Comments on European Commission Consultation Document
'Good Clinical Practices for Advanced Therapy Medicinal Products'
Issued 01-Aug-2018
Ref. https://ec.europa.eu/health/sites/health/files/files/advtherapies/2018_gcp_atmp_en.pdf

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This document constitutes the joint EBE/EFPIA response document to the European Commission targeted stakeholder consultation on the draft Guidelines on '*Good Clinical Practice for Advanced Therapy Medicinal Products*'.

EBE (European Biopharmaceutical Entreprises) operates as a specialised group within the European Federation of Pharmaceutical Industries and Associations (EFPIA). EBE is the European trade association that represents biopharmaceutical companies of all sizes operating in Europe.

EFPIA (the European Federation of Pharmaceutical Industries and Associations) represents the pharmaceutical industry operating in Europe. Through its direct membership of 33 national associations and 40 leading pharmaceutical companies, EFPIA is the voice on the EU scene of 1,900 companies committed to researching, developing and bringing to patients, new medicines that will improve health and the quality of life around the world.

Both trade associations are registered in the transparency register of the European Commission :

- EBE Register ID number : 768792210017-73
- EFPIA Register ID Number: 38526121292-88

General comment(s) if any :

The document provides useful guidance in identifying specific challenges encountered with the development of ATMPs and recognises the need for a flexible and pragmatic approach with respect to GCP standards relative to development of these products, which is a welcome step.

Further clarification throughout the document with illustrative examples is welcome.

A suggestion is made to add a reference to Paediatric Investigation Plan (PIP) where the age categories, clinical benefit justification of the treatment and paediatric formulation are discussed and agreed with PDCO.

Compared to prior guidance **(Detailed guidelines on good clinical practice specific to advanced therapy medicinal products,** March 2009), there are several changes in the content of the draft guideline:

1) Prior guidance included a definitions section. *This section is removed in draft guideline.*
2) Prior guidance contained a much more detailed traceability section (Section 6) and a 4-pages Annex spelling out the responsibilities for multiple parties. *The current draft guidance shortens the traceability section, eliminates the traceability annex and refers to the GMP for ATMP guidance (see page 35 for sponsor requirements).*
3) Prior guidance included an essential documents section (Section 15) which describes documents that should be available in the investigator and sponsor files. *This section is missing from the new guidance.*

The previous traceability annex was helpful as it called out the responsibilities of multiple parties (not just the sponsor). Also, if there are ATMP specific essential documents (for example, flow chart of logistics of therapy), which are not outlined in ICH E6 R2 (Section 8.0), it would be helpful for those to be listed in this guidance.

With respect to the scope of the draft guideline, there is overlap with the IMP draft guidance.

Several sections (see below) which appear to relate to the handling of IMPs, might more appropriately be included in the recent draft guidance on handling of IMPs:

- Section 3.2 – Reconstitution
- Section 4.0 – Storage, transport, handling
- Section 7.0 – Retention of Samples
- Section 8.3 - Administration of out of specification products. We recommend to harmonise with the Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products, adopted by the European Commission on 22 November 2017

Reference to IMP draft guideline:

" Draft Guideline on the responsibilities of the sponsor with regard to handling and shipping of investigational medicinal products for human use in accordance with Good Clinical Practice and Good Manufacturing Practice, April 2018"

Requirements or recommendations in relation to ethics committees (EC) are missing in the document. EC review and approval are important parts of clinical trial process, especially in the area of ATMPs. It is recommended to include EC review and approval process and the need to take necessary expertise into considerations for a holistic assessment, including consultation with ATMP-expert(s).

Specific text comments

# section	Line no.	Comment / Rationale	Proposed change / suggested text
1.1	67	Add proposed text, for more clarity	add "including gene therapies, somatic cell therapies, and tissue engineered products" (source EC action plan)
1.2	69	Currently there is only a description of ATMPs as "complex and innovative" but this is not helpful in defining the scope for the reader.	We recommend adding the ATMP definition, e.g., "as defined by Article 2 of Regulation (EC) No. 1394/2007.
1.2	70-71	Suggestion to add underlined/italicized text	For example, manufacturing constraints *and consistency of the production condition in manufacturing process;* the short shelf-life *and shedding effect*
1.2	75-76	Suggestion to add underlined/italicized text	Moreover, it is recognised that it may not always be feasible *due to lack of relevant animal model(s)* to generate preclinical data before the product is tested in humans.
1.2	81	Suggestion to add underlined/italicized text	traceability requirements for ATMPs that contain cells or tissues of human origin, *might impact the design and the duration of the long term* follow up studies
2	85-87	Suggestion to add underlined/italicized text	*The design and duration* of the clinical trials with ATMPs should take into account the specific characteristics *and nature* of these medicinal products, as well as the potential risks to subjects, offspring, close contacts, investigator's team and others *by applying a risk-based approach*.
2	95-105	In the recently published ICH E11-R1 (Section 4. AGE CLASSIFICATION AND PEDIATRIC SUBGROUPS, INCLUDING NEONATES), care is taken to note that " *... arbitrary division of pediatric subgroups by chronological age for some conditions may have no scientific basis and could unnecessarily delay development of medicines for children by limiting the population for study*." This Consultation Document utilizes language that is	"When the clinical trial subjects involve a paediatric population or foetuses (in utero treatment), consideration should be given to the implementation of additional safeguards, which should be adapted to the specific characteristics of the product, the treated disease **and the disease state in the targeted population, as well as** the developmental stage of the population. Thus, in some cases, it may be advisable to stagger trials by age i.e. first enrolling subjects between 18 and 12 years, then between 12 and 6 etc. **Depending on factors such as the condition, the treatment, and**

