~~	Accepted. The section has been reworded in line with other investigational guidance.
659-662	3	**Comment**: This implies that product used in confirmatory trials is manufactured with a validated process and is not aligned with line 198 – 199. The three consecutive validation batches that are required for the marketing authorization have to be manufactured with the same "mature" process used for production of confirmatory trial product, but the process does not have to be validated to manufacture product for confirmatory trials.	Accepted. The section has been reworded in line with other investigational guidance.
659-662	10	'It is noted that for the confirmatory clinical trial to be used in support of a marketing authorisation process validation is required to demonstrate that the manufacturing process of the ATIMP ensures consistent production.' Why is this a specific requirement for ATMPs that is not required for other IMPs? Referring to EMA/CHMP/QWP/5545525/2017 which states S.2.5 Not applicable for drug substances to be used in clinical trials. P.3.5: Data are not required during the development phases, i.e. clinical phases I to III, <u>except for non-standard sterilisation processes not described in the Ph. Eur., USP or JP.</u> In this case, the critical manufacturing steps, the validation of the manufacturing process as well as the applied in process controls should be described). Nor is it a requirement in Eudralex vol 4, part IV.	Accepted. The section has been reworded in line with other investigational guidance.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		It is understood that terminal sterilisation is not commonly an approach that can be used with an ATMP, and agreed that even for a FIH study aseptic process validation is performed. This, however this is quite different to process validation, which implies that the process and product is fully characterised, that CQAs of the product are known, that process steps that influence CQAs are known and that process parameters of those critical steps that influence CQA of the product are known and controlled. Only then would you validate a process. So by making this request prior to confirmatory clinical studies the EMA are essentially requesting that complete process understanding, equivalent to what would be expected for MAA is actually available for a CTA submission, but this is only relevant to ATMPs not for other biological products. While we have no issue with the concept that it would be advantageous for the company to use their commercial process for the production of product that will be used in the confirmatory study and that the company should demonstrate a certain level of consistency in the manufacturing, it is at their risk whether or not that process is validated or not for a confirmatory trial. While regulators could recommend it is advisable, it should not, in our opinion be a clear expectation, and if it is for ATMPs it should be the same level of expectation for other biological products. Finally, it would be helpful to further clarify the validation requirements for starting materials such as viral vectors used for generation of GM cells when approach confirmatory studies. Are you also expecting those processes are validated at that time? **Proposed change** We suggest that the concept is softened and aligned with what is specified in Eudralex vol 4 part IV: 10.46 and 10.47: The manufacturing process for investigational ATMPs is not expected to be validated but appropriate monitoring and control measures should be implemented. Additionally, it is	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		expected that the aseptic processes (and, where applicable, sterilising processes) have been validated. It is noted that for a clinical trial to be used in support of a marketing authorisation application it is important to demonstrate that the manufacturing process of the investigational ATMP ensures consistent production, as such consideration should be given to validation of the manufacturing process prior to confirmatory trials. Furthermore, it is strongly recommended to use the process that is intended for commercial supply for the manufacture of product to be used in confirmatory studies. Where critical raw materials are manufactured specifically for the purpose of generating an ATMP final product, for example a viral vector used to genetically modify cells, the manufacturing process for the starting material should be validated prior to MAA. For a clinical trial to be used in support of a MAA, data to demonstrate the consistency of production of the raw material should be provided, and consideration should be given to validating the process prior to confirmatory studies also.	
659-662	15	**Comment**: Different to tenor in line 356 and in GMP f ATMPs 10.47. Statement should be harmonised or deleted as repeating GMP **Proposed change** (if any): It is noted that for the confirmatory clinical trial to be used in support of a marketing authorisation ~~process validation is required~~ it is important to demonstrate that the manufacturing process of the ATIMP ensures consistent production.	Accepted. Section has been rephrased.
663-669 677-696	3, 5	**Comment**: Process characterisation data are part of process development and should be included in S.2.6 as per ICH M4Q and ICHQ11. Process	Partially accepted. Section has been rephrased.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		characterisation is not the same as process validation/verification and the two activities should not be confused. It is suggested to relocate this text to under Line 697 with a new heading. **Proposed change** (if any): ***Process Characterisation*** Process characterization/evaluation data should be collected throughout the development. It is acknowledged that some degree of variability of the active substance due to the characteristics of the starting materials is intrinsic to ATMPs. In this regard, it is recommended that critical process parameters, critical quality attributes and the associated acceptance criteria should be set based on the development data and current knowledge. This is achieved through implementation of appropriate monitoring and control measures. Summaries of the process characterization ~~and verification~~ studies need to be provided, but the reports themselves are not required to be submitted as part of the IMPD. Also add lines 677-696 ("-CBIMPs:" to "viral production system.")	
665-666	3	**Comment**: It would be helpful to clarify the extent of critical quality attribute identification and evaluation required for FIH studies. Additionally, a critical quality attribute may not have a direct test. A test method may measure some proxy of a CQA and the acceptance criteria would be applicable to the measure, not necessarily directly to the CQA.	Rejected. Product and specific-development process-dependent
665-669	5	**Comment**: It is important to note that critical process parameters can vary depending on phase. **Proposed change (if any)**: "In this regard, it is recommended that **phase appropriate** critical process parameters, critical quality attributes and the associated acceptance criteria should be set based on the development data and current knowledge. This is achieved through implementation of appropriate monitoring and control measures. Summaries of the process characterisation and verification	Accepted. Section has been rephrased.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		studies need to be provided, but the reports themselves are not required to be submitted as part of the IMPD."	
668-672	15	**Comment**: This document should not address formal requirements for clinical trial application dossiers/IMPDs. Moreover, a more stage specific approach is supported; reference to EMA/CHMP/BWP/187338/2014 is misleading as addressing requirements for MAAs **Proposed change** (if any): ~~Summaries of the process characterisation and verification studies need to be provided, but the reports themselves are not required to be submitted as part of the IMPD. Reference is made to the Guideline on process validation for the manufacture of biotechnology-derived active substances and data to be provided in the regulatory submissions (EMA/CHMP/BWP/187338/2014) and to the GMP for ATMP Guidelines~~	Accepted. Section has been rephrased.
668-676	17	**Comment**: In early stage development, formal validation of the process has not yet taken place. Only Viral clearance properties of the process are addressed in Section 3.2.A.2. Summaries of Process characterisation (defining the commercial manufacturing process) and corresponding Process verification studies cannot be provided for early stage development. **Proposed change** (if any): Paragraph and reference to Guidelines to be revised to take into account the data available at the different stage of development	Accepted. Section has been rephrased.
670-672	3	**Comment**: Reference is made to the Guideline on process validation for the manufacture of biotechnology-derived active substances and data to be provided in the regulatory submissions (EMA/CHMP/BWP/187338/2014). However, this guideline explicitly states that the data requirements described therein are for inclusion in the marketing application of post-approval variation.	Accepted. Section has been rephrased.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
673-674	3	**Comment**: It is more appropriate to describe requirements for validation of aseptic processes prior to FIH studies in P.3.5	Rejected. Section A2 is appropriate, however, cross-reference would be acceptable.
673	1	**Comment:** The word "to" is missing after "in addition" **Proposed change:** *"In addition **to** the process characterisation/evaluation summaries, validation of the …"*	Accepted
673	15	**Comment**: according to previous comment. **Proposed change** (if any): ~~In addition the process characterisation/ evaluation summaries,~~ validation of the aseptic process and the viral removal/inactivation steps are expected to be validated prior to the FIH clinical trials.	Accepted
673-674	3, 5	**Comment**: Characterisation is not relevant here, so deletion is proposed. **Proposed change (if any)**: ~~In addition the process 137haracterization/ evaluation summaries,~~ Validation of the aseptic process and the viral removal/inactivation steps ~~are **recommended** to be validated~~ are to be demonstrated prior to the FIH clinical trials. Details on manufacturing steps intended to remove or inactivate viral contaminants should be provided in the section A2, Adventitious agents safety evaluation.	Accepted
673-674	1, 6	**Comment**: It is written that purification steps intended to remove or inactivate viral contaminants should be validated before FIH clinical trials. Can the meaning of "validation" in this sentence be clarified? Considering that the manufacturing process, upstream and downstream, is	Partially accepted, the section has been reworded.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		susceptible to be further developed throughout clinical trial phases and that manufacturing process validation is not expected before the confirmatory clinical trial, it may be considered that verification of the sterile filter (of 0.22 micron pore size) integrity, in addition to a media fill test (aseptic process simulation test using a sterile microbiological growth medium and/or placebo), might be sufficient in terms of aseptic processing validation for early phases clinical trials (when in addition appropriate controls are performed such as adventitious agents testing, sterility test etc.). If the meaning is that viral clearance studies are expected prior to FIH studies, this could be clarified and it is proposed to include this notion only for manufacturing processes involving the use of viruses (other than the viral vector) as part of the starting materials (such as baculovirus). Indeed, it may be considered that for other manufacturing processes, the use of a risk-based approach including all appropriate safety controls, in addition to process controls such as sterile filter integrity and media fill test studies, appropriate raw material and starting materials control, manufacturing environment monitoring etc. could suffice to ensure lack of viral contamination of the product. **Proposed change:** "*In addition the process characterisation/ evaluation summaries, validation of the aseptic process* ***(by aseptic process simulation test, as described in the GMP for ATMP Guidelines)*** *and the* ***control of*** *viral removal/inactivation steps* ***(e.g. sterile filter integrity test, control of the chromatography equipment)*** *are expected to be* ~~*validated*~~ ***implemented*** *prior to the FIH clinical trials****. The manufacturing process viral clearance is expected to be validated for the confirmatory clinical trials, except for manufacturing processes involving viral starting materials (other than the viral vector e.g. baculovirus) for which viral clearance studies should be provided prior to FIH clinical trials****."*	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
673-676	3, 5	**Comment**: Could the Agency elaborate on the viral removal/inactivation studies requires for ex vivo gene therapies?	Rejected. The strategy needs to be justified by the risk based approach and taking existing guidance into consideration.
673-676	1, 8	**Comment:** It would be helpful if more details for ATMPs would be provided. Would studies for virus inactivation be required, e.g. detergent treatment for AAV? It is suggested to include an example.	Rejected. Approach to be justified in a product specific manner and taking existing guidance into consideration.
683-691	15	**Comment**: This paragraph may be shortened as indicated below. Repeating to a large extent GMP (10.41 +42) is not regarded reasonable. **Proposed change** (if any): ~~The l~~Limited availability of the cells/tissues e.g. autologous ATMPs, allogeneic cell stocks ~~where there is no expansion of cells to MCB,~~ may require~~s~~ the development of pragmatic approaches for characterization/evaluation of the manufacturing process or subsequent changes (see GMP for ATMP 10.41, 10.42).	Accepted
688	3, 5	**Comment**: Could the Agency provide more detail on the use of patient derived versus surrogate material for autologous ex vivo gene therapy process validation studies?	Rejected. Details depend on the specific product.
695	1	**Comment:** The word "be" is missing after the word "should" **Proposed change:** *"Absence of formation of replication competent virus should <u>be</u> demonstrated…"*	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
695-696	1	**Comment:** Please state these data should be included in the initial IMPD if that is the intent. Please also correct the following typo. **Proposed change:** **"***Absence of formation of replication competent virus should* ***be*** *demonstrated at the level of the viral production system*.''	Accepted
695-696	5	**Comment**: GTIMP "Absence of formation of replication competent virus should demonstrated at the level of the viral production system." **Proposed change (if any)**: Please clarify if there is no need to show RCV in ex vivo genetically modified cell or not.	Accepted. This is clarified in the text.
697	1	**Comment**: Section S.2.6. focuses on changes made to the manufacturing process during development. A mention of changes in manufacturer would also be useful. Discussion on tech transfer to new manufacturers and scale up/comparability of IMP would be useful even in the general terms used elsewhere. This could still be applicable to exploratory trials (particularly those performed initially using a hospital manufacturing facility) but certainly confirmatory trials.	Accepted
697-719	11	**Comment**: ICH M4Q refers to this as the developmental history; we suggest this heading would better align. 711-714 relates to comparability, suggest move into the section starting line 720. 715-719 is this not also true of biotech products? We fail to see the value of this statement, point made in general text above. Proposed change (if any): see above	Partially accepted. Headers prescribed by IMPD structure and aligned with other investigational guidance. 711-714 has been moved.
699-701	1	**Comment:** It would be helpful to add some examples of manufacturing process changes occurring during product development, including some which need to be submitted as substantial amendment (such as examples	The general principles are provided. ATMPs are too heterogeneous to provide meaningful examples.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		presented in EMA/CHMP/BWP/534898/2008 rev. 1 corrigendum and CHMP/QWP/185401/2004).	
700-701	17	**Comment**: We suggest providing examples/non-exhaustive list of process modifications that are typically considered as "substantial" (ie. need to be notified to the competent authorities) or "non-substantial" in a separate paragraph.	The general principles are provided. ATMPs are too heterogeneous to provide meaningful examples.
701	17	**Comment**: To confirm that "improvements and optimisations" of the process do not require the submission of substantial amendments	Rejected, these terms are too vague.
716	15	**Comment**: This is normally the case for vector-based GTIMPs only. **Proposed change** (if any): It is recognised that in particular for vector-based GTIMPs, only a limited number of batches may be produced prior to MAA.	Rejected. Wording reflects current experience.
720	1	**Comment:** Additional text is suggested to the section on comparability. The limited availability of the cells/tissues may require the use of model cells to perform comparability studies. A clarification on the expectations with regards to the justifications to provide when surrogate cells are used to establish comparability would be welcome. This also applies to Process Validation.	Partially accepted. Use of surrogate materials is acknowledged in S.2.5.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
720-759	11	**Comment**: The first statement is general, the guideline relates to early clinical studies (possibly later ones also). Such statements are clear from ICH Q5E. We recommend focusing on advice for changes in early development, e.g. preclin to FIH and FIH to P2. 726-727 – repeated point. 728-734 – we appreciate these important points that are often not understood. 735-736 – please be more specific, critical parameters is vague, it is assumed you mean cQA, cPP, and IPC. However, given the main scope of early clinical studies, these will not yet be known. Please elaborate and clarify what is meant. 737-738 this statement is not very helpful, developers in early clinical studies may not understand what a full comparability study looks like. We consider the term 'data filiation' could be stated in clear English given many developers are not native English speakers. We didn't find this term in ~50 guidelines we searched. While the regulators perspective for clinical trials is safety, it should be stated that the developer needs to establish the function is not lost. 747-748 we suggest 'sameness' is not a helpful term here; it may add to confusion as comparability is not sameness. Please also use plain English for 'data filiation program'. 753-755 while we accept this is what ICH Q5E says, animal models rarely have the sensitivity to statistically support comparability (considering also the 3R's), and we don't understand how a clinical study could be undertaken to demonstrate comparability. Please elaborate these points, e.g. can uncertain safety be addressed in the next clinical study by e.g. dose escalation of the first few patients? 758 We understand that a TEP in law is not a TEP in science. But we find the term 'tri-dimensional structure' peculiar, perhaps cells organised in 3 dimensions, e.g. tissue; would be clearer? We didn't find any comments about the use of the reference material in comparability studies.	Partially accepted. Wording has been revised and is consistent with the Q&A on comparability.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Proposed change (if any): see above.	
720-759	15	**Comment**: As the document is focussing on exploratory trial, this paragraph is not regarded to have the right emphasis and seems to rather address requirements for MAA or variations. Changes of product are common in clinical development and analysing the impact of changes on safety and efficacy, when safety and efficacy have not been established yet, appears not reasonable. Especially, a potency test needs to be developed and established during clinical development but may not serve to address comparability. **Proposed change** (if any): adapt and shorten text accordingly, e.g. During early phases of non-clinical and clinical studies, comparability testing is ~~is generally not as extensive as for an approved product. When only non-clinical data has been generated, normally at an early stage of development, and prior to clinical exposure, analytical results should support safety data filiation, i.e. demonstrating representativeness of the non-clinical safety profile of the batches studied to those to be used in exploratory clinical trials.~~ only needed in a limited way. The main purpose of this exercise is to provide assurance that the post-change product is suitable for the forthcoming clinical trials and that previous non-clinical and clinical data are still relevant. In the case of exploratory clinical trials, it is recommended to use investigational product representative of the material used in non-clinical studies (see Guideline on Strategies to Identify and Mitigate Risks for First-In-Human Clinical Trials with Investigational Medicinal Products (EMEA/CHMP/SWP/28367/07)). More stringent equivalence	Partly accepted, section has been reworded.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		is required when toxicity and dose finding studies have been conducted. A comparability exercise should normally follow a stepwise approach, including comparison of quality attributes of the active substance and relevant intermediates, using suitable analytical methods. The analytical tools for comparability need to be chosen based on critical parameters identified throughout development. ~~When exploratory trials already took place, data filiation program should expand to a full comparability exercise where a higher degree of sameness is expected and a more comprehensive analytical package should be in place. For confirmatory trials, the principles as can be found in ICH Q5E Comparability of Biotechnological/Biological Products should be applied. During the confirmatory clinical studies~~ For confirmatory trials, introducing changes to the manufacturing process and the final product should be avoided, because comparability issues may impact the acceptability of the data. Where the relevant information is not sufficient to assess the consequences introduced by the change and if a potential risk to the patients cannot be excluded, a comparability exercise based only on quality considerations most likely will not be sufficient and further non-clinical data will be required. It is particularly important that all stages of development are fully evaluated, justified and tracked within the evolving dossier. In case of complex CBIMP with a tri-dimensional architecture, the extended characterisation for comparability should consider possible structural changes as well as functional changes.	
721-723	12	**Comment**: Editorial comment on sentence. **Proposed change** (if any): Depending on the consequences of the change introduced and the stage of development, a comparability exercise may be necessary to ensure that the change does not have an adverse impact on ~~impact on~~ the quality of the product and therefore on the safety and clinical efficacy of the product.	Accepted.
722 – 723	1, 5, 17	**Comment**: Please correct the following typo.	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Proposed change: *"…comparability exercise may be necessary to ensure that the change does not have an adverse* ***~~impact on~~*** *impact on the quality of the product"*	
728-734	12	**Comment**: Reference to any applicable guidelines would be helpful. Proposed change (if any):	Accepted. References have been included.
730-731	12	**Comment**: Clarification is requested for routine tests; does this include in-process as well as release testing? Proposed change (if any):	Reference inserted to EMA/CAT/499821/2019
735-736	1	**Comment:** Guidance on a core battery of critical parameters to be assessed for comparability would be useful. **Proposed change:** **"***The analytical tools for comparability need to be chosen based on critical parameters identified throughout development.* ***Early in development it may not be possible to define critical quality attributes and CQAs may change with increasing knowledge. It is acknowledged that some analytical tests may be removed from comparability testing over time."***	Rejected. Proposed sentence gives the false impression that the number of tests will become less rather than more for the assessment of comparability during development.
735-736	10	*The analytical tools for comparability need to be chosen based on critical parameters identified throughout development.* Analytics are generally based on critical quality attributes of the product, not critical parameters (which infer the process parameters). **Suggest revising** as follows: The analytical tools for comparability need to be chosen based on the critical quality attributes of the product identified throughout development.	Accepted. Text has been reworded.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
737-738	7	It would be helpful to clarify the differences that would be allowed between the comparability testing requirements for the early phases of non-clinical and clinical studies and that for an approved product as stated in this sentence as this often causes much concern amongst sponsors.	Rejected. Generalization is not possible. The principle is that safety for the patient and robustness of data need to be ensured.
739-740	1	**Comment:** Please clarify the sentence, particularly the word "filiation"	Rejected. Concept is explained in the paragraph.
740 747	9	**Comment**: The term 'filiation' is not understood and would benefit from additional clarification.	Rejected. Concept is explained in the paragraph.
740-745	10	*to clinical exposure, analytical results should support safety data filiation, i.e. demonstrating representativeness of the non-clinical safety profile of the batches studied to those to be used in exploratory clinical trials. In the case of exploratory clinical trials, it is recommended to use investigational product representative of the material used in non-clinical studies (see Guideline on Strategies to Identify and Mitigate Risks for First-In-Human Clinical Trials with Investigational Medicinal Products* (EMEA/CHMP/SWP/28367/07)). These sentences seem to be saying the same thing i.e. quality of material used in non-clinical studies should be representative of that which will be used in clinical studies. **Suggest revising** as follows: i.e. demonstrating the non-clinical safety of product that is representative, from a quality perspective, to that which will be used in exploratory trials (see *Guideline on Strategies to Identify and Mitigate Risks for First-In-Human Clinical Trials with Investigational Medicinal Products* (EMEA/CHMP/SWP/28367/07)).	Accepted. Text has been reworded.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
745 – 746	1	**Comment**: It would be helpful to outline what kind of more stringent equivalence tests would be expected where the guidance says: "More stringent equivalence is required when toxicity and dose finding studies have been conducted." It is proposed to add examples of acceptable comparability tests for this more stringent scenario.	Generalization is not possible. The difference arises from the different perspectives of clinical trial review (safety for the patient needs/robustness of data) and Marketing Authorization Review
745-746	5	**Comment**: "More stringent **equivalence** is required when toxicity and dose finding studies have been conducted." Change "equivalence" to "comparability".	Accepted
745-746	10	*More stringent equivalence is required when toxicity and dose finding studies have been conducted.* It is not abundantly clear what is meant by this, but we think you are suggesting that the impact of process/analytical assay changes to product quality once the toxicity and dose finding have studies have been completed needs to be significantly more robust. If our interpretation is correct, it would be preferable to state this more clearly. However, this concept is actually expanded upon in rows 747-750, so perhaps this sentence can simply be removed. **Proposed change:** Suggest removing this sentence, and revising rows 747 – 749 as follows: The comparability exercise performed when process (or analytical methods) changes are made after exploratory studies have been conducted, should be more extensive and robust compared to early clinical development, as a higher degree of 'sameness' will be expected. At this stage a more comprehensive analytical package should be in place.	Accepted, section has been reworded
747-749	1, 8	**Comment:** Expecting a full comparability data package for confirmatory trials is a very high requirement. While it is acceptable for chemical and biotech products, it appears very demanding for ATMPs, especially in therapeutic areas such as oncology where the clinical development is fully integrated, for adaptive study design and in rare diseases with	Accepted, section has been reworded

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		limited data package. It would be of value to adopt a more pragmatic approach by offering the comparability to be run in parallel with the clinical development (provided the characterization, IPC, specs are met to ensure the product quality for patients). In addition, it is unclear what is meant exactly by higher degree of sameness.	
747-752	5	**Comment**: the full comparability data package expected for confirmatory trials is very high. While it is understood for chemical and biotech products, it appears very demanding for ATMP especially in therapeutic areas such as oncology where the clinical development is fully integrated, for adaptive study design and in rare diseases with limited data package. It would be of value to adapt a more pragmatic approach by offering the comparability to be run in parallel of the clinical development (providing the characterization, IPC, specs are met to guarantee the product quality for the patients). **Proposed change (if any)**: Add at the end of line 752 "Comparability exercise may continue to run in parallel to clinical development providing characterization, IPC, specs are met to guarantee the product quality for the patients if it is not possible to complete this before start of confirmatory clinical trial.	Accepted, section has been reworded
750-752	1	**Comment:** Changes to the manufacturing process during confirmatory studies might not always be avoidable. This provision should also not be interpreted as a disincentive to improve the manufacturing process and introduce stepwise process changes during the product development. Such changes may actually improve the efficacy and safety profile of the product. It is understood that changes introduced during or after confirmatory trials may require comparability studies, depending on the risk-based analysis. Additional guidance on comparability would be welcome to understand when and what studies should be carried out to demonstrate comparability. **Proposed change:**	Accepted. Section has been reworded.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		"***~~During the confirmatory clinical studies introducing changes to the manufacturing process and the final product should be avoided, because comparability issues~~*** ***The introduction of changes to the manufacturing process and the final product during confirmatory clinical studies are undesirable as they may impact the acceptability of the data because of comparability issues. The aim of the comparability exercise is to determine the product is similar enough not to expect an impact on quality, safety or efficacy.***"	
750-752	3, 5	**Comment**: Due to the nature of ATMP development, including the need to address supply of critical components, there are occasions where changes to the manufacturing process and materials is needed during the confirmatory clinical trials. Could the Agency provide feedback on the comparability expectations in these situations? It would be helpful to give examples of what kind of non-clinical data would be necessary in this situation as animal models can have limited utility. Alternatively, clarify to indicate that non-clinical and / or clinical data may be required. **Proposed change (if any)**: A comparability exercise based only on quality considerations most likely will not be sufficient and further non-clinical **and/or clinical data** will be required.	Section has been reworded. Requirements will depend on the product and specific changes. More information in the Questions and answers on comparability considerations for advanced therapy medicinal products (ATMP)
750-752	8	**Comment:** This provision may inhibit incorporation of modifications expected to improve the safety / efficacy of the ATMPs during its early stages of development. It is a serious risk to be addressed as pharma might prefer de-risking rather than introducing improvements to the product being developed, while they can capitalize on high market value and potential benefits such as market exclusivity in case of orphan designation. Academia-driven innovation and improvements of ATMP that are reaching or have reached the market might thus become very challenging. The regulatory framework should thus	Comment noted.

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		support to every possible extent any stepwise improvements to the process and product profile of an ATMP, always safeguarding patients' safety but alleviating the burden of non-clinical comparability studies (for instance when an improvement in the backbone of the vector used or of the expression cassette design has already been proven to be ameliorative for another clinical application using a different transgene) and of clinical entry.	
753-755	10	In the situation where the product does not have a good animal model i.e. human cells can't be used in rodents, or the GT vector and transgene (TG) would have to be a species-specific surrogate, is the provision of additional NC data really useful in demonstrating product comparability after process changes (see comments given to rows 1450 – 58)? Surely come consideration should be given to this situation, which is common for most if not all classes of ATMP, in the guidance. Also when you say NC studies we presume you are talking about both in-vivo and in-vitro testing, perhaps you should make this clear too, as perhaps in-vivo NC testing is less relevant for these types of products and the reliance on NC testing to show comparability more aligned with in-vitro or ex-vivo studies instead (perhaps cross referring to the relevant NC section of the guidance would help too).	Rejected. The guidance refers to general situations, product specific data requirements are an essential part of the risk-based approach.
758	3, 5	**Comment**: "In case of complex CBIMP with a tri-dimensional architecture, the extended characterisation for comparability should consider possible structural changes as well as functional changes" Don't all cells have complex 3D architecture? Or does the above statement only refer to cases where the CBIMP has a scaffolding function related to structure?	Accepted. Example has been included.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
S.3 Characterisation			
760	7	S.3. Characterisation: It would be helpful to clarify which assays used during the characterisation activities need or do not need to be performed to GLP as again this often causes confusion amongst Sponsors.	Out of scope of the quality section.
761 (Section S.3.1)	1	**Comment:** It is unclear whether and where genomic sequence is required. It would be helpful for developers if this section was aligned with the FDA IND draft guideline for GTs to provide an annotated sequence, etc. (See also general comment above).	Requirements for virus seed banks are outlined in S.2.3.
761-785	11	**Comment**: 764: we feel the use of literature should be explained further. It cannot substitute for characterisation, so should only be seen as supportive. The possibility of citation bias should be mentioned. 764 "characterisation data could……" sounds optional, please reword. 769-770 characterisation in S.3 should identify the QA and suitable test methods for release (and extended characterisation), whereas characterisation data in S.2.6 would be used to set process parameters and tests. These are all routine controls. We suggest the text here is more specific and clearly states release testing. 771 – we feel this could be made clearer, e.g. when a medical device is included, when 2 active substances are present etc. Or omit as covered later. 772-785 potency is consistently referred to in the singular, it may be necessary to have a matrix of tests. The meaning of surrogate potency may not be understood by all, we assume you mean a physicochemical method instead of a biological assay. We recommend this text is expanded to explain, e.g. needs to be supported by a true potency assay of some sort.	Partially accepted. Section has been reworded

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Proposed change (if any):	
770	10	Characterisation is also basis for the setting controls applied to final product, not just active substance, especially for ATMPs where there may not be a fully defined active substance **Revise as follows:** Ultimately, characterization allows setting the routine controls that will be applied for release of the active substance and final product.	Accepted. Text has been modified.
772	1	**Comment**: Please correct the following typo. **Proposed change:** "*Biological characterization of the product is* ***an*** *essential part of the documentation*."	Accepted.
772-774	10	*It is 152haracteri that the extent of characterization data will increase in later phase* – this sentence seems out of place as it is a general comment, but this paragraph is relating only to biological activity. The sentiment is of course correct, but it should be moved perhaps to the first paragraph. **Suggest revising** as follows: Characterisation of the biological activity of the product is essential, and the strategy to demonstrate biological activity should be explained and justified. The extent of data demonstrating the characterization of biological activity is expected to increase as product development progresses.	Accepted, section has been reworded

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
775	1	**Comment:** "Generally the biological activity measurement will become the potency test for DS and DP." It should be noted that in certain instances, potency tests cannot be done on a singular DS, particularly if there are two DS which independently don't have any activities (e.g. genome editing products).	Noted. Revision not considered necessary. In case biological activity needs more than one DS, the biological activity assay could potentially be used for potency of all relevant DSs.
775	10	*Generally the biological activity measurement will become the potency test for DS and DP.* Why is this sentence a separate paragraph and why is put before the discussion on potency? It is better placed after rows 776-780 as the last sentence of that paragraph A number of characterization assays that measure biological activity may be required, but it is highly unlikely all of them will be used as a measure of potency for release, particularly if the MOA of the product is not straightforward, and in general potency may be measured by more than one assay, as such we consider this statement should be revised. **Revise as follows:** In general, one (or more) of the methods used for characterization of the biological activity of the product will be developed as a quantitative assay and will be defined as potency test for DS and/or DP.	Accepted. Text revised.
776-780	10	**Suggest revising** as follows: Potency is the quantitative measure of biological activity, which is itself related to the relevant biological properties and the claimed mechanism of action of the product. The methods used for characterization and evaluation of the biological activity of the product will help to define the quality attribute(s) relevant for potency. In general, one (or more) of the methods used for characterization of the biological activity of the product will be	Partially accepted text has been revised.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		developed as a quantitative assay and will be defined as the potency test for DS and/or DP.	
770-780	15	**Comment**: The approach to define potency without referring to consistency with 'clinical lots' is questioned. **Proposed change** (if any): From the characterisation and evaluation of the biological activities, the quality attribute(s) ~~relevant~~ supposed to be suitable ~~for~~ as a ~~the~~ potency marker should be identified. ~~Potency is the quantitative measure of biological activity, which is linked to the relevant biological properties and the claimed mechanism of action.~~ The putative potency assay should be developed based on the biological activity (i.e. the specific ability or capacity of a product to achieve a defined biological effect) but should be validated by its clinical relevance.	Rejected. Implicit. The proposed change is not an improvement. The current text gives clearer guidance. Further, it is not clear how the clinical relevance can be used in validation.
780	1	**Comment**: It should be mentioned somewhere that *in vivo* potency test could be useful for characterization purpose during product development, but *in vivo* test should be avoided for product release or at least replaced by *in vitro* tests whenever possible prior to confirmatory clinical trial or should justified (3R's).	Accepted, text reworded – see S.3.1.
781	10	Depending on the complexity of the MOA more than one measure of biological activity may be needed, and it is much better if the development of those assays are started sooner rather than later. This sentence seems to suggest only one assay is needed, but this may not be the case for a lot of products.	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Suggest revising as follows: It is strongly recommended that suitable methods to quantitatively measure the biological activity of the product are developed as soon as possible.	
781-785	1	**Comment**: Development of potency assays may need to be conducted in parallel. For example, autologous cell therapy based ATIMPs being investigated in exploratory trials. To recommend that a suitable potency assay is in place by FIH trials may prove difficult for some ATIMPs. We recommend options for parallel assay development protocols to be included in exploratory trials for ATIMPs that require potency testing as ATIMPs are developed in early phase trials.	Rejected. The wording reflects a recommendation.
782-785 989-990	5	**Comment**: We recommend this section be consistent with lines 1188-1191. (Lines 1188-1191: "Process characterisation / evaluation data should be collected throughout the development preparing for Marketing Authorisation Application. At that stage the entire manufacturing process, storage etc. should be validated. Refer to S.2.5 for further details on the extent of evaluation / validation data required throughout development.") **Proposed change (if any)**: "Preferably, a suitable potency assay should already be in place when material for the FIH clinical trial is produced and ~~it should be~~ **the suitability of the methods for their intended use should be confirmed through phase-appropriate method qualification or validation** ~~validated~~ prior to confirmatory clinical trials unless otherwise justified. Surrogate potency markers can be considered for release tests, but appropriate justification on their relevance in the context of the intended action of the ATIMP is needed."	Accepted. Wording has been modified.
782-785	10	The topics discussed here are better placed in S.4.3, S.4.1 and S.4.5/P.5.6 rather than characterisation.	Rejected, considered informative.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
782-783	15	**Comment**: Without clinical experience, a potency assay which should be indicative of clinical efficacy, cannot be in place prior to a FIH trial. **Proposed change** (if any): suggest to delete first part of sentence: ~~Preferably, a suitable potency assay should already be in place when material for the FIH clinical trial is produced and it~~ A suitable potency assay should be validated prior to confirmatory clinical trials unless otherwise justified.	Rejected. Potency assay should reflect the biological activity and needs to be considered prior to efficacy data.
787	10	*The characterization should encompass all the components present in the active substance.* Of course that is correct, but if the manufacturing process does not have a defined active substance, characterisation could be performed on drug product / final product. This concept should be added for clarity **Proposed change**: The characterization should encompass all the components present in the active substance, however if there is no defined active substance, due to the manufacturing process being continuous through to final product, characterization can be performed on the final product.	Accepted, the wording has been modified.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
787-791	15	**Comment**: Not adequate for early phases and complex cell mixtures like e.g. bone marrow **Proposed change** (if any): The characterisation should encompass ~~all the~~major components present in the active substance. Characterisation may prove particularly challenging for where cells are combined with matrices, scaffolds and innovative devices. At minimum characterisation of the cellular component should be established in terms of identity, purity, impurities (see also S.3.2), viability, quantity (cell number)~~ and potency~~.	Rejected. Reference is to components as opposed to impurities
794-813	11	**Comment**: General: This section does not explain how early clinical trials can differ from MAA, and mostly reiterates other guidance. There is no mention that the identity test for an active substance should be able to distinguish it from other substances, especially other active substances in the same facility. Some developers may have several products based on the same type of cell, e.g. T cell, MSC, in their pipeline. It would be helpful to address this question, given that many developers use well-known identity markers for the cell. 805-6 please clarify if these belong in M3 or M4 or should be in both. 807-813: perhaps explain that an active substance can be (article 3a, Directive 2001/83/EC) "Any substance or mixture of substances". In the case of more than one cell in a mixture comprising the active substance, how is identify addressed? This paragraph fits better under the product-related impurities, particularly replacing lines 900-901 under the headline S.3.2. Impurities. Either move the paragraph under the impurities headline or elaborate further the extent of characterization of product-related impurities under the S.3.2. headline. 810 – technical error: "i.e. acceptance criteria for the amounts of ~~contaminating cells~~ cellular impurities should be set."	Partially accepted. Other products in the same facility should be addressed under GMP. Accepted Rejected. Reference is to parts of the active substance as opposed to impurities. Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Proposed change (if any): see above.	
797	15	**Comment**: Although not always possible to identify single identity markers, applying a relevant panel should be aimed at. Later sentences implement "should" anyways. **Proposed change** (if any): When addressing the phenotype of the cells, relevant identity markers should be used.	Accepted
800	15	**Comment**: Strict specificity of a marker often may not be achievable. **Proposed change** (if any): They should be ~~specific~~ suitable for the intended cell population(s) and should be based on an understanding of the biological or molecular mechanism of the proposed therapy.	Accepted
805-806	1	**Comment**: Please provide more guidance or a reference on appropriate testing methods. Please clarify at which point (MCB/WCB/DS/DP) the testing should be performed.	Rejected. Considered too specific for the GL
805-806	5	**Comment**: Additional specific guidance regarding requirements for tumorgenicity/ genetic stability characterization at various stages of development would be valuable (e.g. would testing need to be *in vitro* for characterization or would there be a need for *in vivo* studies?).	Rejected. Considered too specific for the GL
805	1	**Comment:** "Tumourigenicity/genetic stability for stem cell preparations that undergo extensive in vitro manipulation such as prolonged cell culture." Please define prolonged culture and whether there are any other factors that may necessitate tumorgenicity such as novel starting materials/reagents.	Rejected. Product specific justification by the risk based approach required.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
807-813	1	**Comment:** **"**contaminating cells" are considered as product-related impurities; if it is the case it should be referred to appropriate sections concerning impurities and need for controls.	Accepted
808-811	1	**Comment:** *"other cell populations should be defined and their amount in the final product should be controlled by appropriate specifications"*: in early development, it is not always possible to have all cell populations characterized.	Reject. Characterization is required, case by case assessment is not excluded
814-838	11	**Comment**: 829-831 – we feel this is implausible if the ATMP is an IMP in early development, given this draft GL covers early stage clinical studies and there are currently no combination ATMP on the market (MACI is no longer authorised). Its use in an ATMP would be outside its CE-mark. Consideration should also be given to acknowledging that after combining some medical devices with cells, e.g. collagen sponge, the medical device may no longer have its original properties (e.g. Haemostasis) and would no longer meet the definition. This is partly acknowledged in lines 835-838. Proposed change (if any):	Rejected. The GL needs to cover anticipated situations, too.
826 – 827	1	**Comment**: Please correct the typo. **Proposed change:** *"…physical characterization such as porosity, density, microscopic structure and ~~particular~~* ***particle*** *size."*	Accepted
826	10	ISO 10933 parts 1826 and 1927 – are these the correct references?	Text removed
833-834	10	*Also it should be ensured that the non-cellular component is of consistent quality* – isn't this concept better placed in raw materials S.2.3. than in characterisation?	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
839	5	**Comment**: Please specify what material characterisation should be performed on – HV material?	Rejected. Considered too specific for the GL
839-869	1, 6	**Comment**: In this paragraph on GTIMP characterisation studies, it is unclear if the use of phages, phage-like particles or nanoparticles containing the gene(s) of interest to genetically modify bacteria or cells *in-vivo* has been considered. The same applies for the potential use of gene editing tools *in-vivo*, other than DNA or viral vectors. **Proposed change**: "*Tests should be included to show integrity and homogeneity of the recombinant viral* ***(including genetically modified phages) or non-viral*** *genome* ***(including phage-like and nanoparticles containing the gene(s) of interest used for genetic modification of the target cells)*** *or plasmid and the genetic stability of the vector and therapeutic sequence****.*** • *Tests performed on harvested vector should as a minimum include identity (desired transgene and vector), purity and yield. For viral vectors* ***(and nanoparticles containing the gene(s) of interest used for genetic modification of target cells)****,* ~~*titre and*~~ *particle to infectivity ratio* ***(for viral vectors only) and titre*** *should normally be determined.* • *For complexed nucleic acids, the structure of the complex and the interaction between the vehicle(s) and the negatively charged nucleic acids should be addressed. Suitable tests should be included to establish, for example, that the complexed nucleic acid has the desired biochemical and biological characteristics required for its intended use.* • *For bacterial vectors* ***(including phages and phage-like particles)****, the presence/absence of inserted/deleted sequences necessary for the safe use of the GTMP should be confirmed. It should be demonstrated that there is no inclusion of known oncogenic/tumorigenic sequences.* ***As applicable, p****henotypic identity, immunological identity (including the genetically modified bacterial components) and analysis of the therapeutic sequences*	Rejected. In this scenario, phages would be starting material, therefore no discussion in this section.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		and selectivity/regulatory elements delivered by the bacterial vector should be included. The absence of contaminating bacteria and bacteriophages, fungal sterility, and inter vial homogeneity of cell bank stocks should be assured. • *For genetically modified cells, in vitro assays for transduction efficiency and transgene copy number per transduced cell should be conducted. For ~~GM cells derived using~~ genome editing tools **~~used to edit target cells genomes ex-vivo or in-vivo~~**, in vitro assays for editing efficiency and off-target editing should be conducted.* • *The intended action of regulating, repairing, replacing, adding or deleting a genetic sequence should be demonstrated. The potency assay should normally encompass an evaluation of the efficiency of gene modification (infectivity/transduction efficiency/delivery efficiency) and the level and stability of expression of the therapeutic sequence or its direct activity or deletion. Where possible the potency assay should include a measure of the functional activity of the therapeutic sequence or the product of it."*	
839-869	11	**Comment**: This section provides clearer advice than the preceding section for CBMP, it could be used as a template for revision. Proposed change (if any):	Noted
845-847	15	**Comment**: These are tests which are normally part of release. In characterisation test complementary to the release test are presented. **Proposed change** (if any): suggest to clarify	Acknowledged, test are part of characterisation and might additionally be used for release - can be presented in either section (if not in release, they should be included here)

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
846	3, 5	**Comment**: Yield is not a characteristic of the molecule, but rather an indicator of manufacturing process efficiency. **Proposed change** (if any): Tests performed on harvested vector should as a minimum include identity (desired transgene and vector), and purity ~~and yield~~.	Accepted
846	3	**Comment**: It is not clear why particle to infectivity ratio should be determined if the sponsor has a potency assay	Noted
848-850	1	**Comment:** "*For complexed nucleic acids, the structure of the complex and the interaction between the vehicle(s) and the negatively charged nucleic acids should be addressed. Suitable tests should be included to establish, for example, that the complexed nucleic acid has the desired biochemical and biological characteristics required for its intended use.*": Could you please define tests to address "interaction"?	No general statement possible, depends on the product.
852-859	5	**Comment**: Information on control strategy and product design/characterization should not go in S.1.3, but rather is divided across the dossier (e.g. S.1.2 for genetic construct, and S.3.1 characterization for data showing replication deficiency or competency, cell line screening for RCV in A.2, tests for DS in S.4.1 and S.4.5). It is proposed to move information in Lines 296-313 from S.1.3 to S.3.1, and to delete any information that is also addressed in other parts of the IMPD. Also, there was no guidance for viral vectors on what to include in S.3.1 so it is proposed to include it as part of this edit. **Proposed change (if any)**:	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Move lines 296-313 to S.3.1, and merge. See proposed changes to S.3.1 below. • For bacterial **and viral** vectors, the presence/absence of inserted/deleted sequences necessary for the safe use of the GTMP should be confirmed. It should be demonstrated that there is no inclusion of known oncogenic/tumorigenic sequences. Phenotypic identity, immunological identity (including the genetically modified bacterial **or viral** components) and analysis of the therapeutic sequences and selectivity/regulatory elements delivered by the ~~bacterial~~ vector should be included. The absence of contaminating bacteria and bacteriophages, fungal sterility, and inter vial homogeneity of cell bank stocks should be assured. • For replication deficient viral vectors, the strategy taken to render the viral vector replication incompetent should be clearly documented, and replication deficiency demonstrated during characterization. ~~The drug substance and where appropriate intermediates, as well as any packaging/producer cell lines, should be screened for Replication Competent Viruses (RCV).~~ The possibility of any recombination events leading to RCV or replication via *trans* regulation should be considered. ~~In the case of genetically modified cells, RCV testing at the Drug Substance or other intermediate levels is not deemed necessary provided that absence of RCVs has been demonstrated at the level of the virus starting material and RCV formation during manufacturing of the genetically modified cells can be excluded.~~ • For replication competent viral vectors or replication-conditional viral vectors, a clear rationale for the construct and the individual genetic elements that control replication should be provided regarding to its safe use for the proposed clinical indications. It should be demonstrated that there is no inclusion of known oncogenic/tumorigenic sequences, and that if the parental viral strain is a known pathogen, the infectivity, virulence and	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		pathogenicity of the RCV should be characterized after the desired genetic manipulations. ~~• Consideration should be given to the following factors:~~ ~~○ i) That replication competence is required for the efficacy of the medicinal product;~~ ~~○ ii) That the vector does not contain any element(s) known to induce oncogenicity/tumorigenicity in humans;~~ ~~○ iii) That if the parental viral strain is a known pathogen, the infectivity, virulence and pathogenicity of the RCV should be determined after the desired genetic manipulations and justified for the safety of its use;~~ ~~○ iv) The tissue specificity of replication.~~ • For genetically modified cells…	
857	3	**Comment**: What is the rationale for demonstrating homogeneity for bacterial vector cell banks if this is not required for other types of banks? What statistical approach should be taken to assess homogeneity?	Rejected. Inter vial homogeneity is required to ensure manufacturing consistency. No recommendations on the statistical approach are considered needed. It is up to the applicant how homogeneity is ensured.
857-858	15	**Comment**: Redundant to line 637. **Proposed change** (if any): propose to delete ~~The absence of contaminating bacteria and bacteriophages, fungal sterility, and inter vial homogeneity of cell bank stocks should be assured.~~	Accepted
859-861	10	Where vectors integrate, shouldn't the predominant integration sites also be characterized? This seems to be missing.	Wording on integration sites has been added.
859-861	15	**Comment**: Suggest to use "vector" instead of "transgene" for consistent terminology and add a further sentence.	Accepted. The paragraph has been reworded.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Proposed change (if any): For genetically modified cells, in vitro assays for transduction efficiency and vector~~transgene~~ copy number per transduced cell should be conducted. For GM cells derived using genome editing tools, in vitro assays for editing efficiency and off-target editing should be conducted. In addition the cells should be analysed for large DNA-fragment inversions, deletions, duplications or chromosomal rearrangements	
860	15	**Comment**: "GM cells" probably should read genetically modified cells (or gene edited cells) **Proposed change** (if any): Please clarify	Accepted
863-865	15	**Comment**: Description of potency here differs to the definition in line 777 (Potency is the quantitative measure of biological activity). The parameters proposed here are considered to be surrogates for the actual potency. **Proposed change** (if any): suggest to rephrase	Rejected. The reference here to potency is general and not a definition.
870-904	11	**Comment**: Many inexperienced developers do not fully understand the difference between product- and process-related impurities (nor contaminants); sometimes they know process-related impurities as process residuals. We suggest this could be explained at the start (rather than line 885-887). 872-975 It isn't stated if this refers to early clinical studies, given that regulatory science says all impurities should be identified, and those that pose a risk controlled. It would be preferable to say residual raw materials, rather than reagents. The meaning of clinical impact may be unclear to some, some examples might help, e.g. hypersensitivity reaction to a protein impurity. It should be acknowledged that some	Accepted. Reworded

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		ATMP enter the clinic without first being tested in animals; how then do they address impurities? 876-879: purity is commonly interpreted as absence of impurity rather than a test for purity; this could be clarified here. 902-904: non-viable cells could in some circumstances be active, but the text implies they would never be, this is too absolute. Potency can for example be due to release of soluble factors by a cell, and this may occur after it is no longer viable. As a product-related impurity, the normal approach would be to quantify how much is present. While %viability is a universally used, often it isn't particularly useful, e.g. without total cells it is meaningless. We suggest that this text is modified as measures such a total viable count can be more useful than total cells and %viability. We see no reason why, for example, total non-viable cells wouldn't be suitable in combination with total viable count. We also question the apparent absolute certainty of potency being directly correlated with potency; we suspect this isn't always true. Please reword. Proposed change (if any): see above	
871-875	12	**Comment**: Clarification/guidance is requested on when residual assays are appropriate for characterization purposes only or release purposes. Proposed change (if any):	No general statement possible, however, the following sentence gives the general consideration for this issue: *Ultimately, characterisation allows setting the routine controls that will be applied for release of the active substance and final product.*
872	15	**Comment**: Also other impurities for which clinical impact is not known or unclear should be addressed. **Proposed change** (if any): suggest to rephrase	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
872-874	1	**Comment:** Please clarify whether it is also acceptable to present that residual reagents are removed during the production process hence their levels in the final product are not a concern?	Accepted, wording modified
876-879	15	**Comment**: This paragraph again appears to focus on late stage confirmatory trials, e.g. by requesting demonstration of consistency; reduced requirements for exploratory trials have to be addressed **Proposed change** (if any): re-phrase accordingly	Accepted, wording modified
885-888	15	**Comment**: Typical GTIMP product-related impurities are not listed, such as empty particles or non-infectious particles. **Proposed change** (if any): Process related impurities (e.g. media residues, growth factors, host cell proteins, host cell DNA, column leachables) and product related impurities (e.g. cell types not linked to the therapeutic effect, cell fragments or non-viable cells, precursors, non-infectious and empty vector particles, degradation products, aggregates) should be kept to the minimum or a risk assessment provided.	Partially accepted. Added to product related impurities
895-896	15	**Comment**: Full absence of helper viruses may not be feasible for all virus vector types. **Proposed change** (if any): The absence or level of any helper or hybrid viruses generated or used during manufacture or components of the production system should be demonstrated.	Accepted
900-904	5	**Comment:** Clarify at which phase of development it is expected to have specifications for these parameters (other cell populations and the ratio between non-viable and viable cells).	Rejected. Specifications are required from the beginning, when they are considered relevant for patient safety.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
902	3, 5	**Comment**: Minor edit proposed. **Proposed change** (if any): Irrespective of the cell type, the cell population can contain ~~with~~ non-viable cells	Accepted
902-903	10	Some typo's in this paragraph to correct. It is unclear why a ratio of non-viable to viable cells should be set rather than a limit on % viability for example. More flexibility on the type of specification should be permitted, with justification **Suggest revising** as follows: Irrespective of the cell type, the cell population can contain ~~with~~ non-viable cells. Since cell viability is an important parameter for product integrity and directly correlates to the biologic activity a specification should be set, and justified, for the content of non-viable cells, such as the ratio of non-viable to viable cells, % viability or a limit on the total number of non-viable cells per dose.	Accepted
S.4 Control of the active substance			
905-913	11	**Comment**: 911-913 Some may not be clear what this means, we assume DS versus DP but also acknowledge that in-process testing can in some circumstance be included. Likewise, due to time constraints, some test results are not known until after release – these points could be acknowledged here. Proposed change (if any): see above.	Accepted. Reworded
908-910	10	*Therefore the quality attributes controlled throughout the development process should be more comprehensive than the tests included in the specification for which preliminary acceptance criteria have been set.*	Accepted. Reworded