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		implying the same. However, the Consultation Document could convey the same intended message by placing the recommendation in a more positive manner that better fosters (rather than limits) earlier paediatric inclusion in drug development, when appropriate.	**the study design (i.e. overall benefit/risk assessment), it may be justifiable to include paediatric patients in adult studies, or initiate trials in younger children** ~~However, in some other cases~~ (e.g. severe genetic diseases **or life threatening conditions**)~~, treatment of the subject at a very young age may be necessary~~ without a staggered approach. Prior studies in adults should have been performed if ~~feasible~~ **appropriate** for the condition in question, or else a rationale should explain why these are unethical, not feasible or not relevant (e.g. in cases of diseases exclusively affecting paediatric patients)."
2	106-107	Suggestion to add underlined/italicized text	The relation of the anticipated benefits to the *potential* risks of the ATMP should be at least as favourable *versus existing conventional treatments including consideration of medical need*
2	111-114	The cited example of the use of an intra-subject control arm in ophthalmology studies of ATMPs, is in conflict with the recommendation issued by FDA that the contralateral eye should not be used as a control. [Human Gene Therapy for Retinal Disorders, draft Guidance for Industry, July 2018; see rows 191-204]. A cautionary statement is recommended.	For some ATMPs an intra-subject control might be appropriate, **where randomized controlled clinical trials are not feasible**.For example, the investigational product could be injected into one eye and the untreated eye is used as a control, **should both eyes be at the same stage of disease at trial entry. Also it should be considered that the disease progression in both eyes is not necessarily similar over the duration of the trial. When these factors have been considered and if deemed appropriate, such intra-subject control may allow comparison of local effects without inter-subject variation.** **Selection of suitable control groups should be based on established guideline and knowledge on the nature of the ATMP, on a case-by-case basis with robust justification.**
2(iii)	115-117	**Clinical Trial Design** With regard to double-blinding, this may be impractical for ethical and/or feasibility considerations. It is proposed that this is explicitly stated in the guidance.	While comparison to standard of care or no treatment sometimes makes double-blinding not feasible **nor ethical** for investigators/for the surgical investigator team, blinding for subjects should take place where feasible **and ethical**.
2	127-129	"In early phase trials where it is not possible to re-administer the product (e.g. gene therapy) or when the	This is an important and general statement. Concrete example(s) will be helpful to understand this general guidance.

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		re-administration involves the additional risk of a surgical procedure, the exploratory dose chosen should aim to be a therapeutic dose for the subject." Suggestion to add underlined/italicized text within the parenthesis.	Alternatively, the sentence should reflect the need to balance the safety risk, since therapeutic aim might not always be considered safe. (*e.g.* gene therapy, *early considerations of most appropriated vector (sero)type and the need for immune suppression of patients*).
2	135	Challenges in recruiting investigator sites that are equipped/experienced and able to recruit adequate cohort size are well-known. Considerations should be made about extending site feasibility assessment to sites that have the potential to be equipped and trained, to prevent bias in recruiting in general a limited population in a few countries.	
2	136	Addition of a section highlighting the importance of training the monitors on the product specific requirements would be welcome (e.g. on specific adverse events of ATMPs).	
3.1	150	Consider including I/E criteria for study enrollment / IMP administration as patient condition could have changed after initial enrollment and cell collection. Enrollment could be limited to subject who will likely be able to later receive IMP. This would be in line with the FDA guidance "Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products" page 19: *"[...] the subject's condition may have deteriorated so that the subject is no longer expected to tolerate the study procedures or survive for the study duration.* *To adjust for the possibility of a change in the subject's condition, the enrollment criteria may need to include selection for factors that would improve the likelihood*	