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		It is not completely clear how to interpret what is meant by this sentence. It is presumed you mean the quality attributes controlled as in-process controls during process development should be more comprehensive? If so that also has implications on the qualification status of the IPC tests during early stage development, as these methods should be qualified to a similar extent as those used for release, given their purpose would be to ensure product quality – and presumably appropriate specifications should be defined as early as possible. This is not abundantly clear in the S.2. section of the guidance. Please try to rephrase so the intent is clear to the reader and revised other sections that may be implicated to ensure the guidance is consistent.	
908	15	**Comment**: Requirements should also address early trials; quality attributes are always important, even when process validation has been completed **Proposed change** (if any): During ~~the~~ all clinical trial phases~~, where process validation data are incomplete~~, the quality attributes to control the active substance are important to demonstrate pharmaceutical quality, and depending on the stage of development product consistency and comparability after process changes. Therefore the quality attributes controlled throughout the development process should be more comprehensive than the tests included in the specification for which preliminary acceptance criteria have been set.	Partially accepted. Wording modified
911-913	10	*If justified, it can be acceptable to have reduced testing at one level provided an exhaustive control is performed at another.* Why are you not using DS and DP rather than loose wording such as 'level'? **Proposed change**:	Accepted. Reworded

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Where justified, it can be acceptable to have reduced testing for drug substance provided an exhaustive control is performed at drug product, or vice-versa.	
912-913	5	**Comment**: Minor editorial change proposed to clarify level of the process. **Proposed change (if any)**: For quality control the active substance should be subjected to release testing, whenever possible. If justified, it can be acceptable to have reduced testing at **release** ~~one level~~ provided an exhaustive control is performed at another **stage of the process.**	Partially accepted. Reworded
914-952	11	**Comment**:915-916: a specification is a set of tests and acceptance criteria, it is *de facto* defined. Suggest rewording first sentence. 99-920: recommend acknowledging the specification is justified in S.4.5. 921-924: specifications based on limited data 'should' be wide, statistically the range is uncertain when data are limited. 925-929: We are surprised by this statement, a test without acceptance criteria does not provide a specification. Such a test is therefore merely the collection of characterisation data and we see no value in including in the specification. If the agencies would like to be reassured additional testing is undertaken, is S.4.1 the right place? We agree inclusion in S.4.4 could be appropriate, perhaps mentioned in S.4.1 but not within the specification. We suggest it is stressed that the specification includes end of shelf-life, this is not understood by many developers. Proposed change (if any): see above.	Partially accepted. Reworded
918-920	10	*The release specification of the active substance should be selected on the basis of parameters defined during the characterization studies. The selection of tests is product-specific and needs to be defined and justified by the applicant.*	Accepted, wording modified

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		The use of the term 'parameter' for describing product quality attributes has the potential to lead to significant confusion when read in conjunction with ICH guidance (8, 9 and 11). We would suggest parameter is reserved for process parameters and for product you could use 'quality (or material) attributes'. **Suggest revising** as follows: The release specification of the active substance should be selected based on the quality attributes of the active substance defined during the characterization studies. The selection of analytical methods used to measure these attributes will be product-specific and should be defined and justified by the applicant.	
924	5	**Comment**: Clarify what is meant by: *"parameters cannot replace existing and sufficient specification"*	Accepted, wording modified
925-928 932-933	3, 12	**Comment**: These two statements are conflicting	Accepted, wording clarified
925-933	10	This section seems to give conflicting advice with respect to tests performed for information only where no acceptance criteria could be set. With 925 – 926 suggesting this is acceptable but 932-933 suggesting the use of such testing should be limited. This could be rectified perhaps by suggesting the use of 'for information testing' can be acceptable in early phase development, but as product development continues (and process and product characterization is better defined), their use should be limited, and the testing introduced in the product specification with acceptance limits defined based on process capability and historical batch data, or it could be justified to remove testing of certain quality attributes if the data demonstrates they are of limited value to ensure product safety and efficacy.	Accepted, wording clarified

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
925-938	11	**Comment**: We appreciate in early studies it can be difficult to set acceptance criteria for potency. However, we question the value of including a test that has no acceptance criteria in a specification (a specification being a list of tests and acceptance criteria), although those data should be collected where possible for characterisation purposes. We have concerns that some developers have specifications that lack so many acceptance criteria, the product is largely released based on viability and sterility, and this should not be encouraged, particularly given the limited preclinical data many of these products have. We suggest it should be stressed that inability to undertake animal studies does not justify limited or no characterisation, instead that gap in the characterisation needs to be filled by other *in vitro*/*ex vivo* studies, as far as possible. Some developers, an example being those developing MSC, have multiple identity markers and as such consider they have a comprehensive specification, e.g. based on ISCT criteria (despite those criteria not being intended for clinical release). Yet the relevance of those markers to the mechanism of action is often obscure or likely doesn't exist. What value do some of those markers have, if they are not all needed to establish identity (likely they are not) for release purposes. Is it not beholden on the developer to establish the relevance of the QA tested, for the particular clinical application? Is identity and viability sufficient together with microbial testing? Impurities are mentioned in a very general way, which are meant? Product-related (e.g. cells not considered to be the active substance, dead cells) are sometimes (e.g. MSC) defined as part of identity; we consider this isn't the right approach. Process-related (residual raw materials) are rarely tested in early clinical studies, at best developers estimate the level in the DP through calculation. Is this acceptable (link to comments in S32), and if so, when is it not acceptable? While we accept the diversity of ATMP makes this difficult, we had hoped for more comprehensive advice on what is the minimum needed for early clinical studies. Line 939 – validation of what? Neither the methods nor the process is validated in early clinical development. Please reword to clarify the meaning. We assume the guideline means the initial release (as this	Noted. Wording has been amended

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		is S41) specification is based on engineering batches etc from healthy volunteer starting material and not patient-derived. Once patient-derived batches are manufactured, these should be used to revise the acceptance criteria. We also feel it should be acknowledged that for CBMP, a DS is not usually defined, so these points would be applied to the DP release (P51). **Proposed change** (if any): More clarity as to which criteria, e.g. product-related impurities, potency, are acceptable to omit (effectively what is proposed by accepting FIO results) during early studies, and when these must be included, e.g. start of confirmatory trials. No mention that the end of shelf-life specification also belongs here; many do not understand this. Clarify the meaning of 'validation' on line 939.	
935-936	1	**Comment:** "*For a FIH trial the absence of quantitative limits for potency / biological activity would have to be justified by the applicant.*": Please provide examples of acceptable non-quantitative specs for potency assay.	Rejected. The diversity of ATMPs and indications precludes generalization
935-936	15	**Comment**: (see also comment to lines 782-783) Without clinical experience, a potency assay which should be indicative of clinical efficacy, cannot be in place prior to a FIH trial. **Proposed change** (if any): suggest to delete ~~For a FIH trial the absence of quantitative limits for potency / biological activity would have to be justified by the applicant.~~	Rejected, as above.
941-944	1, 6	**Comment:** From the way the paragraph is written, it looks like it excludes *in-vivo* genome editing tools other than viral vectors or nucleic acid particles such as plasmids. If this paragraph is only applicable to some, but not all, GTMP, this should be clearer. **Proposed change**:	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		*"In case of GTIMP, **when applicable,** the genetic identity and integrity of the drug substance …."*	
943-945	12	**Comment**: Clarification is requested on whether confirmation of identity using expression/activity would be recorded/presented as identity, potency, or both. Proposed change (if any):	Rejected. Generalization is not possible. Parameters defining identity and potency need to be independently listed.
945	11	**Comment**: There is no heading or subheading entitled Potency assay. **Proposed change** (if any): please clarify which section is the one referenced in this line.	Accepted. Reworded.
947-952	11	**Comment**: The word 'parameter' could imply process parameters, yet this is S.4.1 (DS specification), so could be confusing. **Proposed change** (if any): Assume you mean QA and their associated test methods and acceptance criteria. The last sentence is too vague to be useful; expand or remove. We question whether this sub-heading is in scope.	Rejected. Aligned with EMA/CHMP/BWP/534898/2008 Rev. 2
952	5	**Comment**: It is not likely that specifications can be linked to clinical outcome prior to completion of confirmatory trials (if ever). **Proposed change (if any**): Remove text "that is linked to clinical outcome". (replace with "inclusion of a relevant potency test?)	Accepted. Wording modified.
953-961	11	**Comment**: So many examples of test methods that might be part of a specification are unnecessary. Biological assay is repeated. Considering the last sentence (line 961) in S.4.2, we suggest it is stressed that the specification in S.4.1 includes end of shelf-life, so these methods are described here also (if they differ from those used for release). We refer back to our concerns about encouraging the use of tests without acceptance criteria (S.4.1). We note the absence of comment on the importance of appropriate reference materials for analytical methods, in particular the units for	Rejected. Aligned with EMA/CHMP/BWP/534898/2008 Rev. 2

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		potency are normally defined by the in-house reference material (S.5). Explaining that a calibrator is a reference material is likely useful. Proposed change (if any): see above	
961	10	*Stability methods should be demonstrated as suitable to monitor product degradation.* Normally only the method descriptions are provided in this section. If you need to demonstrate the ability of the method to monitor product degradation that seems to be more related to method qualification / validation than the description and this concept is probably better placed in S.4.3. / P.5.3.	Accepted.
963-987	11	**Comment**: There are divergent uses and (assumed) meanings for qualification and validation, so it would be appreciated to be as clear as possible on what is meant. We believe qualification is defined by the second sentence (line 964-965), but not clearly enough. Our understanding is all methods should be at least qualified, and this means shown to be fit for purpose. The explanation of how you show a method is fit for purpose (971-976) is potentially valuable but could be explained more clearly. We suggest validation should only be used where it is expected a method is validated (as described in ICH Q2), e.g. safety critical tests such as sterility. Reproducing the list of validation criteria is of limited value (refer to ICH Q2) and doesn't acknowledge that the relevant criteria depend on the type of test method. This is not always understood by developers. Then the question for most developers is how do they qualify the method? The text in this GL doesn't provide a distinction from validation. Definitions could be provided under the heading in line 1988 (currently empty). The clarification of the status of pharmacopoeia tests is endorsed as useful for some developers: it would be helpful to clarify that those other (other than Ph.Eur.) pharmacopeia are applicable during clinical development (we known this is stated in other guidance).	Accepted. Reworded. This is stated in S.4.2.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Line 981-982 lacks clarity as to what is suggested. This section, S43, relates to method qualification/validation, so a comment about process characterisation and process robustness doesn't make sense here. Please clarify how this relates to analytical methods or move/remove. Please clarify if data demonstrating a test is stability-indicating should be presented here (we have not seen this for clinical trials) or within S.7. If S.7, please cross reference the comment here. Even if linked forward to lines 1064-1066, there is little clarity as to what is expected for early CT. Our experience suggests few developers appreciate the need to demonstrate a QA is stability-indicating, and many likely dismiss ICH Q5C (let alone Q1A) as not relevant to ATMP. It would therefore be appreciated is the GL could provide clarity on what is expected for early CT, since we observe many stability protocols rely primarily on viability (some not yet having a potency assay, let alone one for which they can set a specification). **Proposed change** (if any): See above, significant revision recommended.	Text has been modified Text has been modified
966	12	**Comment**: Clarification is requested on whether confirmation of identity using expression/activity would be recorded/presented as identity, potency, or both. Proposed change (if any):	Rejected. Generalization is not possible. Parameters defining identity and potency need to be independently listed.
972-974	1	**Comment:** For early clinical trials, it is suggested not to include such level of detail in the IMPD.	Rejected. Required to assess robustness of data.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
972-974	1	**Comment:** "*The parameters for performing qualification of the analytical methods (specificity, linearity, range, accuracy, precision, quantitation and limit of detection, as appropriate) should be presented in tabulated form.*": It should be clear that not all of these parameters will necessarily be required for qualification as they will be for validation, especially for potency assay.	Rejected. Wording is flexible as is.
972-976	15	**Comment**: No information usually provided with exploratory trial applications. Use of a staggered approach is suggested here. **Proposed change** (if any): Paragraph requires re-working	Rejected. Required to assess robustness of data.
977-980	15	**Comment**: Underpinning required that all safety relevant methods have to validated prior start of human trials and that this also includes demonstration that the test article does not interfere with the validated method (product-specific qualification). **Proposed change** (if any): Irrespective of the clinical trial phase, all safety relevant methods such as those used for microbiological and viral testing have to be validated prior start of the clinical trial and demonstrated by confirmatory documentation that the test article does not interfere with the validated method. ~~The suitability of the analytical methods used~~ For viral testing, either as a qualitative or a quantitative method, ~~should be substantiated~~. ICH Q5A Chapter 3.2 "Recommended Viral Detection and Identification Assays" is applicable. ~~Validations of sterility and microbial assays, as well as RCR testing are required whatever the clinical trial phase.~~	Partially accepted. Wording has been modified.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
978	5	**Comment**: "either as a qualitative or a quantitative method, should be substantiated. ICH Q5A Chapter 3.2" **Proposed change (if any)**: If strictly, in the ICH guideline the chapter is III.B instead of chapter 3.2 It is chapter 3.2 in EMA of this guideline. Please, specify for avoiding misunderstanding	Partially accepted. ICH Version added. Numbering as in ICHQ5A(R2) has been used.
980	1	**Comment:** Is RCR is typo, to be replaced by RCV? If not, RCR acronym should be explained.	Accepted.
981-982	3	**Comment**: It is suggested that this text is out of place here and is not relevant to method validation. **Proposed change (if any)**: Propose move to under Line 913.	Accepted.
983-986	17	**Comment**: **Assay for replication of competent virus:** Due to the lack of positive results from replication of competent virus for lentivirus assays on vector lots To be clarified by the expectation of agency whether this testing should be made on MCB and working cell bank and/or on the patient dose, and also from different constructs. Clarifications are requested on whether a validated method for replication competent virus is required for both early and late stage products, or if a qualified assay would be acceptable for early stage Proposed change (if any):	Accepted. Information has been included in S.2.3. Wording has been modified. Full validation is expected.
984	5	**Comment:** Clarify – does the RCV method need to be qualified or validated? It is unusual to have fully validated methods during exploratory studies.	Wording has been modified. Full validation is expected.
988-992	11	**Comment**: We suggest developers would look at MA-level guidance for confirmatory trials. The text remains somewhat ambiguous as to whether analytical methods must be validated for all confirmatory studies, or whether this is merely recommended. The experience of	Partially accepted. Wording has been modified.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		our members suggests most plan to, or undertake, validation of methods during confirmatory studies, not before. Confirmatory study data may lead to alterations in the specification, and some methods might be dropped from routine use, and others previously used for characterisation (so qualified only) adopted as alternatives. Significant resources might have been spent validating a method that proved not to be useful. **Proposed change** (if any): Please clarify as far as possible, or considering he scope this comment might be better removed. Please address any intended deviation from other guidance, e.g. the CBMP guideline (2006, MA-level) says "*All release testing should be performed using methods validated at the latest at the time of submission of an application.*" We appreciate this position may have changed, but is a guideline for early exploratory studies the right place to address this?	
989-992	1	**Comment:** Analytical method validation occurs in a step-wise approach with methods validated at a time relevant to their use. Method validation prior to confirmatory studies may not be feasible for expedited clinical programmes, and would result in disharmony in global requirements for method validation. The requirement should be method validation at MAA. Methods should be qualified, and ideally validated, before confirmatory studies. A hierarchy of validation should be applied, with potency and safety being key, followed by stability indicating assays. **Proposed change:** ~~"*For confirmatory clinical trials, the guidelines applicable to Marketing Authorisation Applications do apply. Validation of analytical methods for batch release and stability testing is expected. It is not necessary to provide full validation reports. A tabulated summary of the results of the validation carried out should be provided.*~~ *Analytical methods should be qualified prior to confirmatory studies and validated prior to MAA. A hierarchy approach may be taken to assay validation, with*	Wording has been changed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		emphasis on potency and safety assays first, followed by stability indicating assays."	
989-990	15	**Comment**: Formally, guidelines applicable for MAA are not mandatory for confirmatory trial though they may provide relevant guidance to be considered. The document should not elaborate on documents which have to be provided for CTAs. **Proposed change** (if any): For confirmatory clinical trials, the guidelines applicable to Marketing Authorisation Applications ~~do apply~~should be considered. Validation of analytical methods for batch release and stability testing is expected. ~~It is not necessary to provide full validation reports. A tabulated summary of the results of the validation carried out should be provided~~	Partially accepted. Wording has been modified
993-1009	11	**Comment**: Firstly, we feel the purpose of this section (S.4.4) should be more clearly stated, it is primarily tabulated release data results only; with no particular need for discussion, except footnotes etc to explain deviations or other anomalies. In particular a discussion on acceptance criteria does not seem appropriate here (beyond stating the acceptance criteria in use at the time should be included in the tables), such discussion belongs in S.4.5 (justification of specifications). The main point that our members need clarified is whether all batches manufactured to date, or only selected batches should be provided; in particular for autologous products as they near or reach confirmatory studies. We note that many developers only provide a few example batches (for autologous sometimes only healthy volunteer batches), we are surprised this is being accepted. Line 1004-1005: This statement is potentially confusing. The manufacture and control of a vector starting material (for GM-cell DP) belongs in S.2.3; and most developers use a separate DS section to describe this. Is the suggestion that the vector S.4.4 section is	Accepted. Wording has been modified.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		reproduced here in the GM-cell S.4.4? We feel this is an unhelpful suggestion, and inconsistent with ICH M4Q. Also, we should note that for most CBMP (including GM cells) there is no defined/released DS anyhow, so S.4.4 would be empty of release test results, there would only be results for the DP in P54, depending on how the applicant choses to populate the CTD (see also other comments on use of CTD for CBMP). We therefore recommend removing the last sentence, and possibly instead reminding the reader that there should be an equivalent to S.4.4 for the vector (or any other manufactured starting material), where it is a starting material. Proposed change (if any): See above.	
1002-1003	1	**Comment:** "*For exploratory clinical trials, provision of batches to be used in the given clinical trial, when available*.": Does this mean that only data on healthy donor batches would be acceptable in the CTA?	In justified cases, where it is not ethical or otherwise possible to manufacture batches from patient material prior to the trial. Other control measures might be implemented prior to administration of the first batch.
1002-1005	17	**Comment**: Typically batch data presented in S.4.4 are limited to released clinical trial batches, if available at time of submission. Non-clinical/toxicological batch data are often provided in S.2.6 **Proposed change (if any):** To confirm the scope of lots presented in S.4.4 and possible flexibility to provide clinical batch results at a later stage (but before human studies are initiated)	Not generally agreed. If adequately cross referenced, provision of information in other sections is possible. With the exception of justified cases, the provision of batch results is required during the approval procedure.
1004-1005	1, 6	**Comment:** The following sentence may need clarification: "In case of genetically modified cells, the batch data on the vector used to produce the active substance should be provided ". Which vectors are considered here? Does it include any genome editing tool used, including viral	Partially accepted. Wording has been modified

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		vectors? Can it be confirmed if for such starting material batch analysis data should be presented in S.4.4 instead of the starting material section S.2.3? **Proposed change:** *"In case of **ex-vivo** genetically modified cells, the batch data on the ~~vector~~ **genome editing tool** used to produce the active substance should be provided"*	
1004-1005	3	**Comment**: What is the rationale for submitting batch analyses data for a vector if it is considered a starting material (line 559) as batch analyses data is typically submitted only on drug substance and drug product?	Accepted. Wording has been clarified.
1004-1005	12	**Comment**: Clarification is requested as the batch analysis section is submitted on drug substance and drug product, while the vector is considered a starting material and as such, the material's batch analysis data would not be included in this section. Proposed change (if any):	Accepted. Wording has been clarified.
1010-1025	11	**Comment**: The first sentence doesn't make sense, we assume '…quality attributes included **in** the specification and " but even then it isn't easy to follow. At MA both the QA and the method used to test for the QA are justified, as are the acceptance criteria. We feel it would be better to start by explaining what needs to be justified, which tests are included was already addressed in S.4.1. This means the last sentence on line 1014 is redundant (covered in S.4.1). However, it could be useful to state that no further justification of tests for contaminants, e.g. sterility, viruses, is required (i.e. negative, no growth etc is sufficient). Considering the comment on line 961 (P42), would this be the right place to justify stability test methods are stability-indicating? From our experience, developers often don't entirely understand what a justification should look like, e.g. they might say only 'confirms the cells are viable' for a viability test method, or similarly limited	Partially accepted. Aligned with EMA/CHMP/BWP/534898/2008 Rev. 2. S.7 or S.4.2. are suggested, cross-references will be accepted No further wording added.

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		comments. It might therefore be helpful to provide one or more examples or otherwise elaborate on the detail expected. It seems to us this would be the right place to justify omitting certain tests, e.g. process-related impurities, e.g. by calculating likely limits. Yet strictly speaking, if those tests are not on the specification (S41), they wouldn't need to be justified. Clarity on the preferred approach is welcomed. We also feel it would be helpful to mention that data in S.4.4 and S.7.3 can be referenced from this section to justify acceptance criteria. Likewise, the limitations of the analytical methods used, e.g. LoD/LoQ, could reference method qualification summaries in S.4.3. We also note no comment on the situation where some tests will be finalised after the product is released, should the justification here discuss this? Proposed change (if any): see above.	Accepted. Wording has been added in P.5.1.
1013-1014	15	**Comment**: see above (989-990) **Proposed change** (if any): ~~Early selection of a potency assay and its proposed acceptance limits is recommended.~~	Accepted.
S.5 Reference standards or materials			
1026	3	**Comment**: How do reference standards and materials differ? It is possible that none of the analytical methods used to test and release a batch of an ATIMP will use reference material, especially if the potency assay is not a relative potency assay. In this case, what is the value of a reference standard/material?	Acknowledged. Difference between reference standard and material clarified in ICH Q6B. Reference to ICH Q6B included.
1026-1041	10	Reference standards are generally applied to analytical methods to i) trend the performance of the assay ii) to give assurance that the	Accepted. Wording has been modified.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		measured value of the test article is a 'true' value. On the basis of the reference meeting certain acceptance criteria the assay is valid, and the result obtain for the test article can be applied to the batch to be released, and only then, on review of the batch release data, can you evaluate batch to batch consistency or comparability. The reference materials themselves to not ensure consistency between batches and comparability, it is the means in which the reference materials are applied that can support that evaluation. The first sentence is therefore considered misleading and should be revised. While product specific references are possibly the ideal, it will depend on the assay in question and also the product being developed. The use of assay specific references instead of the product or a process intermediate should be permitted where justified. For example, for FACS analysis of cell surface markers, is a recombinant cell line expressing a certain level of particular surface marker(s) (or perhaps a commercially available bead) a better reference than a product batch, particularly if the product is autologous and there will be significant batch to batch variability which makes qualification of new references more challenging? A recombinant cell line can be banked, and primary/secondary reference strategies employed. This section also does not mention reference requalification in any detail. For FIH studies this may not be relevant, but for confirmatory studies thought should have been given to the reference materials to be applied and how replacement reference materials will be implemented and in later stages of development where more than one reference material has been used we would have thought all references and their qualification data should be presented. We presume the concept of reference qualification being performed with orthogonal methods as per product characterisation should be upheld in accordance with EDQM recommendations? If so this concept should probably be mentioned here too. **Proposed change**: We would recommend this section is revised to perhaps try to address some of the issues raised in the comment section.	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
1026-1042	11	**Comment**: We note that there are few if any GL that address reference materials (e.g. in-house) and reference standards (e.g. pharmacopeia, or other certified reference materials such as WHO), so additional explanation on their importance and use would be appreciated. In particular, the product reference (batch) has more then one use, and while this is mentioned it isn't explained, yet for potency it provides the units of measurement which is particularly important. Line 1027 – the type of reference material mentioned here (product reference batch) only applies to 'biological' medicinal products, we suggest saying this as the role of reference materials is poorly understood. We didn't note a comment in S.2.6 about their use in comparability studies. 1029-1030 – we are surprised this statement isn't aligned with biotech, where a reference material would be established even in preclinical development. While we accept this is not possible in the usual sense for autologous cell products (acknowledged in GL), there is no obvious barrier for gene therapy vectors. The usual need for the reference material to be fully characterised and a CoA issued, and on-going stability isn't mentioned. 1041-1042: we find it curious that it is mentioned that other reference materials should be characterised, when this wasn't said for the product reference material. Other reference materials are assumed to mean those used for analytical methods (see comment in S42), these might be sourced from e.g. EDQM, WHO etc, where additional characterisation is not required. Many will assume calibrators supplied with test kits, e.g. for measuring cytokines, do not need characterisation. Please expand this to explain more fully if possible. 1035-1037: The paragraph presents the challenge but doesn't provide a suitable guidance in that case. It would be helpful to elaborate on the agency opinion for developing reference standards and material in such situations.	Accepted. Wording has been modified.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Proposed change (if any): see above.	
1026-1042 1314-1316	12	**Comment**: Clarification is requested on the difference in reference standard versus reference material and appropriateness of use for each type in light of the challenges facing identification of suitable product standards for ATMPs.	Accepted. Clarified in ICH Q6B.
1029-1030	17	**Comment**: Regarding the reference standard for the replication-competent vector/virus assay (e.g. a positive control) and for method validation, what would be Agency expectation at exploratory /confirmatory clinical studies	Method's suitability is the Applicant's responsibility.
1035-1037	1	**Comment:** In relation to reference standards for CBIMPs, the challenges are acknowledged but no advice is provided. Could an example be provided where one would be expected to have a cell-based reference standard? Consider adding guidance in such situation, with examples.	Accepted. Section has been modified.
1035-1037	5	**Comment**: Suggest for CBIMPs to expand the chapter on reference materials with recommendations on how to handle autologous products where reference materials cannot be kept in practice or would be produced from cells from healthy donors and thus would not be representative for the whole spectrum of products **Proposed change (if any)**: **For CBIMPs, identification of a suitable product reference standard may be challenging, especially in cases where the manufacturing process for the clinical product does not include a freezing step, in such cases a reference standard that has been stored frozen might appear to differ from the product leading to false product failures… or similar.**	Accepted. Section has been modified.
1035-1037	10	It is unclear what guidance is actually being given in this paragraph, all this does is acknowledge applying a reference material may be complicated. See comment above. This section could be significantly improved by giving examples of how complications might be	Accepted. Section has been modified.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		overcome, or at least by suggesting scientific advice is sought to get regulatory feedback on the approach to be proposed by the company.	
1040-1042	10	If orthogonal methods are used for reference qualification, that are not routinely used for manufacturing IPC or release testing purposes, should the methods be described in S.5, and would that be required only for MAA or for confirmatory studies too? Clarification would be helpful.	Accepted. Wording has been added.
S.6 Container closure system			
1043-1047	1, 6	**Comment**: Integrity of the DS immediate packaging, in case of a sterile DS, is not mentioned. As it is expected that the integrity of a sterile DS container-closure is tested before FIH, it is proposed to add this notion in the appropriate paragraph under S.6. **Proposed change:** *"The immediate packaging material used for the active substance should be stated. A description of the container closure system should also be provided. It should be indicated if the container closure per se has a CE marking for the intended use under the EU legislation on medical devices. Information on the sterilisation procedures of the container and the closure should be provided**, as well as information on the container closure integrity**. A possible interaction between the immediate packaging and the active substance should be considered (see stability)."*	Accepted. Reworded.
1043-1048	11	**Comment**: It isn't clear if sterilisation needs to be discussed if the container closure is a CE-marked medical device. Where the container closure is not a medical device, normally the materials should be compendial, this is mentioned in the biological IMP guideline. It isn't clear if compatibility data should be presented here in S.6, or in S.7 (stability).	Partially accepted. Reworded. A CE mark is not required, but information should be provided, when relevant.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
1045-1046	17	**Comment**: Container closure is no classified as medical devices according to Medical Devices Directive (93/42/EEC). Hence, a CE mark is not required. **Proposed change** (if any): To remove the sentence: ~~"It should be indicated if the container closure *per se* has a CE marking for the intended use under the EU legislation on medical devices"~~	Partially accepted. Reworded. A CE mark is not required, but information should be provided, when relevant.
S.7 Stability			
1049	5	**Comment**: In many ATMPs the Drug Substance is not held (continuously manufactured into DP). **Proposed change (if any)**: Add note that depending on manufacturing process, S.7 section may not be required.	Rejected. Implicit and addressed in introductory text.
1050-1079	11	**Comment**: the sub-sections of S.7 are not identified by the sub-headings (this would be S.7.1); in particular it would be useful to clarify that S.7.2 is not applicable to clinical trials. A common issue is the applicant doesn't' clearly state what the shelf-life is; we suggest this should be stated at the start of S.7.1. Normally the stability specification is included in S.4.1, given the specification in use would be included in tabulated data in S.7.3, is this necessary? The wording doesn't appear to describe the test schedule, which is typically expected here as a simple table, e.g. tests methods in rows, test periods in columns. It could be useful to present an example. We note the text is substantially similar to EMA/CHMP/BWP/534898/2008, however that says "The methods used for analysing the stability-indicating properties of the active substance should be discussed, or cross-reference to S.4.3 made, to provide assurance that changes….", considering our earlier comment in S.4.3, we feel this should be aligned.	Partially accepted. Wording has been changed. The structure of this section is aligned with EMA/CHMP/BWP/53498/2008 rev. 1.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
1052	15	**Proposed change** (if any): A stability protocol covering the proposed storage period and storage conditions of the active substance should be provided, including specification with suitable limits, analytical methods and test intervals. Unless justified, the testing interval should follow ICH Q5C. The re-test period (as defined in ICH Q1A guideline) is, however, not applicable to ATMPs.	Accepted
1053-1054	3, 5	**Comment**: There may not be adequate material to test as per ICH. It is proposed that potential reduced testing frequency may be acceptable. **Proposed change** (if any): A stability protocol covering the proposed storage period and storage conditions of the active substance should be provided, including specification, analytical methods and test intervals. Unless justified, the testing interval should follow ICH Q5C. If limited material is available, reduced testing frequency may be acceptable. The re-test period (as defined in ICH Q1A guideline) is~~, however,~~ not applicable to ATMPs**.**	Rejected. This is already covered by the "unless justified" text.
1066	1	**Comment:** Please consider adding a sentence to address the fact that some DS cannot be stored, e.g., in case the DS is directly processed in DP or intermediate and section S.7 is not applicable.	Rejected. Implicit and addressed in introductory text.
1067-1071	3	**Comment**: Accelerated stability studies on live viruses and cells using the typical stress conditions will be of limited value.	Acknowledged. They are not stated as obligatory
1068-1070	10	As currently written, there is an implication that patient derived materials should be used to support later phase (confirmatory?) studies – is that intended? If so it would be preferable to specify that. Perhaps it would be helpful to add the concept that if significant changes are made to a manufacturing process, the comparability	Rejected. The wording is considered sufficiently clear.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		evaluation should also encompass stability and new stability studies using batches manufacture by the 'new' process should be initiated.	
1072-1077	5	**Comment**: "For GTIMP, vector integrity, biological activity (including transduction capacity) and strength are critical product attributes which should always be included in stability studies. It is appreciated, however, that during early development the potency assay may not be fully developed. Where feasible forced degradation studies may also provide important information on degradation products and identify stability indicating parameters to be tested." Is it acceptable to use healthy donor cells for stability studies for GTIMP, if genetic modification occurs ex vivo?	The question is acknowledged and contingent on a sufficient justification for representativeness of the healthy donor cells compared to cells from patients.
1073	15	**Comment**: Appearance is considered as CQA as well. **Proposed change** (if any): For GTIMP, vector integrity, biological activity (including transduction capacity), ~~and~~ strength and appearance are critical product attributes which should always be included in stability studies.	Accepted and included in text.
1075	5	**Comment**: Please explain why forced degradation is only relevant for GTIMP and is there an example? Is there a reference for how to do such a study – conditions etc?	The appropriate strategy to demonstrate stability is Applicant's responsibility.
1080-1094	1, 6	**Comment:** For batch analysis section S.4.4, it was mentioned that "In case of genetically modified cells, the batch data on the vector used to produce the active substance should be provided ". However, for stability data, no such requirement is mentioned. Can it be confirmed if it means that for genetically modified cells, the stability data of representative genome editing tools batches used to produce the active substance should be provided in the starting materials section S.2.3 and not in the stability section?	Accepted. This is addressed in S.2.3.
1080-1094	11	**Comment**: We note the text is substantially the same as EMA/CHMP/BWP/534898/2008.	Partially accepted. Wording has been modified

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		1086-1088 accepting the comment above, it would be helpful to emphasise that the test methods and acceptance criteria in these tables should be those that were in use at the time. Also, the wording could be altered to clarify that each batch should be presented in its own table such that changes over time can be seen. We have noted some don't appreciate this. 1089-1090 it could be helpful to stress that values should be presented to an appropriate number of decimal places or nearest integer, as appropriate to the method qualification (S.4.3). Also, some report values below the LoQ or even LoD; this could be mentioned. Is discussion expected in S.7.3? We expect trends etc to be discussed in S.7.1. 1091-1094 we don't consider this text necessary.	
1081	10	*Stability data should be presented for at least one batch representative of the manufacturing process of the clinical trial material.* If the manufacturing process is continuous with no defined active substance, stability can only be performed on the drug product **Suggest revision** as follows: Where an active substance can be defined with a defined storage period, stability data should be presented for at least one batch representative of the manufacturing process of the clinical trial material.	Rejected. Implicit and addressed in introductory text.
1081-1082	15	**Comment**: For exploratory trials it might be acceptable to provide the stability programme only and to perform concomitant stability studies. **Proposed change** (if any): suggest to rephrase	Rejected. The complete absence of stability studies would not be acceptable without additional oversight measures and only in very exceptional circumstances.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
1095-1108	11	**Comment**: we would expect this text to relate to S.7.1, so positioning it at the end, and not identifying S.7 sub-sections may lead to confusion (accepting the approach is the same in EMA/CHMP/BWP/534898/2008, but those developers are usually more experienced). 1103-1105: EMA/CHMP/BWP/534898/2008, states "The maximum shelf-life after the extension should not be more than double, or more than twelve months longer than the period covered by real time stability data obtained with representative batch(es)." In this draft, additional words have been added, "whichever is the longest", we assume this was supposed to be "whichever is the shortest". However, we see no need for those extra words. It isn't clear why "However, extension of the shelf life beyond the intended duration of the long-term stability studies is not acceptable." (EMA/CHMP/BWP/534898/2008) is not repeated here also.	The structure of this section is aligned with EMA/CHMP/BWP/53498/2008 rev. 1. Comment partially accepted; wording has been modified.
1100-1102	10	*Extension of the shelf-life beyond the period covered by real-time stability data may be acceptable, if supported by relevant data, including accelerated stability studies and/or relevant stability data generated with representative material.* It is not really clear whether accelerated studies would be particularly relevant to many types of ATMPs. For example, most cell therapy products (if frozen) are cryogenically stored (<-150^{o}C), what would be the accelerated temperature in this case and what would be the duration of the accelerated study and how do you interpret the findings to justify the shelf life? If they are stored at RT, their shelf would be very short (a matter of days) so again is an accelerated study particularly useful in this setting beyond real-time data? ICH guidance does not seem to be readily applicable to ATMPs in general given these extremes. ICH Q1A does not require any accelerated stability data for products that are stored in freezer, rather short-term temperature excursions at an elevated temperature are suggested. Perhaps consideration should be given to aligning the stability expectations with that	Rejected. The text implies that data from RELEVANT accelerated studies may be used. Therefore, it is implicit that this would not be a general requirement.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		guidance rather than implying accelerated studies per se could be useful.	
1100-1102	15	**Comment**: For exploratory trials the extension of the shelf-life is considered acceptable without accelerated stability data as long as the time frame is covered by the stability programme. **Proposed change** (if any): suggest to rephrase	Correct. The text does not suggest mandatory accelerated stability data.
1103-1105	1	**Comment:** Recommendation for cell-based products is needed here since accelerated stability studies are not possible with cell-based products and extrapolating from such studies may not be safe. More data should be obtained for cell-based products to assess stability via tests rather than extrapolation.	Correct. The text does not suggest mandatory accelerated stability data.
1103-1105	1, 6	**Comment**: The wording of the following sentence "*The maximum shelf-life after the extension should not be more than double, or twelve months longer, whichever is the longest, than the period covered by real time stability data obtained with representative batch(es)*." is contrary to our interpretation of EMA guidance on shelf-life extensions provided in Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials. The text "whichever is the longest" should be removed: as currently written, it would enable, for example, shelf life extensions of 12m on 1m real-time data, or a 24m extension on 24m real-time data. **Proposed change**: "*The maximum shelf-life after the extension should not be more than double, or twelve months longer**~~, whichever is the longest,~~** than the period covered by real time …".*	Accepted. The wording has been modified**.**

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
P. Investigational medicinal product ***P.1. Description and composition***			
1114-1123	11	**Comment**: Reference to P.7 "A complete description should be provided in section P.7" is lacking	Accepted. Reference has been added.
1116-1119	1	**Comment:** *"List of all components (active substances, excipients and any other structural components) of the product":* It would be useful to have examples of components and structural components for gene/cell-based gene versus cell therapies. In addition, should the need for an overfill, with a justification not be added here?	Rejected. No additional text deemed necessary.
P.2 Pharmaceutical development			
1125-1158	11	**Comment**: Fully align this section with EMA/CHMP/BWP/53498/2008 rev. 1: P.2. It is also advised to subdivide this section into P2.1-P2.6 and provide additional guidance for these sub-sections. (see guideline EMA/CHMP/QWP/545525 /2017). This is also in alignment with the ICH M4-CTD format.	Subsection headings are aligned with EMA/CHMP/BWP/53498/2008 rev. 1.
1127-1128	11	**Comment**: "The usage of cryopreservation agent and its concentration should be justified". This is a confusing comment. The usage and amount used of any excipient or mixture of excipients as well as the storage condition (fresh, frozen, lyophilised) needs to be justified, not only the cryoprotectant. If the specific concern was DMSO, this could be included as a separate comment.	Accepted. Wording has been modified.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Proposed change: "The usage of any excipient or combination of excipients and storage condition needs to be justified and references should be made to the appropriate CTA sections (e.g., P.4, pre-clinical, pharmacy manual, IB)." Otherwise, delete this sentence.	
1132	17	**Comment**: Add reference to the Pharmacy Manual document **Proposed change (if any):** … (reference may be made to a full description in the clinical protocol or in a separate document **such as the Pharmacy Manual**)	Accepted. Pharmacy Manual has been included as example.
1132-1135	17	**Comment**: Add reference to guideline(s) regarding recommendations and minimum expectations on "appropriate studies"	Rejected. Generalization not appropriate.
1049-1158	15	**Comment**: see comment on lines 720-759 **Proposed change** (if any): re-working needed	Accepted. Wording modified

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
P.3 Manufacture			
1167	3, 5	**Comment**: It is suggested to clarify that batch formula may not be applicable/be the same as the final product for some products. **Proposed change** (if any): The batch composition / formula for the batch(es) to be used for the clinical trial should be presented. This should include a list of all components to be used. The batch sizes or range of batch sizes should be given. For certain products such as autologous cell therapies, the batch composition may be the same as the final drug product composition.	Rejected. Additional wording not considered needed
1169-1173	11	**Comments**: - Reference to process monitoring tests are lacking (e.g. in-process tests without acceptance criteria). - More guidance regarding the flow chart is appreciated (input materials; process parameters; process steps; IPCs) - Relevant guidance is lacking here (e.g., reprocessing should go in P.3.3, not P.3.4; see also EMA/CHMP/BWP/53498/2008 rev. 1. - Fully align this section with EMA/CHMP/BWP/53498/2008 rev. 1: P.3.3.	Accepted. Wording has been modified
1175-1186	11	**Comment**: Reprocessing should go in P.3.3 (see also EMA/CHMP/BWP/53498/2008 rev. 1: P.3.3 and ICH M4Q(R1). There We question whether it is necessary to say anything different to S.2.4, that could be referenced and any specifics to a DP retained.	Accepted. Wording has been modified

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
1179-1180	11	**Comment**: "Considerations on the manufacturing process should also take into account the product-associated risk profile." It is not clear what is meant here. This statement does not only apply to cell differentiation, but to any manipulation step of the cells/tissue(s), with/without scaffold/device, etc..	Rejected. Relates to the risk-based approach for ATMPs.
1183-1184	5	**Comment**: The volume of a DP batch can be fairly small (< 100mL). If sterilisation by filtration is required, the volume available for bioburden testing cannot be 100mL as per pharmacopoeia requirements. In addition, as this step is critical for sterility of material, suggest adding a reference to the limit. **Proposed change (if any)**: "For sterilisation by filtration the maximum acceptable bioburden prior to the filtration must be provided in the application. **In most situations NMT 10 CFU/100mL will be acceptable. Test volumes of less than 100 mL may be used if justified."**	Accepted
1183-1184	15	**Comment**: The proposed bioburden limit can only be assessed in context of the filter characteristics (retention capacity) and maximum filtration volume. In addition, there is information required demonstrating integrity testing of the sterilizing-grade filters pre- and post-use (see also EudraLex Vol. 4 Annex 1). **Proposed change** (if any): For sterilisation by filtration the maximum acceptable bioburden prior to the filtration must be provided in the application and justified in context of the filter retention capacity and maximum filtration volume Information is furthermore required how integrity of the sterilizing-grade filters is ensured prior and post filter use.	Accepted
1188-1191	10	*Process characterisation / evaluation data should be collected throughout the development preparing for Marketing Authorisation Application. At that stage (which is inferred to mean MAA as mentioned in the preceding sentence) the entire manufacturing process, storage etc. should be validated. Refer to S.2.5 for further*	Accepted. Wording modified

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		details on the extent of evaluation / validation data required throughout development. This paragraph infers process validation is required prior to MAA which is quite different to what is specified in S.2.5 for confirmatory studies (and is also reference in the section) as such there is conflicting information given in this paragraph. The validation requirements should be aligned between S.2.5 and P.3.5, and our recommendation would be that process validation is a MAA requirement not a requirement to support a confirmatory clinical study (see comments above with respect to S.2.5.).	
1188-1207	11	**Comment**: - EMA/CHMP/BWP/534898/2008 rev. 1: "The state of validation of aseptic processing and lyophilisation should be briefly described, if applicable. Taking into account EudraLex Vol. 4, Part IV, the validation of sterilising processes should be of the same standard as for product authorised for marketing. The dossier should particularly include information directly relating to the product safety, i.e. on bioburden and media fill runs. - ICH M4, Q: "Description, documentation, and results of the validation and, in early clinical development, evaluation studies should be provided for critical steps or critical assays used in the manufacturing process (e.g., validation of the sterilisation process or aseptic processing). Viral safety evaluation should be provided in 3.2.A.2, if necessary. Reference ICH Guideline: Q6B. " - ICH M4Q Q&A says information on compatibility of reconstitution diluents or dosage devices should be provided in P.2.6, and the data from those stability studies (after dilution) in P.8.3. We recommend including this and clarifying what additional qualification or validation data would be here.	Accepted. Wording modified

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
1192-1195	5	**Comment**: It is suggested that this text may be misleading. Characterisation of Cell harvest, cell manipulation etc. is part of drug substance manufacture, and so information on this is addressed in S.2.6. **Proposed change (if any)**: ~~The manufacturing process for CBIMP includes cell harvesting, cell manipulation, combination with other components of the product, filling and packaging. Characterisation/evaluation of the production process of a combined product should encompass all steps from separate components up to the final combination to ensure consistent production.~~	Accepted. Wording modified
1196	5	**Comment**: Suggest making a reference to the Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products. **Proposed change (if any)**: "**Taking into account EudraLex, Vol. 4, Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products,** aseptic processes (and, where applicable, sterilising processes) should be validated."	Accepted. Wording modified
1197-1207	3	**Comment**: Reconstitution and compatibility is usually addressed in P.2.6, not P.3.5 as it is unrelated to process validation. **Proposed change** (if any): It is proposed that the information in Lines 1197-1206 is relocated above Line 1129 with the other info on reconstitution under P.2. Line 1207 should be deleted as reconstitution is not a process validation activity under GMP. Reconstitution of product: Reconstitution activities can be performed… **…**substantial manipulation can, however, be considered reconstitution (e.g. cultivation).	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		The reconstitution process has to be qualified and needs to be described. The description of the reconstitution process should include all components that come into contact with the cells as part of the clinical application (e.g. membranes for local containment, fibrin glues). ~~For confirmatory clinical trials the defined reconstitution process is expected to be validated.~~ **~~For products requiring additional preparation of the medicinal product (e.g. reconstitution),~~ The compatibility with the used materials (e.g. solvents, diluents, matrix) should be demonstrated and the method of preparation including the equipment used should be summarised (reference may be made to a full description in the clinical protocol or in a separate document). Through appropriate studies it should be demonstrated that the specified reconstitution process is sufficiently robust and consistent to ensure that the product fulfils the specifications and can be administrated without negative impact on quality/safety/clinical properties of the ATMP.**	
1198-1201	17	**Comment**: We suggest to add reference to the guideline on good manufacturing practice for investigational medicinal products for human use Annex 13, pursuant to the Article 9(2) of the Directive 2005/28/EC) where - clarification on the meaning of "reconstitution" is given (which includes dilution) - and confirmation that reconstitution step are not part of the manufacturing process and therefore not subject to Manufacturer's Authorisation for Investigational Medicinal Products. **Proposed change (if any):** Proposal is to add the following sentence: **"In addition reconstitution activities (including dilution) are not subject to the authorization referred to in Article 13(1) Directive 2001/20/EC, cf. Article 9 (1)**	Rejected. The text already clearly states that reconstitution is not considered as manufacturing step. However, related information is essential for the assessment of safety for the patient and thus trial approval.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Directive 2005/28/EC. as per the guideline on good manufacturing practice for investigational medicinal products for human use Annex 13, pursuant to the Article 9(2) of the Directive 2005/28/EC)"	
1204-1207	17	**Comment:** As reconstitution process is not part of the manufacturing process and to avoid redundant information in different section of the CTA, we recommend that all information related to this step has to be part of the P.2 Manufacturing development process section where summary of the reconstitution protocol together with "appropriate studies" are requested (see lines 1129-1141). In addition we would like to highlight that the term "qualified" and "validated" related to this step are not appropriate as reconstitution process is not part of the manufacturing process. Proposed change (if any): To delete lines 1204-1207: ~~**"The reconstitution process has to be qualified and needs to be described. The description of the reconstitution process should include all components that come into contact with the cells as part of the clinical application (e.g. membranes for local containment, fibrin glues). For confirmatory clinical trials the defined reconstitution process is expected to be validated."**~~	Accepted. Wording modified
1205	5	**Comment**: The sentence refers to cells only whereas the section on reconstitution is not explicitly dedicated to CBIMP. Reconstitution can be necessary also for cell-free GTMP (e.g. lyophilized nucleic acid-based products). Will a description of the lyophilisation process in the IMPD also be required in this case? **Proposed change (if any)**: Clarify which part of the section applies to which type of ATMP.	Accepted. Wording modified

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
1206-1207	1	**Comment:** It may be challenging to have the reconstitution process validated at the time of confirmatory trials, so it is proposed that qualification of the reconstitution process is also acceptable for confirmatory trials.	Accepted. Wording modified
1207	10	*For confirmatory clinical trials the defined reconstitution process is expected to be validated.* Again, this is not consistent with lines 1188 – 1191 which suggests process validation is required for MAA, yet here you state reconstitution should be validated prior to confirmatory clinical studies. The process for reconstitution should be fully defined for confirmatory studies including acceptable equipment to be used and be available at the site; the CTA submission should include supportive data to demonstrate the reconstitution process does not negatively influence product, but we would consider formal validation of that process is data that should be presented in the MAA as it would make sense to perform that study during confirmatory studies where the company has easier access to a number of sites that could participate in the validation activity (as reproducibility between different sites should form part of that validation exercise). Cross reference to Part IV of Eudralex Vol 4 as to what is defined as reconstitution activities would be helpful here. **Suggest revising** as follows: For confirmatory studies the reconstitution process should be fully defined, including equipment to be used and requirements at the site of administration. Data should be presented to demonstrate, when performed according to those procedures, the quality of the product remains unaffected until the point of administration.	Accepted. Wording modified

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		The defined reconstitution process should be formally validated prior MAA including the demonstration of the reproducibility of that process between different sites.	
P.4. Control of excipients			
1209-1231	11	**Comment**: Align with S.2.3 and other applicable guidance's	Accepted
1211	17	**Comment**: Information on the vendor is typically not provided in clinical trial applications. **Proposed change** (if any): "Information on the ~~**vendor and**~~ source should also be provided"	Accepted
1228-1229	1	**Comment:** "*Complexing materials for formulating the GTIMP drug product are considered as excipients and have to be qualified for their intended purpose*" Please describe and provide examples of "complexing materials" and whether these are intended to be as subset of "non-viral vectors".	Rejected. This is beyond guidance scope
1220	1	**Comment:** Please provide additional guidance on what is acceptable regarding the qualification of excipients with respect to their combination with cells.	Rejected. Needs to be addressed in a product-specific manner
1242	11	**Comment**: It is suggested to state here "not applicable' in case of excipients as this guideline concerns (early) clinical development (see also EMA/CHMP/BWP/534898/2008 rev. 1). In case of complex matrices and scaffold, it is suggested to also refer to ICH Q2A/Q2B,	Rejected. The header is "validation" as per structure, see text in S.4.3

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		and Q6B.	
1251-1254	15	**Comment**: Add additional reference for human prion diseases. Quoting only animal TSE safety (as in section above) has been misinterpreted as an recommendation to switch toward human excipients without consideration human TSE. **Proposed change** (if any): If human albumin or any other plasma derived medicinal product is used as an excipient, information regarding adventitious agents safety evaluation should follow the relevant chapters of the *Guideline on Plasma-Derived Medicinal Products* (EMA/CHMP/BWP/706271/2010) and CHMP Position Statement on Creutzfeldt-Jakob disease and plasma-derived and urine-derived medicinal products (EMEA/CHMP/BWP/303353/2010).	Accepted
1256-1259	1	**Comment:** If the excipient has a marketing authorization, but for a different route of administration or a different indication, can a reference to the marketing authorization replace the quality data requested in these lines?	The question is acknowledged. And no, this information would be insufficient
P.5 Control of the investigational medicinal product			
1262	1	**Comment:** Alternative wording is proposed to add clarity **Proposed change:** **"***Quality control tests should be performed at the drug product level,* ***~~unless~~ but, where*** *appropriate justification can be provided,* ***~~based on~~*** *release testing* ***may be conducted*** *at the drug substance level* ***or in-process control on intermediate step but as close as possible to the drug product level"***	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
1270	1	**Comment:** Bioburden may be utilised in place of sterility and a sterility test may not be included in drug substance or drug product specification. It is suggested to amend the wording to allow for different approaches to ensuring sterility.	Rejected, results of sterility/microbial assays are mandatory for product release
1279-1281	1, 6	**Comment**: Impurities which are included in the DS specification still need to be included in the DP specification if there is a possibility they would increase in concentration upon storage. **Proposed change**: "*For the impurities not covered by the active substance specification* ***or which may increase upon storage****, upper limits should be set, …*"	Accepted
1287-1289	11	It is suggested to add here: "and based on extensive process and product characterisation data, collected throughout process and product development".	Accepted
1290-1293	11	Recommend adding reference to GMP for ATMPs guidance.	Rejected. Text reworded by adding more details
1291	1, 6	**Comment:** Grammatical error **Proposed change**: "*It may be needed to release the drug product batch prior to all results of specification testing* ~~***is***~~ ***being*** *available.*"	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
1290-1291	1, 6	**Comment**: It would be helpful to provide additional guidance on the minimal set of release testing required for DP batch release for circumstances in which batches are released prior to all testing being completed.	Rejected. Not accessible to general guidance
1290-1292	15	**Comment**: Statement (of EMA/CAT/GTWP/671639/2008) required that missing information at IMP release has to be compensated by in-process testing **Proposed change** (if any): In some specific cases (for example due to the short shelf-life), it may be needed to release the drug product batch prior to all results of specification testing is available. This approach needs to be justified and missing information at release level is to be compensated by appropriate in process testing and supported by ~~performed~~ risk analysis.	Rejected. Not all parameters are accessible to in process testing
1301	11	**Comment**: This section needs extension: - For products with a longer production history and/or where data of a considerable number of autologous batches is provided, it could be acceptable to provide results for only a number of representative batches, if appropriately justified. - In-vivo GT and allogeneic off-the shelf products: A statement should be included whether the batch analyses data presented are from the batches that will be used in the clinical trial, or whether additional batches not yet manufactured at time of submission of the IMPD might be used.	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
1301	17	**Comment**: Typically batch data presented in P.5.4 are limited to released clinical trial batches, if available. Non-clinical/toxicological batch data are often provided in P.2 **Proposed change** (if any): To confirm the scope of lots presented in P.5.4 and possible flexibility to provide clinical batch results at a later stage (but before human studies are initiated)	Acknowledged. Cross reference is acceptable, as long as the information is provided.
1302-1308	3	**Comment**: Is this testing required if residual testing is completed on the drug substance and no additional manufacturing reagents are used in the process during preparation of the drug product?	Acknowledged. Testing may be justified based on the risk based approach
1306-1308	12	**Comment**: Clarification is requested on whether residual impurities testing is required on drug product if the testing was completed on the drug substance and no additional reagents are used during drug product formulation.	Acknowledged. Testing may be justified based on the risk based approach
1306-1308	15	**Proposed change** (if any): The final product should be tested for residual manufacturing reagents with known or potential toxicities and the test procedure described. ~~Limits need to be included in the specifications, unless otherwise~~	Accepted, the wording was modified.
1310-1313	11	**Comment**: JOS: FIH trials: discussion on representation of batch data of non-clinical batches for autologous product release needs to be discussed.	Accepted. Wording modified

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
1311	17	**Comment**: to provide "MoA" definition	Accepted. Included in the glossary.
P.6 Reference standards or materials			
1314 (see also 1026)	3	**Comment**: How do reference standards and materials differ?	Text clarifi
P.7 Container closure system			
1318	17	**Comment**: to precise location of compatibility data typically provided in P.2 section **Proposed change** (if any): "The intended primary packaging to be used for the IMP in the clinical trial should be described and compatibility with the product should be justified **in P.2 section**."	Accepted
1318-1326	11	**Comment**: Align with EMA/CHMP/BWP/534898/2008 rev. 1: "The intended primary packaging to be used for the IMP in the clinical trial should be described. Where appropriate, reference should be made to the relevant pharmacopoeial monograph(s). If the product is packed in a non-standard administration device, or if non-compendial materials are used, description and specifications should be provided. If a medical device is to be used for administration, it should be stated whether the device is CE marked for its intended purpose. In the absence of a CE mark for the intended purpose, a statement of compliance with the relevant essential requirements for medical devices with regards to safety and performance related device features is required. An integral device component of a drug-device combination product, as defined in the Medical Device regulation, is exempt from CE-marking. For products intended for parenteral use	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		where there is potential for interaction between product and container closure system, more details may be needed (e.g. extractable/leachable for phase III studies).	
1321-1324	10	Would be helpful to include reference to EMA Guideline on the quality requirements for drug-device combinations, EMA/CHMP/QWP/BWP/259165/2019. The consequences of Article 117 in the Regulation (EU) 2017/745 on medical devices regarding integral device components of medicinal products. **Proposed change:** For any device used in / as the container closure system, evidence of CE mark for the intended use should be provided. If the product is packed in a non-certified administration device, a description and specifications should be provided. *In accordance with Article 117 of the MDR, an MAA for an integral Drug-Device Combinations (DCCP shall include evidence of the conformity of the device part with the relevant General Safety and Performance Requirements (GSPRs). For more information, see EMA Guideline on the quality requirements for drug-device combinations, EMA/CHMP/QWP/BWP/259165/2019.*	Partially accepted. Article 117 does not apply to combined ATMPs
1322	5	**Comment**: Please confirm that a CE mark is required for all devices even for exploratory studies. It is possible that the devices themselves will be an integral part of the clinical trial.	Rejected. A CE mark is not mandatory, but if not present introduces the need for a parallel Clinical investigation according to MDR

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
P.8 Stability			
1327- 1328	1	**Comment**: Full reference is made to the drug substance section S.7. Stability but the shelf life extension plan should be unique to the drug product and different to the drug substance in some circumstances, potentially changing the stability profile. A more aggressive shelf life extension approach should be considered, if justified compared to the standard extension of not more than double, or twelve months longer, whichever is the longest, than the period covered by real time stability data obtained with representative batch(es). **Proposed change**: "*The same requirements as for the active substance* ***except if justified*** *are applied to the medicinal product, including the stability protocol, stability results, shelf-life determination, including extension of shelf-life beyond the period covered by real-time stability data and stability commitment*".	Rejected. The document is a guideline and justified deviations are possible
1328	15	**Comment**: "medicinal product" probably should read IMP **Proposed change** (if any): Please clarify	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
1328-1346	11	**Comment**: It is suggested to align with S7 and ICH M4Q: • Stability summary and conclusions • Stability data and results • Shelf-life determination ICH M4Q: 3.2.P.8 Stability (name, dosage form) 3.2.P.8.1 Stability Summary and Conclusion (name, dosage form) The types of studies conducted, protocols used, and the results of the studies should be summarized. The summary should include, for example, conclusions with respect to storage conditions and shelf-life, and, if applicable, in-use storage conditions and shelf-life. Reference ICH Guidelines: Q1A, Q1B, Q3B, and Q5C, Q6A 3.2.P.8.3 Stability Data (name, dosage form) Results of the stability studies should be presented in an appropriate format (e.g. tabular, graphical, narrative). Information on the analytical procedures used to generate the data and qualification/validation of these procedures should be included. Information on characterisation of impurities is located in 3.2.P.5.5. Reference ICH Guidelines: Q1A, Q1B, Q2A, Q2B and Q5C.	Rejected. The IMPD structure does not cover all subsections of ICH M4Q.
1330-1332	15	**Comment**: Stability data may be generated in parallel to the ongoing trial **Proposed change** (if any): The storage conditions including temperature range should be defined and stability studies should be set up to ~~provide~~ generate, at least in parallel to the trial, sufficient assurance that the IMP will be stable during the intended storage period.	Partially accepted. Wording has been modified

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
1334-1335	17	**Comment**: Clarifications are needed on experimental data expected by competent authorities to support the transportation conditions, and whether studies are required to all forms of product presentations (e.g., frozen or freeze-dried vs liquid). To clearly identify expectations related to early versus late phases of development. Typically formal transportation validation studies are initiated by Phase 3 and completed prior to submission of a MAA.	Acknowledged, but not general answer can be provided. Sufficient assurance needs to be provided that the transport has no negative impact on the product.
1334-1335	17	**Comment**: To clarify if considerations of the impact of the transport conditions on the stability of DS or DP are limited to materials with a short term shelf life as specified in the Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products EMA/CAT/80183/2014 - 4.6 Stability for drug substance and drug product	Acknowledged. No, this is a general point
1335-1336	17	**Comment**: Detailed recommendation such as information on transport condition, thawing … would not be applicable to all ATMP products. For example, stability profile of AAV based gene therapy is more in line with biologics than ex-vivo gene therapy. Likewise, frozen products are not subject to the same transportation stresses than liquid products, and most ATMPs are planned to be frozen due to stability limitations. This has to be highlighted so that level of information provided in the dossier should be adapted depending on the type of ATMPs and product characteristics. If applicable, product-specific methods for thawing should be part of the reconstitution protocol (part of the clinical protocol or in a separate document such as the Pharmacy Manual).	Acknowledged, this is covered in other sections and generally, the development of ATMPs is to follow a risk based approach.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Freezing and thawing rates are of more relevance on Cell Therapy MPs than Gene Therapy MPs. There should be clarity in the type of studies that are expected to justify the methods for freezing and thawing for both types of ATMPs In addition, the thawing freezing studies are typically part of the manufacturing development in P.2.6	
1337-1338	10	The concept of in-use stability is applicable to products that are simply thawed prior to administration with no further reconstitution, dilution or mixing. **Suggest the sentence is revised** as follows: For preparations intended for use after thawing, reconstitution, dilution or mixing …..	Accepted
A.1 Facilities and equipment			
1347-1348	5	**Comment** Please provide explanation of why A.1 Facilities and equipment is considered "not applicable" for ATIMPs and whether this information is expected to be incorporated in another section.	Rejected. In the EU facility aspects are addressed by GMP inspections
1348	3	**Comment:** Guidance on the content of this section would be appreciated.	Rejected. This section is not relevant in the EU as facility aspects are addressed by GMP inspections
1348	12	**Comment**: In light of differences seen with the US FDA requirements for content of this section for ATMP submissions, it would be helpful if some additional guidance on content were provided.	Rejected. This section is not relevant in the EU as facility aspects are addressed by GMP inspections

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
A.2. Adventitious agents safety evaluation			
1350-1383	11	**Comment**: - It is suggested to add here: **Non-viral adventitious agents:** Information should be provided on the avoidance and control of non-viral adventitious agents (e.g., transmissible spongiform encephalopathy agents, bacteria, mycoplasma, fungi). This information can include, for example, certification and/or testing of raw materials and excipients, and control of the production process, as appropriate for the material, process and agent. Reference ICH Guidelines: Q5A, Q5D, and Q6B - It is also suggested to provide additional guidance on viral removal and inactivation steps, where applicable. See ICH M4(Q) and relevant guidances, such as ICH Q5A, Q5D, and Q6B.	Partially accepted. A section on Other adventitious agents was added
1350-1353	15	**Comment**: Experience from assessing clinical trial information showed that it was often necessary to ask for specific information. **Proposed change** (if any): All materials of human or animal origin including cell culture media and medium supplements used in the manufacturing process of both the active substance and the medicinal product, or such materials coming into contact with active substance or medicinal product during the manufacturing process, should be identified.	Accepted
1356-1357	15	**Comment** Clarification missing that there may be different microbiological quality requirements depending on the specific product and administration characteristics (e.g. absence of bacteria is not required for topical IMPs). Endotoxin testing is furthermore required for all parenteral IMPs and testing for mycoplasma at the level of finished	Accepted Wording has been modified.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		(formulated) IMP may not be in all cases the stage with highest chance for detection of these infectious agents but testing at the harvest of the last cultivation stage prior further processing (e.g. lysis, dilution, purification, etc.) **Proposed change** (if any): A thorough testing for the absence of bacteria, fungi, ~~and~~ mycoplasma and endotoxin shall be performed at the level of finished product, if required for the given product including administration characteristics. However, testing for mycoplasma should be ideally performed on the harvest of the last cultivation stage prior to further processing e.g. lysis, filtration, washing or purification as post-treatment testing significantly increases the risk to not detect potential contamination with mycoplasma.	
1357-1359	1	**Comment:** This sentence suggest that a short shelf life of the CBIMP would be the unique justification for testing the absence of bacteria by alternative method as in Ph.Eur 2.6.27 rather than under 2.6.1. Could this sentence to be reformulated? **Proposed change:** "*In cases where* ***~~the short shelf life of the CBIMP is prohibitive for~~*** *the testing of absence of bacteria under the Ph. Eur. Requirements in chapters 2.6.1.* ***cannot be carried out (e.g. in case of the too short shelf life of the CBIMP)****, alternative validated testing methods (as in Ph.Eur 2.6.27) are recommended".*	Partially accepted Wording has been modified
1360-1364	1, 5	**Comment:** This paragraph could be moved and combined to the similar text included in Viral safety section (line 1372)	Accepted. Inserted in Viral safety paragraph and rewording
1369-1371	15	**Comment**: Add reference to human prion diseases. Quoting only animal TSE safety has been misinterpreted as a recommendation to switch to human-derived raw materials without consideration of human TSEs.	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Proposed change (if any): The *Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products* (EMEA/410/01) in its current version and CHMP/CAT position statement on Creutzfeldt-Jakob disease and advanced therapy medicinal products (EMA/CHMP/BWP/353632/2010) are applicable.	
1381-1383	15	**Comment**: This paragraph gives too much emphasis on testing while neglecting other safety measures such as selection of safe raw materials or application of virus inactivation. Virus testing of cell-based medicinal products has been found difficult to implement in cases where cells cannot be stored frozen and might be requested in all cases. There are numerous cell-based medicinal products where end of production testing for viruses is not performed. The concept of testing of different stages of the production process depending on the phase of the clinical trial was not implemented in Guideline on viral safety evaluation of biotechnological investigational products (EMEA/CHMP/BWP/398498/2005). **Proposed change** (if any): The risk of contamination of the drug substance or drug product by extraneous viruses should be minimised by use of safe raw materials, and testing of donors. In addition, cell cultures are tested at appropriate stages such as seed and cell banks, intermediates and/or at the end of production, as applicable, with emphasis on cell bank testing. Methods for virus inactivation/removal are applied as appropriate and feasible. ~~. in preparation of early phase clinical trials.; Intermediates and end-product testing should also be established over time.~~	Rejected, it is part of the risk-based approach

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
A.3 Excipients			
1384-1386	1	**Comment:** Typo error? **Proposed change:** *"For novel excipients, information as indicated in section ~~S~~ **P** of the CTD should be provided in line with 1385 the respective clinical phase"*	Accepted
1384-1386	12	**Comment**: Additional guidance using reference to appropriate guidances is requested for contents of this section. Proposed change (if any):	Rejected, reference made to section P
A.4 Solvents for reconstitution and diluents			
1387	1	**Comment:** Should matrix added before administration (as mentioned on line 1201) also be in section A4? This would be contradictory if these are considered as "excipient" (cfr line 212)? Additional clarity would be welcome.	Rejected. The information needs to be provided and be accessible to the reviewer.

5. Non-clinical documentation

5.1 General aspects

1391-(Section 5: Non-clinical documentation)	1	**Comment:** In general, additional description on how to leverage modularity in context of 3R principles when dealing with therapeutics that leverage identical constructs (eg vectors, non-viral vectors) and/or minimal changes in components, targeting same organ etc. should be considered in this section.	Look at ICH S5 GL on how they mention it there – we accept in vitro data when scientifically justified, perhaps bring this forward (Claire)
1393-1397	1, 6	**Comment:** As each situation is different, it is suggested to include a sentence early on (i.e. in this paragraph) to state that the extent of the required non-clinical data should be determined on a case-by-case basis using a risk-based approach.	OK, see how to integrate in the text
1394-1396	17	**Comment**: The amount of non-clinical data required is not determined by the number of patients. **Proposed change** (if any): The sequential non-clinical development in which the amount of data required and the duration of dosing increase by the phase of clinical development and ~~by the number of patients~~ *by the extent of human exposure*, is not generally applicable for ATMPs.	Partially accepted If go to larger number of patients, increase risk to patients; delete
1398	5	**Comment**: It might be important to state in the general description of the non-clinical data package that proof of concept studies demonstrating the relevance of the strategy should be provided. Such proof of concept is important for the statements regarding efficacy studies described in line 1417 and 1426.	For ATMPs, mostly one dose,

1403-1415	1	**Comment:** In the introductory statements on non-clinical development, a risk-based approach is mentioned but development of ATMPs for rare diseases is not mentioned as a situation where increased flexibility might be considered. Please consider adding this concept, similar to the FDA guidance on early development of products for rare diseases, many of which are ATMPs.	Not accepted - RBA does already allows for data generation on basis of risk; minimum set of data = starting point; if very few pts, need even better justification of dose.
1404-1407	1	**Comment:** The extent of non-clinical data being determined on a case-by-case basis and utilising scientific knowledge and clinical experience with similar types of products is welcomed. It would be helpful to understand what would be considered "similar" product data e.g. literature data from use of the same vector or transgene, in house data using same platform.	See ICHS12 re: BD data See Risk Mitigation GL Not accepted - Difficult to define similar product; GL says 'similar type of products' – not sufficient experience yet to further define
1407	5	**Comment**: Add availability of primary cells **Proposed change (if any)**: It should be determined on a case-by- case basis depending on the type of cells, extent of their manipulation, vector type, transgene expression, genetic modification, availability of primary cells/tissues, availability of appropriate animal models, and the intended clinical 1409 use.	… in vitro or animal models
1407-1410	6	**Comment**: we suggest also to mention the targeted indication: where there is a highly unmet medical need for a devastating/life-threatening disease, more flexibility could be envisaged, like for ICH S9 for advanced cancers. **Proposed change (if any):** In line 1408, please add the italicized text – "…case basis depending***, but not limited to,*** on the type of cells…"	ok
1408	1	**Comment:** Following change is proposed: **Proposed change:** *"**It should be determined on a case-by-**case basis depending**, but not limited to**, on the type of cells…"*	ok

1410-1411	1	**Comment:** The targeted indication and the unmet medical need also affect the anticipated risks. **Proposed change:** *"The extent and duration of exposure* ***as well as the target indication*** *significantly affect the anticipated risks related to the clinical use of an ATIMP.* ***Where there is a high unmet medical need for a devastating/life-threatening disease, more flexibility could be envisaged, like for ICH S9 for non-clinical evaluation for anti-cancer pharmaceuticals".***	RBA – see above Indication doesn't affect size of NC data package RBA is more flexibility than ICH S9
1412-1414	1	**Comment:** "*adapted accordingly*" should be better defined in this sentence, especially limits to how long non-clinical evaluations are required.	No accepted, see to existing guidelines.
1415-1417	5	**Proposed change (if any)**: Suggestion to add the following: The nature and extent of non-clinical development will be dependent on the nature of the ATMP and the availability of relevant models, the clinical use, the targeted clinical population, the intended route of administration, and the treatment regimen. When a nonclinical study is considered appropriate, the route of administration and the application procedure should as closely as possible mimic those used in the clinic.	Already in this paragraph, unclear why to mention second time
1419-1920 and 1564-1566	1	**Comment:** *"…meaningful and predictive extrapolation…",* this could be too restrictive, depending on the interpretation of this line. Sometimes endpoints that are surrogates for human clinical efficacy need to be measured in animals. **Proposed change:** *"The chosen animal models should allow* ***~~meaningful and predictive extrapolation from these species to humans~~*** ***for measurement of endpoints that are feasible in the animal and may translate to an identical or surrogate endpoint in humans***"	Move this info 5.2 Need to emphasise that animal models not compulsory; change animla to non-clincial models
1419-1420	4	"The chosen animal models should allow meaningful and predictive extrapolation from these species to humans".	Agree

		Comment: Section 5.1. is a sub-section that covers the 'general aspects' of non-clinical documentation and is mainly focused on the type of information that non-clinical data should aim to provide. The term 'non-clinical' does not only refer to animal models but to other more human-relevant non-animal methods well. It is therefore not appropriate to mention animal models in this general sub-section especially since it is followed by a dedicated sub-section (5.2.) on 'animal models' anyway. Proposed change: Delete this sentence from the following paragraph (lines 1416-1424: "The administration route and the application procedure should as closely as possible mimic those used in the clinic. The dose levels tested in the non-clinical studies should provide information on the minimal effective and the optimal dose levels to achieve the appropriate therapeutic effects in patients. ~~The chosen animal models should allow meaningful and predictive extrapolation from these species to humans.~~ Products used in non-clinical studies should be sufficiently characterised to provide reassurance that the non-clinical studies have been conducted with material that is representative of the product to be administered to humans in clinical studies. Differences between the non-clinical test article and the clinical material resulting from product development should be highlighted and its potential impact on efficacy and safety of the product should be discussed".	
1420	1, 5, 6	**Comment:** Please define what would be considered "sufficient"	is described in the rest of the sentence; also Q&A comparabilty
1422-1424	1	**Comment:** The guidance indicates differences in non-clinical and clinical test articles should be highlighted and the impact on efficacy and safety discussed. Clinical trial sponsors may use a simplified IMPD approach, cross-referencing to non-clinical and clinical data in the investigator brochure. It would be helpful to understand where the non-clinical data should be located and discussed (IB versus IMPD) and whether this precludes the use of a simplified IMPD.	This is not specific for ATMP

1426	1, 6	**Comment**: Suggest adding the term persistence.	Not accepted Biodistribution already includes persistence as a parameter to describe BD (ICH S12) Persistence if parameter describing kinetic process (like half life) – need both
1428	2	**Comment**: The following statement seems non-specific and it's not clear how a medicine developer can use this to improve or enhance non-clinical study designs for ATMPs. Is there any advice on control groups that can be included in the Guideline? The selection of suitable control groups should be carefully considered. **Proposed change** (if any): Give specific advice. Also consider what should happen if there isn't a suitable control group or comparator?	Non accepted Cannot give more info on his: if suitable model, also suitable control group
1430	1, 5, 6, 8	**Comment**: Does this imply that sponsors could consider a reduced burden of *de novo* non-clinical studies, and the ability to leverage data from previous homologous products? Please note that "adapted" could mean a non-clinical package of reduced *de novo* preclinical studies, including in vitro alone.	This is the principle of the RBA
5.2 Animal models			
1433	4	**Comment**: As suggested in our general comments above, a new section should be added before section 5.2. on 'animal models' to provide guidance on the use of other non-clinical models in the documentation package for ATMPs. This section should provide guidance on the conduct of a weight-of-evidence (WoE) approach supporting the safe clinical use of ATMPs before animal models are even mentioned in the guideline. Indeed, it has been suggested in the literature that "*if a hazard had already been identified (e.g. based on theoretical considerations, in silico or in vitro testing, or findings observed in*	Order of paragraphs changed- reference to 3R See ICH S5 In vivo models in exceptional circumstances Difficult to put in guidance on in vitro models, as product specific Claire to look for wording

		the proof-of-concept studies) and it could be scientifically and ethically determined that animal testing would not further substantiate the risk, animal testing was deemed unnecessary. It was then recommended to take appropriate measures clinically in order to mitigate the risk" (Vestegaard, 2013). The WoE approach should include in vitro and ex vivo cell and tissue-based models, in silico analyses, literature-based evidence and clinical experience with related products. The use and development of 2D and 3D tissue-models, organoids and microfluidics should be encouraged, especially for evaluating the mode of action (all of these things are briefly mentioned in Section 5.2 on animal models (lines 1469-1478) but should be emphasised and expanded upon in this dedicated sub-section). For example, for tumorigenicity testing, a combination of in vitro tests have been proposed by companies developing ATMPs, which include "*evaluation of characteristics (e.g., growth rate and anchorage-independent growth), cytogenetics (e.g., karyotyping), cell differentiation, functionality of cell-cycle-regulation genes (e.g., expression and functionality of oncogenes and tumor suppressor genes), telomerase activity, and senescence (e.g., transduction leading to immortalization or transformation)*" (Vestegaard, 2013). According to another publication, the use of human cell systems, particularly those deriving from patients, are particularly relevant for the testing of gene therapy medicinal products (GTMP) because they include the human components of the disease and better address the intended mode of action. "*Multiple human cell types (e.g. iPSCs) are increasingly available, making it possible to perform GTMP testing in vitro, to study the ability of the GTMP to penetrate the cell, and to express the gene products, which can be analysed and characterised. The advances in iPSC technology are making possible the use of patient-derived multiple cell types, which can be used for pharmacology and for safety assessment studies*" (Lima & Videria, 2018).	
1434-1437	4	"The utility of animal models for non-clinical proof of concept studies and safety testing should be carefully considered, and the	In guidance on 3R, clear

		relevance of selected models justified. The chosen animal model should reproduce the disease or condition of the patients as close as possible with ideally similar pathophysiology in patients". **Comment**: As mentioned in our general comments above, the 3Rs principles and the obligations of Directive 2010/63/EU should be clearly described in the guideline. **Proposed change:** **In accordance with the provisions of the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes and Directive 2010/63/EU on the protection of animals used for scientific purposes), the 3R principles (replacement, reduction and refinement) should be applied.** The utility of animal models for non-clinical proof of concept studies and safety testing should be ~~carefully~~ considered **only as a last resort** and ~~the relevance of selected models justified.~~ **a clear rationale should be provided on the relevance of the selected models and how the data generated from these models would add meaningful value to the risk assessment. It should be acknowledged that appropriate animal models are not always available and that the use of irrelevant models could be as deleterious as their non-use**. The chosen animal model should reproduce the disease or condition of the patients as close as possible with ideally similar pathophysiology in patients.	There should be not the risk of losing information that will add to the safety of the patients; not qualify as 'last resort' Add: GL on 3R and reflection paper on current testing methods under 3R
1437-1442 1444-1447 1448-1449 1462-1463	4	"Appropriate animal models may include naturally occurring spontaneous or experimentally induced disease models, transgenic knock-out or knock-in disease models, as well as specifically humanised animal models. Healthy animals are normally used for standard toxicity studies. However, for ATMPs, standard toxicity studies are not always appropriate to address safety as a whole in the context of its therapeutic use. Instead, disease models can provide clinically meaningful safety data". "If extrapolation from small animal models to human becomes challenging due to e.g. a short or reduced lifespan of the animal model or differences in the body size and anatomy that may	Same as above

		preclude certain administration procedures and devices in small animal models, large animal models may be needed". "The use of homologous animal models is encouraged, wherever such models are expected to provide more reliable data than a non-homologous model". "In case a single animal model might not suffice to address all relevant aspects, alternative animal models should be employed". **Comment**: All of these are examples of various attempts to try and 'improve' on current animal models instead of acknowledging the real issue, which is that animal models are not relevant due to unavoidable species differences that no amount of modification can overcome. They are especially irrelevant in the context of ATMPs and other innovative medicinal therapies, which are becoming increasingly advanced, complex and human-specific. If anything, the continued reliance on animal models without justification will hinder the progress of these innovative techniques that have the potential to revolutionise human medicine and benefit real patients. None of this testing should be done unless there is clear evidence to show that data from large animals or from humanised animals, for example, is essential because its absence would create a deficiency that might pose risks to patients. We urge the EMA and other regulators who have developed strategies and roadmaps to move away from animal models and towards more predictive methods of drug testing, to be consistent with their goals and to prioritise the use of more sophisticated and human-relevant methods in their guidelines rather than encouraging various attempts to make animal models 'work'. This is the only way real progress will be made beyond the creation of theoretical roadmaps and strategies.	
1443-1449	1	**Comment:** The paragraph on reliability of animal models suggests that a single animal species could be sufficient if it is considered	In practice, this is the case. See other GL for GTMP or CBMP.

		representative of the condition. It would be helpful to clarify whether this is the way the wording should be interpreted.	This paragraphs expands on when more than 1 animal model is needed
1448-1449	1, 6	**Comment:** Please define what a "*homologous* animal model" would be. Is this intended to refer to a "homologous product" tested in an animal model? animal models should be Homologous the exception, not the rule. This may be true for efficacy, but it does not always translate to off-target, which can be precisely measured for genome editing products, and DNA repair machinery may differ across species.	For 'similar products' previously mentiond: according to Risk mitigation GL: Experience, both non-clinical and clinical, with molecules having a similar mode of action can also be useful. Not accepted – homologous models should be considered **if** this provides more relevant data. Not encouraged in all cases, but also not exceptional cases only
1448-1449	5	**Comment**: There is no clear definition of what an "homologous model" is. Examples are given in the next paragraph, although they do not constitute a clear definition of a homologous model. Proposed change (if any**): Withdraw the sentence in line 1448**	Not accepted, see above
1450-1458	10	The concepts described in the paragraph have implications on the use of NC studies to support comparability (see comment above regarding rows 753 – 755). If a company has to use homologous product / TG for a given animal model, and further, if the manufacturing process of that surrogate product is slightly different to that of the human equivalent, how can such a surrogate product be used to demonstrate process changes have no impact on product quality/safety and efficacy? The strategy of using NC data to support comparability evaluations when surrogate product has to be used seems questionable and should be specifically addressed in the quality and potentially NC sections of the document.	Use of homologous model is not mandatory (see above) This section is not on comparability; See Q&A comparability
1450-1458	1, 5, 6	**Comment:** This discussion about use of homologous animal cells is concerning, particularly around the word "encouraged". Does this	'should be considered' instead of encouraged

		mean that whenever cells are quickly cleared sponsors need to create an animal cell line to use? This would seem to be in contradiction to ICH S6R1 for biopharmaceuticals where it is stated that creation of homologous test articles is not mandated. The word "encouraged" also seems at odds with the language in lines 1466-1472, where it is stated that sponsors can decide to forego work in animals and evaluate in vitro, ex vivo or in silico models. We assume that sponsors can provide justification to proceed or not with this route of nonclinical study. **Proposed change (if any)**: Please indicate if sponsors are able to provide a justification on whether to perform studies with homologous products or not.	
1458	1	**Comment:** It would be helpful to precise and confirm that: as an option, in vivo studies to evaluate biological activity and safety with human CBIMP could be conducted in immuno-depressed animals (to prevent cell rejection due to healthy immune-competent animal immunogenic response), e.g. using imunosuppressive agents, genetically immunodeficient animals, humanized animals..., when justified and provided that biological activity has been evidenced in the model.	Immunodeficient animal models added
1459-1460	5	**Comment:** Please define what a "***homologous*** animal model" would be. Is this intended to refer to a "homologous product" tested in an animal model?	See above
1459-1465	1, 5, 6, 8	**Comment:** If the most relevant toxicology model is an NHP, is EMA expecting a through biodistribution study with multiple time points? **Proposed change (if any)**: Please clarify the requirements for biodistribution **studies in such large animals, in keeping with 3Rs.**	See ICH S12

1461	1, 5, 6	**Comment:** The use of the terms "pharmacokinetics" and "biodistribution" should not be interchangeable. **Proposed change:** "*The use of the same animal in both the toxicology investigations and the* ***~~pharmacokinetic~~*** ***biodistribution*** *studies may be beneficial, …"*	Not accepted - PK broader than DB
1466-1469	1, 8	**Comment:** A similar challenge applies to genome editing strategy for which the species-specific genome sequence prevents meaningful testing of editing specificity in non-human cells. **Proposed change:** "*For example, in the case where functional immune system of the host is needed (…) testing in animal models may not produce meaningful information.* ***A similar challenge applies to genome editing strategy for which the species-specific genome sequence prevents meaningful testing of editing specificity in non-human cells****. In such cases, …"*	General statement on GE rather that here Addition not accepted: Animal models still relevant for BD studies with GE products. Not include it here
1471	1, 6	**Comment:** Could the Agency provide some guidance on the type of *in silico* analyses to be used to support the product development? Could the Agency specify the standards the Sponsor may be used as references to provide suitable digital evidences in its submission?	No standards for in silico methods, Qualification of new methods is possible
1475-1476	1, 6	**Comment**: Suggest adding the possibility of using *in silico* models if acceptable to the Agency **Proposed change:** "Where appropriate, *animal testing could be replaced by in vitro* ***~~or~~****, ex vivo* ***or in silico*** *studies"*	Accepted
1476-1478	2	**Comment**: Where appropriate, animal testing could be replaced by in vitro or ex vivo studies. To this end, the development and use of cell- and tissue-based models including 2D and 3D tissue-models, organoids and microfluidics, are encouraged, especially for evaluating the mode of action.	Recommendation softened

		Proposed change (if any): Although we understand the wisdom of reducing animal testing we are not sure at this early stage of ATMPs that it should be so directly encouraged to replace animal testing with in vitro or ex vivo models, and specifically 2D and 3D tissue models. Would suggest that the use of 2D and 3D tissues models should be optional for a sponsor.	
5.3 Pharmacology studies			
1480	17	**Comment**: Use of the term Proof of Concept in the context of non-clinical pharmacology studies may be confusing in relation to its usual regulatory meaning in (phase 2) clinical studies.	No agreed, Poc normal term in NC
1484-1487	4	"Generally, animal disease models or experimentally induced models mimicking the condition to be treated are considered most relevant for demonstrating proof of concept. In addition, in vitro and ex vivo cell and tissue-based models can be used to supplement or substitute in vivo animal studies to demonstrate proof of concept". **Comment**: The use of non-animal approaches for demonstrating proof-of-concept should be prioritised before recommending animal models. **Proposed change**: ~~Generally, animal disease models or experimentally induced models mimicking the condition to be treated are considered most relevant for demonstrating proof of concept.~~ In ~~addition, in~~ vitro and ex vivo cell and tissue-based models **and other non-animal approaches should** ~~can~~ be used ~~to supplement or substitute in vivo animal studies~~ to demonstrate proof of concept. **Animal disease models or experimentally induced models mimicking the condition to be treated may be considered as a last resort if their relevance is justified.**	not agreed Most relevant model should be used. Animal studies are not a last resort, flexibility included section 5.2
1488-1491	4	"In the absence of clinical experience from the administration procedure and application devices, the feasibility and safety of the	Agreed

		application procedure and application devices should be tested in animal models before clinical use". **Comment**: Animal models should not automatically be the default option when there is a lack of clinical experience. **Proposed change**: In the absence of clinical experience from the administration procedure and application devices, the feasibility and safety of the application procedure and application devices should be tested in **non-clinical** ~~animal~~ models before clinical use.	A new device will anyway be tested in animals, under the framework of the MDR.
1489	1, 6	**Comment**: Could the Agency clarify the term of safety in the context of Pharmacology studies?	Both feasibility and safety of the MD will be tested together; Safety parameters can be included in the PoC studies.
1489-1490	1, 6	**Comment**: Suggest adding the possibility of using *ex vivo* models and/ or *in silico* models if acceptable to the Agency. **Proposed change**: *"…should be tested* ***ex vivo models, in animal models and/or in silico models*** *before clinical use".*	See above (non clinical)

1492	1	**Comment:** Further guidance would be helpful on methods for suitable extrapolation from animal models to humans to achieve estimation of biologically effective dose, as current guidance on extrapolation methods may not be applicable to ATIMPs due to their characteristics and mechanisms of action. This comment also applies to section 6.2.3 Dose finding and dose escalation. Examples of accepted methods for each of CTIMPs, TEPs and GTIMPs would aid developers. A correction of the following typo is also proposed: **Proposed change:** *"…estimation of biologically effective dose**s**…."*	Typo agreed Cannot provide an extrapolation method, depends on the products, route of administration etc
1492 - 1495	1	**Comment**: Section 5 includes considerations on the importance of justifying the minimally effective and optimal dose levels but there is little information and suggestions given on dose calculation methodologies (MABEL, PAD etc.) or extrapolation methods to clinical starting doses for ATMPs. The guidance First-in-Human Clinical Trials with Investigational Medicinal Products (Doc. Ref. 105 EMEA/CHMP/SWP/294648/2007) is mentioned a number of times and referenced as being useful; however, there is no mention of the utility of the dose calculation methods described in this guideline for ATMPs. It is recommended having a sentence addressing this – even if it is to state that MABEL and PAD may not be appropriate for ATMPs. We recommend introducing the need to derive a minimally effective dose, or the minimum anticipated biological effect level (MABEL) for the selection of the first human dose. **Proposed change**: *"The dose levels for proof of concept should allow estimation of a biologically effective dose**, and the minimum anticipated biological effect level (MABEL) ~~and~~ to allow** a meaningful extrapolation **for ~~to establish~~** the clinical starting dose**.** It is expected to determine an effective dose without toxic effects of the product which exerts the desired pharmacological activity in the most suitable animal model."*	Not agreed Clinical approach to determine the dose; MABEL not acceptable for all products (eg for GTMP, do not agree to look for a minimal biological effect).

1493-1495	4	"It is expected to determine an effective dose without toxic effects of the product which exerts the desired pharmacological activity in the most suitable animal model". **Comment**: Again, animal models should not be the default recommendation. **Proposed change**: It is expected to determine an effective dose without toxic effects of the product which exerts the desired pharmacological activity in the most suitable **non-clinical** ~~animal~~ model.	agreed
1496 1497	15	**Comment**: not all of the GTIMPs are viral vectors; thus transduction does not apply to all GTIMPs **Proposed change** (if any): Change of the title: "transfection/transduction and expression" **Proposed change** (if any): In the case of GTIMPs based on non-viral and viral vectors, respectively, transfection/transduction and subsequent expression of transgene product is important for interpretation of potential therapeutic effects observed in proof of concept studies.	Text amended
1497-1498	1	**Comment:** Transduction efficiency and level of transgene expression can also be assessed in vitro in human 3D cultures or organoids and can be more predictive of the vector tropism in human.	Not agreed, tropism is dependent on different parameter that cannot be captured in in vitro/culture methods. Such methods can complement in vivo studies.
1498-1500	15	**Comment**: The paragraph could be better structured by putting the second sentence at the end of the paragraph. **Proposed change** (if any): ~~Differences in tropism of a gene therapy vector between the animal species and human should be considered when extrapolating the results from animals to humans.~~ Therefore, the duration of the transgene expression and the therapeutic effect, associated with the nucleic acid sequence, shall be described. The relationship with the proposed dosing regimen in the clinical studies should be evaluated. Differences in tropism of a viral vector between the	Current order considered more appropriate (first BD/tropism, then expression)

		animal species and human should be considered when extrapolating the results from animals to humans.	
1500-1501	2	**Comment**: Therefore, the duration of the transgene expression and the therapeutic effect, associated with the nucleic acid sequence, shall be described Proposed change (if any): Please provide scientific and references for clarity	Editiorial change
1503-1507	1, 5, 6, 8	**Comment:** Does this mean that integration site analysis is required prior to each integrating vector clinical trial? Considering the well understood nature of the current versions of lenti- and gammaretro-viral vectors, is this necessary? The integration profiles are largely random and would only be useful in the event of a clonal emergence. Please indicate whether sponsors are able to leverage existing data on the integration profile for a particular integrating viral vector. For vectors such as RV and LV, which integrate quasi-randomly genome-wide, it has been consistently shown that the genomic distribution of vector insertion sites does not change with vector sequence and rather reflects the insertional bias of the parental virus and the gene expression profile of the target cell type and species. Thus, the need for extensive non-clinical characterization of insertion site distribution appears less justified unless a new cell type or a substantially changed vector particle composition - in terms of viral protein and enzyme but not sequence - are used. This notion also applies to the requirement for performing long-term genotoxicity studies, where the genotoxic risk is mainly dictated by vector choice and design - i.e. promoter choice, SIN-LTR... . Thus, the non-clinical studies requirement for a vector using a previously validated backbone/design should be alleviated by the possibility to reference such previous studies and mainly adjusted according to any potential aggravation by the choice of a new transgene.	Wording doesn't included an obligation Prior knowledge with similar vetor backbone/design could be used to justify absence of product specific investigations (risk based approach)

1507	1, 6	**Comment:** Indicating that this work would be performed "during early development" is unclear. Please consider deleting this sentence.	Most of NC data are required before starting the clinical trials; effect on epigenetics on expression important to know early on.
1508-1510	15	**Comment**: The entire paragraph rather belongs to the "pharmacokinetics studies" than to "Transduction and expression" section. **Proposed change** (if any): Move this paragraph to the PK section; e.g. Before the sentence in line 1547.	Paragraphs fits in both sections. Not move. You will investigate this in the BD study.
1511-1512	1	**Comment:** "Genome integration studies (ex vivo tissue culture or in vivo studies) should be performed for GTMPs that are intended for integration in the host genome." : please define 'integration' and include genome "modification" as well.	This section is for integrating vectors and need for integration studies.
1511-1513	15	**Comment**: Also this paragraph rather belongs to the "pharmacokinetics studies" than to "Transduction and expression" section. Suggested to keep the same structure as in the Guideline on quality, non-clinical and clinical aspects of gene therapy medicinal products. **Proposed change** (if any): Move this paragraph to the PK section; e.g. After the sentence in line 1547.	Not agreed, most of the time integration studies are separated from PK studies
1512 - 1513	1	**Comment**: We recommend citing the guideline reference number. **Proposed change**: *"For more information, see Guideline on quality, non-clinical and clinical aspects of gene therapy medicinal products* ***(EMA/CAT/80183/2014).***"	Accpeted

1516	1, 5, 6	**Comment:** How does "migration" differ from "distribution"? **Proposed change:** Assuming these mean the same thing, to maintain consistency in language, please delete the word "migration".	Accepted
1517-1521	5	**Comment**: Suggest the addition of additional text **Proposed change (if any)**: For cell- based ATIMPs, including genetically modified cells, **when an appropriate disease model is available,** distribution, migration and persistence of cells should information on the persistence of cells should be understood in order to identify relevant risks related to unwanted biodistribution, and to focus the nonclinical safety studies to the aspects that are relevant for the intended clinical use.	Not accepted, do not request a BD in disease model.
1520-1521 1522-1523	15	**Comment**: There is some redundancy in these lines **Proposed change** (if any): Rephrase to streamline and to reduce redundancy.	agreed
1526-1527	1	**Comment:** Guidance on acceptable detection methods for biodistribution would be helpful.	Ref to ICHS12
1526-1528	5	**Comment**: If the virus and construct are well characterised based on non-clinical and/or clinical data, the need for biodistribution studies may be reduced and it is proposed that this is reflected in the guidance. However, the impact of the transgene should also be considered. **Proposed change (if any)**: "The need for biodistribution studies is dependent on the administration route as well as the structural or physiological containment of the cells. **However, if the vector and construct are well characterised based on non-clinical and/or clinical data, biodistribution studies might not be needed. Although, in making that**	Ref to ICHS12

		decision, consideration should also be given to the transgene.”	
1532-1534	2	**Comment**: Suggest provide an improved scientific explanation for practical and real-life use. The structural integrity of the containment method at the site of administration needs to be demonstrated to ensure that there is no unintended leakage of the cells.	Not accepted. Examples in lines above Eg. Leaking of cells from medical device or scaffold or matrix containing the cells;
1533	10	**Typo** **Proposed change:** …the concomitant method at the site of administration…	agreed
1533-1534	1	**Comment:** Typo: a space is needed between “at” and “the.” **Proposed change:** *“The structural integrity of the containment method **at the** site of administration needs to be demonstrated to ensure that there is no unintended leakage of the cells.”*	agreed
1535-1540	1	**Comment:** *“Distribution profile of the gene therapy vector…”* This paragraph should be expanded to also include genome modification and whether permanent or transient.	Biodistribution of the GE in-vivo tools (vector used) as other vectors GTMPs; BD of GE-cells as genetically modified cells. on/off site integration studies not PK/BD; but BD studies can be combined with PoC and tox studies
1539	1, 5, 6	**Comment:** We are concerned that a publication, not a guidance document where feedback had been obtained from all affected parties, is now effectively guidance. The title of this publication is also incorrect – it is “General Principles to Address the Nature and Duration of Follow-up for Subjects of Clinical Trials Using Cell Therapy Products”. Please cite existing regulatory guidance that addresses	Replaced by ref to ICH S12

		conduct of biodistribution studies.The following typo should also be corrected: **Proposed change:** *"… **~~asessssments~~** **assessments** for gene therapies…"*	
1539	2	**Comment:** Is there any EU guidance that can be cross referenced for a more authoritative position on biodistribution analysis?	See above
1540	1	**Comment**: We recommend citing the date of the latest version. **Proposed change:** *"the IPRP Reflection Paper on Expectations for biodistribution (BD) assessments for gene therapy (GT) products) **(12-Apr-2018)**"*	See above
1543	15	**Comment**: It is unclear what the appropriate safety margins with regard to the administration route and the treatment regimen could be. Suggested to delete. **Proposed change** (if any): The route of administration and the treatment regimen (frequency and duration) should be representative for the clinical use ~~with appropriate safety margins.~~	Agreed
1549	1	**Comment**: We recommend citing the latest reference number: **Proposed change:** "*Guideline on non-clinical testing for inadvertent germline transmission of gene transfer vectors **(EMEA/273974/05).**"*	Agreed

1552	1	**Comment:** 5.3 Pharmacology studies – Shedding We recommend including additional guidance on requirements for shedding studies, as it would be helpful for developers. It is proposed to include guidance on design and expectations for non-clinical shedding studies, expectations for justifying the use of existing clinical data or published data and cross-reference to existing guidance.	ICH RP on shedding - Cross ref to be included We accept previous clinical experience instead of formal NC shedding studies.
1552-1557 1634-1636	5	**Comment**: Requirements regarding "Shedding" are referring to GTIMP in general, but it is not clear that this may not be relevant for certain moieties such as mRNA. **Proposed change (if any)**: Add a statement "Shedding data are generally not required for ATIMP with only transient expression such as oligonucleotides (e.g., RNA, mRNA)..." and refer back to it in line 1636.	Clarification added
1553-1555	15	**Comment**: There are some inconsistencies in the two sentences: The first sentence indicates that shedding data are needed. The following sentence indicates that information can be based on human or published data and/or a justification. However, information/data cannot be based on a justification. Only lack of data could be justified. **Proposed change** (if any): Rephrasing of the following sentence is required: This information can be based on human data, published data and/or a justification.	Reworded
1556-1557	1, 6	**Comment:** We suggest clarifying "novel types of GTIMPs", does the agency mean GTIMPs not already used in clinical trial? Not already documented in the scientific literature for nonclinical development? Can you please provide an example of a "novel GTIMP"	Text clarified

5.4. Toxicity studies			
1558	1	**Comment**: It is suggested to include expectations for different sexes in the toxicity studies in the non-clinical data requirements.	Agree, Clarification added.
1558	5	**Proposed change (if any)**: In the section of toxicity studies, suggestion to add the following: **The number of animals used per dose level tested has a direct bearing on the ability to detect toxicity. A small sample size may lead to failure to observe toxic events due to low frequency, regardless of severity.**	Very general, not ATMP specific. Also suggested to look into requirements in the CBMP and GTMP mother guidelines Size of study depends on the model / statistically power
1564-1566	1	**Comment:** ICH M3 (Non-clinical safety studies for the conduct of human clinical trials with pharmaceuticals) requires the conduct of non-clinical studies in one rodent and one non-rodent species. This is normally not applicable to investigational ATMPs. It is suggested to clearly state that ICH M3R2 may not be applicable by adding a sentence such as "*In contrast to what is indicated in ICH M3R2, testing two species, one rodent and one non-rodent, is generally not required for investigational ATMPs*"	Not agreed, The last paragraph of the tox sections is already clear enough that 1 species can be sufficient
1564-1566	5	**Comment:** "…meaningful and predictive extrapolation…", this could be too restrictive, depending on the interpretation of this line. Sometimes endpoints that are surrogates for human clinical efficacy need to be measured in animals. **Proposed change (if any):** Please change to - "…should allow for measurement of endpoints that are feasible in the animal and may translate to an identical or surrogate endpoint in humans"	Non agreed A NC model means that many aspects have to be adapted and interpreted.
1565-1566	5	**Comment**: It is suggested that the relevance of the animal species should be justified. **Proposed change (if any)**: Safety studies in non-relevant species may be misleading and are discouraged. **The relevance of the animal species should therefore be justified (e.g. pharmacological activity of the ATIMP, anatomical and cellular similarity to human tissue(s) at the side of action,**	Not accepted, relevance of the animal model is discussed in section 5.2 (not only relevant for tox section)

		appropriate age, sufficiency of meaningful, predictive extrapolation of dose etc).	
1566-1567	5	**Comment**: It is currently unclear if the guidance that '…studies…should be chosen to represent clinical use with appropriate safety margins' refers to an optimal dose level in terms of efficacy without adverse safety findings or if Maximum Tolerated Dose should be achieved to establish a safety margin. Appropriate safety margins could be defined. A 10x dose is considered as a rule of the thumb in other guidance (e.g. ICH M3(R)2. Is it still a valid option for ATMPs? **Proposed change (if any)**: It is suggested that referencing the most appropriate regulatory guidance to help determine safety margins would be valuable.	For ATMPs, 10x dose not possible , see also ICHS12 guidance on dosing. Relevant safety margin = at least max clinical dose, and exceeded. Max tolerated dose = for chemical, rather maximum feasible dose.
1568-1571 1574-1575	15	**Comment**: There is some redundancy in these lines. It is therefore suggested to delete the sentence in lines 1574-1575. **Proposed change** (if any): For ATIMPs intended for single administration, single-dose toxicology studies with an appropriately extended post-dose observation period shall be performed to capture relevant safety concerns, e.g. ectopic tissue formation or tumour formation. ~~Multiple dose studies are needed only when repeated dosing in patients is foreseen.~~	agreed
1572-1574	1	**Comment:** "*ATIMPs intended for single administration, single-dose toxicology studies with an appropriately extended post-dose observation period shall be performed to capture relevant safety concerns, e.g. ectopic tissue formation or tumour formation. Multiple dose studies are needed only when repeated dosing in patients is foreseen*." Further recommendations on duration and number of animals particularly if using primates would be desirable.	For primates, refer to animal model section – 3R - discouraged unless really needed. Would not require stand alone monkey studies for an ATMP

1572-1578	5	**<u>Comment</u>**: As below (1930-1934), additional guidance regarding duration of follow-up in toxicology studies should be incorporated into the guidance and should recognize that different GTIMP vectors (e.g. integrating vs non-integrating) and routes of administration (e.g. subretinal vs systemic) carry different risks.	Duration: reworded Clearance or reaching a plateau of expression
1575-1576	1	**Comment:** "*The duration of follow-up should cover the time of persistence of administered cells.":* Please note that advice should be provided for non-cellular products.	reworded
1579-1582	15	**Comment**: For most GTIMPs appropriate safety/toxicity studies in accordance with GLP would be expected. The capturing of safety concerns should not routinely be determined solely on addressing some safety endpoints that are included in the PoC studies. Such an approach should only be done exceptionally. **Proposed change** (if any): Rephrasing to clarify that this approach is rather an exceptional approach for GTIMPs. In case that this approach is common for cell-based ATIMPs this should be indicated.	Comment not understood – for both GTs and CTs we encourage to combine NC studies.
1582-1584	4	"In justified cases in vitro and/or ex vivo data can be used to replace or supplement in vivo animal data". **Comment**: The use of non-animal approaches should be prioritised before recommending animal models. **Proposed change**: ~~In justified cases~~ **Where appropriate and applicable, toxicological endpoints should be addressed in** in vitro**,** ~~and/or~~ ex vivo**, in silico or other non-animal approaches. In vivo animal studies should be considered only as a a last resort.** ~~data can be used to replace or supplement in vivo animal data~~".	Not accepted, already in the introduction of NC part (3R approach) and selection of NC models

1583-1584	15	**Comment**: This statement seems to refer to cell-based ATIMs, which should be indicated. In addition the persistence of the ATIMPs should be addressed in the PK section. In case that combined biodistribution/safety studies should be performed, a appropriate and clear statement should be included. **Proposed change** (if any): Rephrasing or deleting as appropriate.	Rephrased: The overall safety evaluation should take into account cell persistence and biodistribution data.
1585	1	**Comment:** "One animal species can be considered sufficient if the model is considered predictive.": This should be the norm, not the exception as implied here. It is proposed to change the term "predictive" to "pharmacologically relevant".	Rephrase Keep 'predictive', is broader, allows to follow toxic effect not linked to the pharmacology of the product itself (e.g. AAV integration in the liver); not always needed to have a pharmacologically relevant model
1585	1, 6	**Comment**: It is suggested to mention clearly that "In contrast to what is indicated in ICH M3R2, generally, testi*ng two species is not needed for ATIMPs".*	Not accepted ICH M3 refers to ICH S6; this guidance provides more specific information for ATMPs
1589	1	**Comment:** "*Pivotal non-clinical safety studies are carried out in conformity with the principles of GLP.":* It is suggested to define "pivotal"	Not accepted, this definition is provided in the GLP document: "The term "pivotal non-clinical safety studies" refers to toxicity studies which support the non-clinical safety conclusions. Among others, the following are not considered non-clinical safety studies: basic research (primary and secondary pharmacology), proof of concept studies, dose response studies, analytical quality control testing for clinical and commercial studies, stability testing on commercial products and feasibility studies."

5.5 Minimum non-clinical data requirements before first-in-human studies			
1594	5	**Comment**: Are there any pharmacokinetics studies required before first-in-human studies in addition to biodistribution and shedding? If yes, this could be indicated.	BD studies are sufficient For shedding, often not studies but jusification
1602-1605	4	"The extent of the non-clinical data package is determined on a case-by-case basis taking into consideration the risks, or the lack of risks, associated with the product and the intended clinical use, the availability of animal models and publicly available information from similar type of products. In exceptional cases, where appropriate in vitro, ex vivo or in vivo data with predictive value cannot be generated, a comprehensive risk assessment addressing risks related to the ATMP and its clinical use should be provided, and measures to mitigate the risks should be described". **Proposed change**: The extent of the non-clinical data package is determined on a case-by-case basis taking into consideration the risks, or the lack of risks, associated with the product and the intended clinical use, the availability of **relevant non-clinical** ~~animal~~ models and publicly available information from similar type of products. In exceptional cases, where appropriate in vitro, ex vivo or in vivo data with predictive value cannot be generated, a comprehensive risk assessment addressing risks related to the ATMP and its clinical use should be provided, and measures to mitigate the risks should be described.	Accepted
1607	1	**Comment:** *"-demonstration of proof of concept in a relevant model":* Please specify that relevant proof of concept models can possibly be *in vitro* or *ex vivo* alone.	Not accepted, this refers to the section above on the selection of NC models
1608	5	**Comment**: Does the term "relevant model" also comprise in vitro or only in vivo models? **Proposed change (if any)**:	See above

		Add "…in a relevant in vitro and/or in vivo model"	
1617-1619	1	**Comment:** "*The duration of such study should be sufficient to demonstrate relevant functionality of the product that can be considered predictive of therapeutic effect (e.g. formation of a repair tissue for tissue engineered products).":* Please expand "relevant functionality" to include "pharmacodynamic biomarker".	Not accepted. This terminology does not exclude the use of a PD parameter: it is up to the developer to justify that a PD biomarker is producing relevant functionality data.
1622	2	**Comment:** Safety pharmacology data are not routinely needed for ATIMPs **Proposed change (if any):** Please comment about including GTIMPs, if not why.	Not accepted. Investigational ATMP included investigational GTMPs
1626	5	**Comment**: The section of "Biodistribution" mainly refers to viral vectors. Any specific guidance with regard to other moieties such as oligonucleotides, mRNA would be helpful.	BD does not specifically refer to viral vectors. Shedding is specific to viral vector, rest if applicable to all, also for mRNA that is administered using a non-viral vector (eg LNP). Oligonucleotides not covered by this GL
1627	1, 5, 6	**Comment**: Is it acceptable for sponsors to take biodistribution studies out no longer than the length of the toxicology studies?	Ref to duration sentence in tox part.
1639	1, 5, 6	**Comment:** If validation is not required prior to first in human studies, what is meant by "further validation" being conducted to support later clinical development?	Sentence clarified
1643-1645	5	**Comment**: The guidance that safety information from well-designed proof-of-concept study(ies) incorporating adequate safety endpoints may support first-in-human studies is noted. However,	Not accepted This is described in GT and CBMP specific guidelines.

		further guidance on how these endpoints should be determined would be valuable. For example, are there common safety endpoints (i.e. histopathology, clinical chemistry) or are they product specific and therefore to be discussed with an Agency as relevant? Additionally, guidance on the impacts of specific issues such as differences in viral tropism or routes of administration between non-clinical and clinical studies would be valuable.	Anyway, the safety/toxicity study and endpoints will depend on RBA and knowledge similar products.
1646	5	**Comment**: In addition to genotoxicity, evaluation of consequences of gene editing at the chromosomal level could also be required by the regulatory agency. These could be performed by karyotype analysis or FISH.	Partially accepted: the section has been updated to provide general guidance for all ATMPs, including genome editing. Reference to the specific type of analysis not included.
1646-1660	5	**Comment**: The section of "Genotoxicity" and "Tumorigenicity" should more explicitly comment on the need of such studies for non-integrating, transient ATIMP such as oligonucleotides/mRNA.	Partially accepted: the section has been updated to provide general guidance for all ATMPs. Note that oligonucleotides not ATMP; for mRNAs, if delivery via liponanoparticles (LNP), genotoxicity studies may be required for the LNP.
1646-1660	17	**Comment**: Acceptability of use of *in-silico* data/models to complement *in-vitro data,* (and where needed based on the type of product) *ex-* and *in-vivo* data should be reflected	Not accepted: this is already addressed in the section 5.2 on Selection of non-clinical models
1648-1651	1	**Comment:** **"***The requirement for genotoxicity studies of GTIMPs involving host-DNA integration will depend on the way the final product will be delivered (local versus systemic), to which tissue/organ the GTIMP will be targeted and the biological status of the cells to be targeted. Standard genotoxicity assays are generally not appropriate...":* Further clarification of genotoxicity requirements in context of genome editing intended to make modification to the genome should be provided. This could include an *in silico* and *in vitro* off-target assessment.	Not accepted: this is already addressed in the section 5.2 on Selection of non-clinical models
1653-1660	6	**Comment:** Up to now, often, *in vivo* tumourigenicity studies were conducted by using a "positive control group", with e.g. HeLa Cells. If an *in vivo* tumourigenicity testing is considered necessary for an	Not accepted. No change to the text.

Commented [CP1]: Check if this is also to be included in the section on GE in the Tox section of the GL

		ATIMP, would such a positive control group be really compulsory? Is it not in contradiction with the 3Rs principle?	In vivo tumourigenicity study are rarely conducted for ATMPs (step by step/RBA: starting with in vitro experiment, only if real risk in vivo studies to be conducted); if they are needed, a positive control might be required – HeLa cells might not be the best model. This is a case-by-case decision, not for general guideline.
1655-1567	1, 8	**Comment:** More specific guidance on acceptable methods for assessing tumourigenic and oncogenic potential would be appreciated. Up to now, often, in vivo tumourigenicity studies are conducted by using a 'positive control group'. If in vivo tumourigenicity testing is considered necessary for an investigational ATMP, would such a positive control group be compulsory taking into account the 3Rs principle? Please consider additional clarification	Not accepted, see above
1658-1660	15	**Comment**: This is a difficult statement for GTIMPs that may persist long-term after administration and might have delayed toxicities. Rewording is suggested to indicate that such an approach should be carefully considered on a case-by-case basis. **Proposed change** (if any): Rewording in order to indicate that such an approach is only possible under exceptional cases and appropriate case-by-case considerations – at least for GTIMPs.	Not accepted, already mentioned that it is on case-by-case basis & broad guidance provided for all ATMPs
1666	1, 5, 6	**Comment:** Would this guidance indicate that a biodistribution study would need to be repeated under the conditions of an immunogenic response?	Not accepted: we are not asking for an additional BD study. This is addressed in ICH S12; this sentence relates to the timing when this information needs to be available.

5.6 Non-clinical data that can be provided at later stages of development			
1667	1	**Comment**: We support the inclusion of this information and it would be welcomed by the industry. We expect regulatory authorities will issue conditions on the progression of dosing in the clinical trial when interim safety on non-clinical data is provided. It would be useful to draw developers attention to data being provided at specific points or before specific stages of the clinical trial as defined by the national regulatory authority.	Thanks for the feedback, no changes to be made
1672-1675	15	**Comment**: These two sentences are not clear, as the second refers to the previous one, although two different scenarios seem to be described. **Proposed change** (if any): Suggested to reword the second sentence: However, a clinical study with multiple administrations could be initiated without repeat-dose toxicity data provided that such data are available before multiple dosing in humans commences. Lack of multiple administrations ~~This approach~~ might also be justifiable on a case-by-case situation e.g. in the case where dosing interval is very long or when the ATIMP has been shown to be eliminated from the body before subsequent administrations.	Accepted, text reworded to clarify the second scenario.
1680	10	How to understand this sentence? Literature data of similar type of products might not be available. **Proposed change:** For tumourigenicity, a comprehensive risk assessment including karyotype, genomic stability and possible literature data from similar type of products, should always be available before exposing humans.	Accepted, text has been amended to refer to literature data if available.

1680-1682	15	**Comment**: This statement seems to be specific for cell-based ATIMPs which should be indicated. **Proposed change** (if any): Rephrasing to make clear, that this statement refers to cell-based ATIMPs.	Accepted, text rephrased without specifically mentioning cell-based ATMPs.
1683	1, 6	**Comment:** We suggest to the Agency to clarify "long-term persistence can easily be monitored". What kind of control could be required and considered as accurate according to the guideline? What techniques? What is the level of limit to "monitor"? What is the ethical acceptance criteria for the manipulation of non-healthy patients?	Accepted: Sentence removed, the essence is a risk assessment
1688-1689	1	**Comment:** Guidance on immunogenicity assessment appears to contradict lines 1661-1666. Please provide clarity and/or examples of types of information expected before first in human vs. during development.	Accepted: sentence removed
1690-1691	1	**Comment:** In relation to timing of reproductive toxicity studies, if would be helpful to clarify whether women of childbearing potential are included in the statement 'before exposing larger patient population'.	Not accepted, see guidance in clinical part (on need for contraception)
5.7 Combined ATMPs.			
1697-1698	1	**Comment:** Could existing clinical data from investigational use of the device in a similar situation be supportive? e.g. studies with cadaveric cells used to support the device use with stem cell equivalents?	Relevant available data could always be leveraged in a supportive fashion when it comes to demonstrating the suitability for use in a clinical trial. In case the medical device is non-integral, this is however independent from fulfilling potential requirements from the MDR perspective. In case of integral medical device, this is fully under the remit of EMA/CAT.

1697-1698	10	How and in which format is this to be presented in the IMPD/CTA? How and by whom will this data be assessed, by CA or NB? If by NB how will this work in the CTA procedure. **Proposed change:** For medical device components that are not CE-marked or that are CE marked for another use, non-clinical safety data in accordance with the Medical device legislation are needed before clinical use.	Not ATMP specific
1697-1698	15	**Comment**: It is unclear if this section reflects the current situation under the Medical Device Directive and/or if it will be equally applicable to the future situation under the Medical Device Regulation, and at which time in ATMP development a CE marking will be required.	Not mandatory for CE marking for clinical trials; for combined ATMP CE marking not obligatory

6. CLINICAL			
6.1 General aspects			
1709	10	List can be changed over time. **Proposed change**: Distinctive features of ATMP include *but are not limited to:*	Accepted
1709-1716 1794-1797 1862-1864	4	"Distinctive features of ATMPs include: […] limitations to extrapolate from animal data: starting dose, biodistribution, immunogenicity, on- and off-target effects and tumourigenicity". "The extrapolation from non-clinical pharmacodynamic, pharmacokinetic/biodistribution and toxicity data to the human situation may be limited, depending on the relevance of the non-clinical animal model. This may hamper, amongst others, the prediction of a safe starting dose for FIH trials and the prediction of target organs of toxicity". "Differences in engraftment, differentiation, persistence and immunogenicity between animals and humans may limit the predictive value of non-clinical dose-finding studies". **Comment**: Even in the 'Clinical documentation' section of the guideline, there are warnings that the data generated from animal models may not be relevant or easily translated to humans. It is difficult to see what value this data actually has if it can't even provide reliable enough information to establish a starting dose in humans. Instead of continuing to promote the use of outdated tests in animals, the guideline should encourage the use of more sophisticated and human-relevant technologies that will be able to keep up with the development of ATMPs as well as future advances in other types of complex and human-specific medicinal products and therapeutic approaches.	Partially accepted Animal data are limited, but not directly non-relevant. Other non-animal non-clinical data can be used. Wording change to 'non-clinical'

1710-1712	1, 6	**Comment:** The inherent variability of autologous cells could contribute to the variability of response. **Proposed change:** Consider adding "the inherent variability of autologous cells contributing to the variability of response"	Not accepted. This is a too broad statement - Quality issue addresses variability of starting material; however, uniform clinical response expected
1717-1718	1	**Comment:** Due to practical difficulties to ensure complete absence of all potential impurities, there may be uncertainty about the contribution of any component to the product safety. Please consider adding the uncertainty about potential remaining impurities.	Not accepted. Quality part addresses this issue
1717-1718	15	**Comment**: issue of persistence may be a separate bullet point **Proposed change** (if any): • uncertainty about frequency, duration and nature of side effects, • persistence in humans and immunogenicity	Accepted
1720	6	Comment: we suggest considering also the uncertainty of the contribution of any component due to the practical difficulty to achieve "total removal" of all potential impurities	Not accepted. The Quality part addresses this issue / part of product characterisation; also this is not an exhaustive list
1724	6	**Comment:** Also, "the complexity of dose selection and potential ethical issues related to testing ineffective doses in dose finding studies" could be added.	Not accepted Covered in the dose selection part of the GL; also, this is not exhaustive list
1724	10	Added additional bullet in list. **Proposed change**: *transportation and handling requirements*	accepted
1725-1748	15	Comment: The terms 'anticipated' and 'potential' appear not to be used consistently. It is suggested to use 'anticipated benefits' and 'potential risks' throughout the document. Proposed change (if any):	Anticipated risk = risk that can be expected (in reference safety information)

1729	2	Comment: Add potential risks of insufficient data to support dose selection for FIH studies and then insufficient patients to support dose exploration in further exploratory studies.	Not accepted. The list relates to risks/benefits for the trial subjects – see also the section of dose selection
1729-1746	1	**Comment:** Difficulties for dose selection should be considered in the list of potential benefits and risks (see also comment on lines 1847-1875). **Proposed change:** Consider adding the following: "*the complexity of dose selection and potential ethical issues related to testing ineffective doses in dose-finding studies"*.	Accepted. The reference to 'ethical issues' has been removed from the proposed sentence
1734	13	**Comment**: should be also include information on additional trial interventions related to diagnosis (for stratification) and follow up Proposed change (if any):	Not accepted. Not ATMP specific
1736	3, 5	**Comment**: "Infusion of DMSO" should be replaced by "DMSO or other preservatives" instead of being specific. **Proposed change** (if any): DMSO or other preservatives	Accepted
1737	15	**Comment**: More invasive routes of administration of iATMPs are also increasingly observed for GMOs, e.g. intraparenchymal intracranial injections of AAV or oncolytic viruses. **Proposed change** (if any): • surgical preparatory and/or implantation procedures including anesthesia, e.g. in case of tissue engineered products or challenging ways of administration;	Partially accepted. Bullet amended, anesthesia is considered to be part of surgery
1739	1	**Comment:** It is suggested to clarify that the example about risks related to quality, manufacturing, supply chain is relevant in case of autologous cell-based medicinal products	Not accepted. This is not limited to autologous products
1746	5	**Comment**: Consider specifying inflammatory in addition to immune related reactions	Accepted
1747	15	**Proposed change** (if any): …. benefit-risk assessment how expected known and potential risks are addressed	Accepted

1753-1758	13	**Comment**: The (trial) population should be representative of the real world patients (with similar conditions, age, comorbidities, etc.)	Not accepted. It might not be possible for all indications; already mentioned that trial is done in patients
1753-1754	15	**Comment**: It is suggested to elaborate a little bit more on the trial population **Proposed change (**if any): For any clinical trial, the study population has to be selected such that the anticipated therapeutic and public health benefits justify the risks. For exploratory trials, the population may be further restricted to include patients where a more favourable benefit risk balance may be expected. However, confirmatory trials should be designed to ensure that the trial populations overall are representative for the patient group intended to be treated after obtaining a marketing authorization	Accepted
1757	3, 5	**Comment**: "The stage of disease and the ability of subjects with late stage disease to tolerate the treatment may also be considered when choosing a trial population". Late stage disease is somewhat of a colloquial term. Please be more specific: "patients who have had exhausted currently available classes of therapy". **Proposed change** (if any): Article I. The stage of disease, the ability of subjects to tolerate the treatment and the classes of therapies that patients have exhausted may also be considered when choosing a trial population.	Accepted, reworded
1759	17	**Comment**: In more rare conditions combined studies in adults and paediatrics patients may be considered with a staggered inclusion. **Proposed change** (if any): For paediatric indications, prior studies in adults*, or staggered inclusion of peadiatric patients,* should be considered if feasible for the condition i.e. unless the disease affects children exclusively or if the phenotypical presentation in adult differs from that in children.	Accepted
1759-1761	1	**Comment:**	Accepted

		Regarding paediatric indications, the draft text seems to imply that adults should be studied first. In some cases, it may be appropriate to start studies in children at the same time as adults. Suggest to add the consideration where there is direct possibility of benefit to the child. **Proposed change:** "*For paediatric indications, prior studies in adults should be considered if feasible for the condition i.e. unless the disease affects children exclusively, or if the phenotypical presentation in adult differs from that in children or if there is direct possibility of benefit to the child."*	
1759-1761	7	Given the statement in this sentence relating to studying adults first prior to treating children in clinical studies, it would be helpful to have some guidance where a particular disease only affects children, what the Agency's views are on treating older children first. This is sometimes difficult when the disease is rare and not many patients are available.	Text reworded
1762	5	**Comment on contraceptive differences between male and female subjects** Rationale for male and female subject contraception appear to be different, are there genuinely different concerns? Male subject contraception for three months after no virus shed suggest there is a concern for changes to heritable material (eg, DNA) but no such specific duration/rationale for contraception is provided for female subjects. If there is no risk of changes to heritable material (e.g. DNA), there does not appear to be a science-based rationale for three months contraception in male subjects after no virus is shed.	The 90 days relates to the period of spermatogenesis after the IMP is no longer shed in the semen. This guidance is in line with the CTFG guideline. The period of contraception is warranted as it is not clear when virus is shed in the semen whether it has the potential to effect germ cells or the foetus if exposure occurs during early pregnancy. For female, not further guidance possible as not sure if virus would have biodistributed to gonads.
1762-1775	1	**Comment:** It is recommended that any planned update to the CTFG "Recommendations related to contraception and pregnancy testing in clinical trials" be consistent with recommendations in this guidance.	The section has been reworded and aligned to the CTFG recommendations
1765	3, 5	**Comment**: If "The length of exposure to the ATMP may be lifelong" then this goes beyond subjects of childbearing potential in the context of paediatric subjects. In the future these paediatric patients will be of childbearing potential so defining "the end of the period of potential risk" will be important in such cases.	No accepted. Cannot defined the end of period of potential risk. We expect no long term embryotox risk. No wording change possible, cannot be more specific

1769-1771	5	**<u>Comment</u>**: It is suggested that contraception measures should be included in both the protocol and IB so we have proposed an amendment to the text. **<u>Proposed change (if any)</u>**: "The protocol **and** investigators brochure (IB) should include an evaluation of the period of potential risk and a justification for the duration of contraceptive measures."	Accepted
1773-1775	1	**Comment:** What is the rationale for 3 months after no virus shedding? It is suggested to revise wording to three consecutive timepoints of no virus shedding. **Proposed change:** "*In the case of male subjects who are treated with a gene therapy, at least two methods of contraception including male barrier protection should be used during the time the virus is shed in the semen and for a period <u>covering</u> ~~of~~ three ~~months after~~ <u>consecutive timepoints, relevant for the product, where there is no virus shed</u>.*"	No change, see above
1773-1775	5	**<u>Comment</u>**: **contraception for male subject** The draft guidance text for duration of female contraception is appropriately flexible considering the different types and risks of advanced therapy investigational medicinal products (ATIMPs). It is therefore unusual and potentially confusing that a very specific number (2), type (including barrier), and duration of contraception (3 months) is provided in males only for specifically gene therapy. We would request that the contraception section be modified to address the comments below: **1)** The purpose of male contraception should be provided. Are 2 forms of male contraception (including barrier) to prevent foetal harm by preventing pregnancy (in which case why is barrier specified?) and/or to prevent transmission of gene therapy product via seminal transfer to a partner (in which case non-barrier methods would not be applicable)? If the latter, would this apply only to pregnant partners or all partners?	This section has been reworded to clarify the expected contraceptive measure, including a separate subsection on male contraception.

		2) Male contraception during virus shedding in semen plus another 3 months suggests there is an implicit risk to the dividing germ cells with gene therapy products and this contraception will minimize these changes in offspring of the male patient. If gene therapy products have an implicit risk of changes in dividing germ cells (also present in females) and guidance is provided to minimize transmission to offspring, why would there not be a corresponding recommendation for female contraception using gene therapy products for a defined period (not necessarily 3 months but something appropriate for female reproductive physiology) after virus is no longer shed systemically? Suggestion is to provide aligned contraception guidance in male and female patients if there is specific risk to dividing germ cells in offspring of male and female patients. If the risk is not specific to dividing germ cells then what is the rationale for months in male patients? Female contraception guidance is provided for all in-scope products (ATIMPs), why is male contraception guidance only provided for gene therapy products but not for other ATIMPs? And for gene therapy products as defined on lines 86-87, some are delivered by a non-viral approach so should this guidance be more narrowly provided for gene therapy products delivered by a viral vector (to differentiate from gene therapy products using a non-viral approach)?	
6.2 Exploratory clinical trials			
1781	10	Could include, not always. **Proposed change**: …consideration of clinical safety issues different from other medicinal products (*could include* ~~including~~ extended or permanent adverse events, …..)	Accepted

1789-1787	5	**Comment**: Suggestion to leave out the identification and characterisation of the manufacturing here since this section focuses on clinical. Administration issues will be relevant to investigate in exploratory trials.	Accepted - Text amended
1794-1796	15	**Proposed change** (if any): For example, the possibility to extrapolate~~ion~~ from non-clinical pharmacodynamic, pharmacokinetic/biodistibution and toxicity data to the human situation may be limited, depending on the relevance of the non-clinical animal model.	Accepted
1801-1804	1	**Comment:** For some conditions e.g. monogenetic diseases, a well-controlled Phase 1/2 study may support marketing authorization application. Wording to this effect would also support consistency between draft EU and US guidances. [Draft FDA guidance on gene therapy for rare diseases suggests "designing first-in-human study…potential… to support a marketing application."] **Proposed change :** "~~*Exploratory s*~~*Studies with ATIMPs are often designed as phase I/II trials, combining features of phase I and phase II design. Examples are trials with GTMPs in patients with monogenetic disease, where dose escalation and determination of a recommended dose is followed by an extension phase, to include additional patients on the recommended dose level and to further explore or confirm the efficacy of the GTMP. A well-controlled Phase 1/2 study may support marketing authorization application."*	Not accepted: this is for the MAA stage, for CAT to accept MAA on basis of ph1/2 data only; not within the scope of this GL to give guidance on what is needed for obtaining a MAA. As for non ATMPs, a CMA could be granted on basis of ph1/2 data
1802-1806	7	**Comment**: The use of substantial amendment for additional data for ATIMPs following Phase I study not a common practice: the only agency which currently requests additional data following Phase I is the German Paul-Ehrlich Institute (PEI). In such a case, the PEI does not request a substantial amendment. Consequently, there would not necessarily be a need to issue a substantial amendment, if decision criteria are outlined clearly upfront in the protocol. Proposed change (if any): "The trial protocol should define the methodology to move from the dose-escalation phase to the extension phase~~, and how this is captured in a substantial amendment."~~	Partially accepted: Dose of IMP must be clearly stated in the protocol: as this is not know in case of ph1/2 dose escalation, this needs to be communicated to authoriries via a substantial modification. The reference to substantial manipulation has been replaced by '… and the procedural steps planned to move …'

1805-1806	1	**Comment**: It is suggested to delete the words "and how this is captured in a substantial amendment". If the methodology is defined in the protocol, then a substantial amendment should not be necessary. **Proposed change:** *"The trial protocol should define the methodology to move from the dose-escalation phase to the extension phase, ~~and how this is captured in a substantial amendment~~."*	See above
1807	7	**Comment**: It would be helpful to clarify that major changes in the manufacturing process are defined as those which are likely to affect either the efficacy or safety profile of the product in humans. It would be helpful to provide examples of such changes (if any are known). Many ATMPs are investigated in orphan/ultra-orphan indications and data from early trials may well be an important fraction of the total supplied to support marketing authorisation. In addition, if the manufacturing change made has little impact on measures used to assess comparability of the end product, it seems unlikely that a clinically recognisable change in clinical properties would ensue. For these reasons, it does not seem appropriate to suggest that a separate clinical investigation would be necessary prior to starting wider use, particularly if the product is continuing within an investigational clinical trial program (as opposed to post marketing use). It may be preferable to suggest that applicants consider the potential impact of major manufacturing changes on the efficacy/safety profile observed following use of various batches used throughout the clinical trial program and to describe any changes noted within the IMPD/IB/MAA as appropriate. **Proposed change**: suggest inserting "preferably" or "ideally" (and deleting the word "that") so that the text becomes: "In case major manufacturing process changes are implemented which affect product attributes which may critically affect the efficacy or safety of the product the impact of the change should be clinically evaluated preferably before – or, as part of an early clinical safety run in assessment, during – confirmatory trials."	This paragraph has been reworded and is moved to section 6.3.1 (as it relates rather to pivotal trial setting) The term has been changed to 'substantial' manufacturing changes (this is defined in the Art 2 of clinical trial regulation). A cross reference to the quality and clinical parts has been included.

1807	10	Should or is recommended? **Proposed change:** In case that major manufacturing process changes are implemented, these should be implemented and evaluated clinically before starting confirmatory trials.	See above The paragraph has been amended.
1807-1808	1	**Comment:** It is suggested to delete this sentence. The clinical evaluation of manufacturing changes (post dose-finding) should not be the default. A step-wise approach should be allowed.	See above The paragraph has been amended.
1807-1808	15	**Comment**: It may be considered to move this to chapter 6.2 **Proposed change** (if any): In case that major manufacturing process changes are to be implemented, these should be implemented as early as possible. For conducting a clinical trial with the altered product, the relevance of the non-clinical data and clinical data generated previously with the former product should be justified ~~and evaluated clinically before starting confirmatory trials~~ (see also sections S.2.6 and P.2). This also has to be considered when there are significant changes in the method of administration, dosing or indication.	See above The paragraph has been amended.
1809	7	6.2.2 Safety and Tolerability Objectives: Although there is a section on Contraceptive Measures in this draft Guidance Document, there is no mention of what should happen if a patient becomes pregnant. Clearly the safety monitoring and reporting applied to patients involved in clinical studies involving non-ATMPs would be used for patients in ATMP clinical studies. However, there have now been cases, particularly in clinical studies investigating the use of GTIMPs in children with inherited eye diseases, who have now grown up, reach adulthood and had children of their own. Therefore, it would be helpful to mention in the draft guideline, what if anything, should be done with this information about patients who after treatment do become pregnant and have children.	Not accepted This is not the scope of this GL, and is not ATMP specific.
1812-1815	15	**Proposed change** (if any): The ATIMP dose to be administered is either derived from non-clinical studies with the product, suggesting safe use in humans, or from data of related products, when justified to be relevant. The use of literature data as a reference is expected to be ~~more difficult~~less adequate in cases where the product has been extensively	Partially accepted First addition included in the text

		manipulated, or where a product additionally contains a non-cellular component which may pose additional safety concerns.	
1817-1819	15	**Comment**: Since the following text rather in 6.2.2. addresses considerations regarding B/R, a separate heading may be included or the current heading 'Safety and tolerability objectives' may be amended. **Proposed change** (if any): Factors to consider in the risks assessment of ATIMPs are related especially to the mode of action, the nature of the target, the method and route of administration, the study population, previous experience in humans with the product or the same class of products, if any, and/or the relevance of animal models (see also section 6.1.1).	Accepted
1822	15	**Proposed change** (if any): blood coagulation system) and ~~;~~ when insufficient knowledge on	Accepted
1826	15	**Proposed change** (if any): or the use of immunosuppressive therapy, shall be evaluated and ~~used~~ considered ~~to~~ when justifying the clinical studies	Accepted
1832-1834	15	**Comment**: Changes are aiming to clarify that non-clinical studies being not relevant should not be conducted and, if still performed, have not to be considered for safety evaluation. **Proposed change** (if any): All safety issues arising from the non-clinical development should be addressed in the design of exploratory trials. As non-clinical studies conducted are regarded relevant for the ATIMP, ~~especially~~ this also applies in the absence of an animal model of the treated disease or in the presence of physiologic differences limiting the predictive value of homologous animal model.	Partly accepted; the wording of the second part of sentence have been reworded to clarify concept
1835	15	**Proposed change** (if any): Particular attention should be paid to those biological processes (potentially) including immune response, infections,	Not accepted The sentence has been reworded to clarify its meaning
1842-1846	10	How and in which format is this to be presented in the IMPD/CTA? How and by whom will this data be assessed, by CA or NB?	Not accepted

		If by NB how will this work in the CTA procedure. Would be helpful to include reference to EMA Guideline on the quality requirements for drug-device combinations, EMA/CHMP/QWP/BWP/259165/2019. **Proposed change**: Special consideration should be taken in the design of the clinical study and risk evaluation when medical devices are used for the delivery or implantation of a ATIMP. Information regarding the safety and compatibility of the delivery system should be provided. This information is in general derived from quality and non-clinical studies that have been designed to assess performance of the delivery system. *For more information, see EMA Guideline on the quality requirements for drug-device combinations, EMA/CHMP/QWP/BWP/259165/2019.*	If CE marked device, only the interaction with the ATMP/compatibility - quality If not CE marked, then under the MDR, there needs to be in parallel clinical investigation Reference to CTR cover letter requirements Safety of use of device to addressed in the clinical section; cross reference to where safety and compatibility data are described. If not CE marketed for the intended purpose, MDR requirement apply in full.
1847-1875	1, 6, 8	**Comment:** If the investigational ATMP is intended to treat a serious and unmet medical need, there could be ethical issues in administering a dose that is known to be sub-optimal or unsafe, if a second administration is not possible due to e.g. immunogenicity. Thus, an absence of proper dose finding may be possible, if justified.	First part not understood: if dose is known to be unsafe/suboptimal, should not administered to patients. Partly acceptable: if dose finding not feasible, then absence can be accepted on basis of justification.
1848	3, 5	**Comment**: "A rationale for the selected starting dose, dose escalation scheme and dosing schedule is required in the trial protocol." Is not considered that a dose escalation scheme is necessarily required. Traditional dose escalation studies may not be appropriate for cellular therapy, but could be considered. **Proposed change** (if any): Article II. A rationale for the selected starting dose, ~~dose escalation scheme~~ and dosing schedule is required in the trial protocol."	Accepted, sentenced reworded to make the dose escalation scheme non-obligatory ('when applicable')
1853	15	**Proposed change** (if any):	Accepted
1856	3, 5	**Comment**: "The assessment of a safe and minimal effective dose should be followed by further dose exploration." Please change "Should" as in	Accepted

		required to "may" as in optional since dose exploration is not optional in all cases. **Proposed change** (if any): The assessment of a safe and minimal effective dose ~~should~~ may be followed by further dose exploration	
1856	17	**Comment**: Suggest to replace 'effective' **Proposed change** (if any): The assessment of a safe and minimal ~~effective~~ *pharmacologically active* dose should be followed by further dose exploration.	Not accepted. Text clarified: change to "minimal biological effective dose"
1858-1860	2	**Comment:** Suggest clarification on how measurements for GTMP's should be taken for clinical pharmacokinetics and biodistribution in support of dose selection when there is no therapeutic protein available in systemic circulation. **Proposed change (if any):** Although preclinical and toxicology data are useful to assist in a safe starting dose for GTMP's, FIH studies may be useful to evaluate dose selection if tissue biopsy can be performed, along with PD response data.	Partially accepted: reference to PD marker included, as well as first part of proposed sentence (ref to FIH for dose selection)
1862-1865	5	**Comment**: It is suggested that consideration be given to the totality of all the data available, including the clinical data. **Proposed change (if any)**: "The rationale for **starting** dose and schedule is based on the totality of **clinical and** non-clinical data. Differences in engraftment, differentiation, persistence and immunogenicity between animals and humans may limit the predictive value of non-clinical dose-finding studies, as in the case of e.g. genetically modified CD34 positive cells for treatment of severe immune deficiencies."	Partially accepted; addition of 'starting' not agreed, as not correct if no further dose escalation studies taking place
1866	15	**Comment**: Is autologous vs allogeneic really regarded to impact on the dose selection? **Proposed change** (if any):	Not accepted: more cautious dosing/schedule for allogeneic setting

		…), transduction/editing efficiency, number of transduced cells versus non-transduced cells,	Reference to transduction efficacy removed from the text (not relevant for dose selection, this is based on the number of transduced/edited cells rather); 'edited' added after 'transduced' in the rest of the sentence.
1869-1875	15	**Proposed change** (if any): In case the approach has parallelisms to HCT and a concomitant preceding conditioning regimen is required , the initial dosing can be derived from haematopoietic transplantation, taking into account the necessity to apply a minimum dose of CD34 positive cells required to ensure engraftment, and to avoid prolonged bone marrow suppression.	Accepted, reworded 'in case of product containing gene modified CD34+ cells where a concomitant …
1876	5	**Comment**: Suggestion to add sub section to the 6.2.4. Staggered enrolment section on the following: **Proposed change (if any)**: to discuss that when in FIH includes adults and paediatric patient a more cautious approach should be considered and what might be the recommendations	Not accepted. This is covered in section 6.2.1 trial population
1877-1878	15	**Proposed change** (if any): In FIH studies ~~the~~ starting with a parallel treatment of several patients of a dosing cohort may only be foreseen when justified based on a thorough risk assessment; in principle a staggered enrolment is preferable, at least for the first patients. Similarly, or escalating the dose should be done after ~~without assessing~~ having assessed acute and delayed adverse events in previously treated patients ~~may~~ in order to put study subjects not at risk.	Accepted
1879	1	**Comment:** Is it clear that "FIH" is the first time a product is given to any human, and not the first time a product is used in a specific patient population? Also, for MSCs, available data from the use of these cell types in other trials should allow for a less cautious approach to the FIH trial.	Not accepted. FIH is the first use in human in any indication, or in healthy subjects Second part addressed in risk assessment
1890	15	**Proposed change (if any):** ~~Classical~~ Conventional pharmacokinetic assessment of absorption, distribution, metabolism and excretion (ADME) may not be possible or relevant for some types of ATIMPs.	Accepted

1895	1, 6	**Comment:** It is questioned whether tumourigenicity and immunogenicity belong to the pharmacokinetic assessment. It is recommended to align with the guideline on gene therapy.	Partially accepted. Agreed to remove tumourigenicity Immunogenicity data submitted in PK package.
1897	5	**Comment**: Can you specify which ATMPs would require classical pharmacokinetic assessment? Would this assessment also apply to the vector itself (whether viral or non-viral) administered in vivo?	Not accepted For the vector, immune response, BD and shedding to be studied Conventional PK on transgene
1897	5	**Comment**: Is there any duration advised for the follow-up of patients treated with integrative vectors (e.g. 15 years?)	For clinical trials, the follow-up period should be agreed on a case-by-case basis with the regulatory agency (see section 6.4)
1900	7	**Comment**: The P264harmacodynamics objectives section (6.2.6) describes a PD biomarker but does not offer further guidance on qualification. **Proposed change**: Please provide further guidance on the level of assay verification/validation considered appropriate for the data to be included in a submission (and/or cross refer to other guidelines)	Not accepted: Not ATMP specific - CTR requires validation of assays for primary/secondary endpoint The guideline recommends that bioanalytical assays should be appropriate for the intended purpose. Validation depends on the stage of clinical development.
1909-1912	15	**Proposed change** (if any): In case of an investigational tissue engineered product where the intended use is to restore/replace cell/tissues, ideally with an expected lifelong functionality, structural/histological assays may be potential pharmacodynamic markers.	Not accepted, this part of the sentence is removed from the GL
6.3 Confirmatory clinical trials			
1915	2	**Comment:** As per the general comment from ATEL, the following statement is prohibitively rigid and doesn't account for the likely lack of experience of ATMPs and the probability that the disease area, or sub-group of the disease area, may have little or no therapeutic area guidance. Proposed change (if any): Confirmatory studies for ATMPs should be in accordance to the principles of existing general clinical guidelines. If specific	Partially accepted: proposed sentence has been reworded: In situations where specific therapeutics area guidance does not exist or is not relevant for ATMPs, advice should be sought from regulatory agencies

		therapeutic area guidance exists it should be followed, however, it is recognised there may be situations where specific therapeutics area guidance might not exist and in this situation advice should be sought from regulatory agencies.	
1915	7	Minor grammatical suggestion Proposed change: from "Confirmatory studies should be in accordance to the existing general guidelines" to "Confirmatory studies should be in accordance **with** the existing general guidelines"	Accepted
1918	2	**Comment:** As per the general comment from ATEL, the focus on only very traditional design concepts, for example large controlled randomised blinded studies doesn't reflect ATMP or the rare disease paradigm. For rare disease the use of a control group can be prohibitive and unethical. Suggest include reference to this disease process Proposed change (if any): The main points to address in the designs are: choice of target population, primary and secondary endpoints, study duration, sample size estimation, statistical design and, if applicable, choice of control group and blinding.	Accepted
1918-1920	1	**Comment:** Is the wording "*statistical design*" used to capture both an adaptative design and the statistical methods? More details on requirements for the adaptive designs or a reference would be appreciated. Otherwise, consider "*statistical methods*" instead.	Accepted; change to statistical methods
1923-1925	9	Comment: There are specific considerations in late phase trials. Referring to above logistical challenges, it might not be possible to conduct randomized controlled trials vs other cell therapy products (i.e. issues such as centers that might not be able to access the comparator and /or might not be qualified for the comparator product; production constraints for comparator products). Additionally double blind trials vs. Standard of Care arms or other cell therapy products are never possible.	Accepted, comment addressed in revised text

1924	1, 6	**Comment:** It is proposed to replace "*eliminate*" by "*minimize*" which is more pragmatic. **Proposed change:** *"… as they ~~eliminate~~ minimize confounding baseline variables,…"*	Accepted
1930	15	**Comment**: to be added **Proposed change** (if any): For some indications a comparator treatment may not be available/accessible or it may be unethical to conduct a trial using placebo as a comparator	Accepted, Paragraph reworded
1930-1934	1	**Comment:** Please consider mentioning the possibility of using real world data for comparative purposes in trials of ATMPs, especially when rare conditions are involved.	Non accepted: This is addressed in the following statement: '….historic/prospective controls or data from a disease registry are used'
1930-1934	5	**Comment**: A number of gene therapies are currently under investigation in retinal disorders. Options regarding other comparator methodologies should be mentioned e.g. contra-lateral eye. **Proposed change (if any)**: Using **alternative comparators (e.g. ~~a~~ sham procedure or contralateral eye in certain inherited retinal disorders) may also be considered** ~~as a comparator~~, dependent upon **a number of factors such as** the additional risks posed to the patient **and nature of the condition** under investigation.	Partially accepted (no specific reference to contralateral eye treatment).
1930-1934	11	**Comment**: It was anticipated that the guidelines will discuss the use of historical data in case of the absence of suitable comparator. What are the needed characteristics of the historical data? Moreover, what is the suitable analytical methods to be used (e.g. matched adjusted indirect comparison or network meta-analysis)? In addition, this affects the choice of the effect size and the endpoints of the trial which correlate with the fact that, as mentioned in the guidelines, Phase I/II is a preferred methodology for human testing when it comes to ATMPs. This means choosing a suitable comparator at an early stage of development might be helpful.	Not accepted. This is not ATMP specific; See Guideline on registry-based studies and RP on single arm trials

		Proposed change: It will be helpful if the agency elaborates on the choice of historical comparators and the related points regarding the statistical choice and design of the clinical trial.	
1932	7	Minor grammatical suggestion **Proposed change**: from "…including a justification on the validity of the registry data…" to "…including a justification **for** the validity of the registry data…"	Accepted
1936-1938	15	**Proposed change** (if any): The trial design ~~should~~ may include instructions to reduce potential bias by partial blinding ~~ensure blinding of the trial~~ when appropriate and feasible e.g. where the person involved at the clinical site in the preparation of the ATIMP cannot be blinded, but the health care professional administering the product is blinded.	Accepted - Comment addressed in added sentence
1942-1955	1	**Comment:** Section 6.3.2. on Efficacy: Thoughts/advice on how to deal with missing data would be appreciated. Guidance or a reference for Estimands would be appreciated.	Accepted - Reference to ICH E9 rev.1 (Addendum Estimands) added
1943-1951	13	**Comment**: The endpoints should also capture frequency, duration and nature of side effects, persistence in humans and immunogenicity; there is a need for long-term efficacy and safety follow-up, for instance in the case of cell therapy, based on prolonged biological activity and/or persistence of cells	Not accepted - General principle: you capture all these aspects in confirmatory trial; this heading is only addressing the clinical efficacy aspects.
1945	7, 17	**Comment**: The abbreviation "TEP" (tissue engineered product?) is used for the first time without previously been written in full or listed in the abbreviations **Proposed change**: write TEP in full the first time and include in abbreviations	Accepted
1949	7	**Comment**: The following requirement could be problematic for ultra-orphan diseases such as rare inherited metabolic disorders (e.g. metachromatic leukodystrophy): "As for any conventional medicinal product, any non-validated endpoint or surrogate endpoint, such as	Partially accepted: Non-validated assays are not possible, however the sentence amended to allow validation as part of the clinical development programme

		novel biomarkers, would have to be validated in a prospective study before being used in confirmatory clinical trials" However, there are many ways in which a biomarker endpoint might be justified. For example, the validity of the marker as an indicator of a potential clinical response might be qualified using retrospective analysis of an untreated population. In a clinical trial incorporating both a clinical outcome and the marker of interest, linkage between the change in the marker and the clinical outcome within the same trial should then be suitable to qualify subsequent use of the biomarker as a surrogate marker in future studies/for early identification of response in post marketing use. It is proposed that applicants be warned that the relevance of any outcome measure proposed will need to be justified. **Proposed change**: Suggest amendment to: The use of non-validated endpoints or surrogate endpoint, such as novel biomarkers, should be justified. Where appropriate the GUIDELINE ON CLINICAL TRIALS IN SMALL POPULATIONS CHMP/EWP/83561/2005 should be followed.	
1949-1951	6, 8	**Comment:** if not formally validated, can they be used as supportive evidence, if scientifically justified?	Accepted
1952-1955	15	**Proposed change (if any):** Sometimes, the ~~desired~~ relevant clinical endpoint, such as prevention of arthrosis, can be observed only after a long follow-up. In such cases, (additional) justified surrogate endpoints might be included in the trial to support ~~a later marketing authorisation~~efficacy and a plan for long-term follow up should be provided. If the long-term-efficacy is dependent on the long-term persistence of the product, a long-term follow-up plan of the patients also should be provided.	Not accepted, already addressed in previous paragraph
1952-1954	17	**Comment**: It is expected that the use of surrogate endpoints can enable an earlier (rather than later) marketing authorisation, if needed conditional upon the long-term clinical endpoint. **Proposed change** (if any): In such cases, additional surrogate endpoints might be included in the trial to support *an initial* ~~a later~~	Not accepted, sentence rephrased to capture the need for short term clinical efficacy data together with surrogate endpoint data for initial MA.

		marketing authorisation application*, to be supplemented with data on the clinical endpoint, once available.*	
1955	7	Minor grammatical suggestion **Proposed change**: from "a long-term follow-up plan of the patients should be provided" to "a long-term follow-up plan **for** the patients should be provided" or "**a plan should be provided to follow up patients long-term**"	First proposal accepted
1957	7	**Comment**: This sentence seems to be circular. **Proposed change**: Suggest changing to "Risks should be monitored during the confirmatory clinical trials to allow continued refinement of risk prevention and minimization measures."	See below
1957-1960	15	**Comment**: Current text may have too much emphasis on MAA aspects **Proposed change** (if any): The detection and collection of ~~of the risks~~ adverse reactions should continue during confirmatory phase clinical trials in order to generate an adequate safety profile of the ATIMP and to identify appropriate risk mitigation measures. ~~prevent and/or minimise the risks.~~ The information regarding the important detected ~~(important~~ and potential~~)~~ risks should be contained in both IB and protocol (ICH E6(R2)) and may impact the Reference safety Information. ~~contained in the Development Safety Update Reports could provide the basis for the Risk Management Plan (see ICH E2F on development safety update report).~~	Agree rewording; Add following: This information will form the basis of the RMP at the time of the MAA
1958-1960	2	**Comment:** Suggest clarification on how safety data is collected and then if certain aspects of the current RMP are required for GTIMPs and or ATIMPs given that AEs will not be observed in clinical trials in the traditional sense, especially for one off ATMP treatments. ~~**Comment:** Suggest clarification on how measurements for GTMP's should be taken for clinical pharmacokinetics and biodistribution in~~	Comment not clear; addressed in paragraph below in 6.3 and in 6.4 Second part relates to lines 1856-1860

		~~support of dose selection when there is no therapeutic protein available in systemic circulation.~~ **~~Proposed change (if any):~~** ~~Although preclinical and toxicology data are useful to assist in a safe starting dose for GTMP's, FIH studies may be useful to evaluate dose selection if tissue biopsy can be performed, along with PD response data.~~	
6.4. Long term efficacy and safety follow-up			
1969-1970	1, 6	**Comment:** Following changes are proposed in this sentence: **Proposed change:** "*Long term efficacy and safety follow-up and long term monitoring of patients treated with an ~~ATIMP~~ investigational ATMP needs to take into account the nature of the ~~ATIMP~~ investigational ATMP, ~~and~~ its persistence and life expectancy if relevant for the disease treated*".	accepted
1969	7	Minor grammatical suggestion **Proposed change**: from "Long term efficacy and safety follow-up and long-term monitoring of patients treated with an ATIMP **needs** to take into account…" to "Long-term efficacy and safety follow-up and long-term monitoring of patients treated with an ATIMP **need** to take into account…"	Accepted
1969-1970	13	**Comments:** It is desired to incorporate the QoL and PRO measurements in the endpoints in order to provide regulators with crucial data for decision making, in addition to positioning and HTA assessment. It is important to include this in trials.	Comments noted, however the GL is not describing the specific endpoints to be studied for clinical trial or for long term FU.
1973-1974	15	**Proposed change** (if any): The need for, the duration and the type of primary follow-up including the essential parameters to be monitored should be described in the clinical trial protocol.	Primary FU: this is not clear (not defined anywhere) The clinical study protocol will mention what the monitored
1975-1976	5	**Comment**: Additional guidance regarding the duration of long-term follow-up should be incorporated into the guidance. In particular, this should be based on a risk-based approach recognising that different GTIMP vectors are associated with different risks (e.g. integrating vs. non-integrating vectors).	Reference to RBA included, referring to type of product (without going into detail of integration/non-intergrating), paragraph merged with first paragraph

1979-1981	15	**Proposed change** (if any): This is of specific importance when the ATIMP is intended to provide life-long persistence of biological activity and treatment effects. Similar considerations apply when ~~but also because some~~ ATIMPs have high potential for immunogenicity or relatively invasive procedures are needed to administer them.	agreed
1982	7	Things other than cells, vector or virus may persist. **Proposed change**: Suggest changing text to "ATMP persistence is assessed by looking for evidence of the presence of cells, vector, virus, DNA, proteins or other products…"	agreed
1985	7	Minor grammatical suggestion **Proposed change**: from "Follow-up of patients should be more intensive in first two years after treatment" to "Follow-up of patients should be more intensive in **the** first two years after treatment"	Accepted.
1985-1987	1, 6	**Comment:** What is the rationale for proposing a compulsory 2 year follow-up for iATMPs? Additionally, long term follow-up requirements are not defined or specified. This should be added or additional guidance referenced.	Text changed, bracket of 1-3 year proposed The text has been amended to make reference also to the patient follow-up after the initial 1-3 year follow-up
1985-1987	2	**Comment:** We are concerned that the following sentence and in particular the 2 years of intensive follow-up is not sufficiently supported with evidence. Why 2 years and based on what examples? There may be diseases that require either shorter or longer follow-up depending on the course of the disease. Follow-up of patients should be more intensive in first two years after treatment and for CBIMP and GTIMP with increased risk of late onset of adverse reactions (e.g. tumourigenicity) this follow-up period should be extended. **Proposed change (if any):** Follow-up of patients is expected to be more intensive in the first one to three years after treatment and for CBIMP and GTIMP with increased risk of late onset of adverse reactions (e.g. tumourigenicity) this follow-up period should be	Accepted

		extended. Generally the follow-up period should be agreed on a case by case basis with the regulatory agency. **Comment:** Suggest clarification of the role of vector shedding in the elimination phase. Proposed change: Provide discussion of vector shedding assessments in saliva, urine, and stool collections, assay by qPCR and endpoint assessment.	Second part does not related to these lines.
1987	11	Comment: According to the "Guideline on safety and efficacy follow-up and risk management of advanced therapy medicinal products", for gene therapy medicinal products using integrating vectors or have the potential for latency followed by reactivation, it is usually expected to follow the patients up to 15 years. Proposed change (if any): To add: "For gene therapy medicinal products using integrating vectors or have the potential for latency followed by reactivation, it is usually expected to follow the patients up to 15 years."	Not accepted: this GL is for clinical trials, duration of FU to be agreed with NCAs.