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		that the recipient would still be suitable for product administration when the manufacturing process is complete. Alternatively, the trial might include separate criteria that need to be met at the time of product administration."	
3.1.(i)	151-154	Please clarify the level of information on 'release specifications' to be included in the protocol. Detailed information on 'release specifications' should be provided in the investigational medicinal product dossier (IMPD). Information required in the protocol should be limited to a discussion on the potential variability due to the nature of the ATMP.	Suggest rewording: *Release specifications*: The variability in the nature of the ATMPs (in particular in the case of autologous products or allogeneic products in a matched donor scenario), should be duly considered when defining the release specifications (e.g. cell numbers / range of cell number, transduction efficiency) **in the investigational medicinal product dossier. A discussion on the potential variability can be included in the protocol with reference to the document where details about the investigational product quality can be found, e.g. IMPD.**
3	155-166	Consider adding information on re-dosing	
3.1, 3.2 and 5	173-179; 255-260 and 296-310	The three (sub-)section (3.1, 3.2 and 5), are all titled "administration procedure" and address this topic from a slightly different angle, though conveying a similar main general message about the need for clearly explaining the administration procedure to investigators in particular where it involves some complexity and inherent risk of errors. While the recommendations included in those three section are generally reasonable, there might be a benefit in consolidating the recommendation under a single header and if needed make a simple cross-reference between sections of the document to avoid repetition to the extent possible. Generally, it is suggested to give more flexibility for a case by case assessment to balance information across the protocol and separate documents that are available for the site appropriately. The protocol section "lines	Consider to consolidate guidance on "administration procedure" [...] The description of the administration process should be sufficiently detailed. The level of documentation should be adapted to the complexity and the novelty of the procedure. **The detailed instructions for administration should be described in the protocol or in a separate document available at the site (e.g. handing instructions), in which case a reference to such separate documents should be provided in the protocol.**

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		173-179" should therefore be more open for the possibility to include this information in the protocol or in a separate document available at the site.	
3.1	Line 174	Considerations should be made in regards to surgical procedures that might/might not be part of standard of care in different countries. Reference should be made to international clinical guidelines in such cases.	
8.1	180-181	Section 3.1 Specific considerations concerning the protocol (v) Safety conduct: In practice, detailed information on product handling (including containment and disposal) is normally presented in a separate document (for example, an Investigational Product Preparation Instructions) available at the sites.	Recommend revising this section as follows: (v) *Safety conduct*: Detailed information should be provided on the product handling, containment and disposal. **If this information is provided in a separate document, the protocol should reference that document.**
3.1 and 3.2	and 272-277	Similar comment is also provided regarding lines 180-181 which addresses "safe conduct of clinical trial" with respect to ensuring the provision of information on handling, containment and disposal under protocol and IB. It would be useful to consolidate and clarify the recommendation with respect to expected level of information/detail for those two documents.	Consider to consolidate guidance and/or cross-refer one section to the other, while removing any redundancy.

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	182-186 and 265-271	➢ Each of the above sections refers to risk minimization measures and different language is used to describe measures that should be taken. Clarity is needed whether this information is needed in both the protocol and IB, or in one of these documents only. In addition, the measures to be taken should be clearly described. It would be helpful to represent each circumstance that can be conceived as separate items with the recommended risk-minisation measures provided, where possible.	Recommend modifying this section as follows: (vi) *Risk-minimisation measures*: Where appropriate, information should be provided on the measures that should be put in place to protect clinical trial subjects from identified risks. ~~For example, if the results of the sterility test of the product are not available at release, appropriate mitigation measures should be implemented, including liaison with clinical staff where out of specification test results are obtained after the release of the product.~~ **Known examples include:** **-Sterility: If the results of the sterility test of the product are not available at release, appropriate mitigation measures should be described** **-Out of Specification Test Results (see Section 8.3)**
3.1	187-191	"Definition of end of the trial: The definition of "end of the trial" should be clear and unambiguous. Due to the novelty and scientific uncertainties that exist in connection with ATMPs, there may be a need for subjects to be on long-term follow-up after treatment. In these cases, it becomes especially important to define clearly the event that marks the end of the trial and to explain how follow-up activities will be performed after the end of the trial (e.g. via an interventional study, non-interventional study, registry)." This is a bit of a conundrum, maybe it is not the end of the trial that is most important (if they are very long), but more when critical readouts are available, e.g. what and when defines the primary and secondary endpoints.	Suggest to clarify what is meant by "end of trial" and follow-up after end of trial (e.g. via an interventional study, non-interventional study, ***an open label follow-up study***, registry, etc.) in the text.

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3.1	193-200	Follow up of subject is covered in further detail under section 8.2 although with different perspective. To the extent feasible the discussion should be aligned and consolidated, with possible cross-referencing as applicable.	Consider to consolidate guidance and/or cross-refer one section to the other
3	195-197	Suggestion to add underlined/italicized text	The follow up strategy should be based on a risk-assessment having regard to all information available to the sponsor *in line with the current Guidance and knowledge on the nature of the ATMP*
3.1.	197-198	Regarding the duration of the follow-up and the example given for gene therapy for integrating vector, current expectations may evolve as we gain cumulative experience and knowledge. Integrating vector technology has advanced significantly in recent years to improve safety. Rather than a standard approach of 15 years follow-up for gene therapy medicinal products using integrating vectors or having the potential for latency followed by reactivation, duration of follow-up should be based on the specific construct and characteristics of the product. The scientific justification for the expectation of 15 years follow-up this should be included if this is expected.This would help alignment with the recently issued FDA draft guidance on Long Term Follow-Up After Administration of Human Gene Therapy Products, July 2018.	Suggested rewording: "The follow up strategy should be based on a risk assessment having regard to all the information available to the sponsor. This strategy may need to go beyond the end of the trial. For example, in the case of gene therapy medicinal products using integrating vectors, a follow-up of **up to** 15 years after administration ~~is~~ **may be** expected; **however, a shorter duration of follow-up may be considered based on the specifics of the construct and characteristics of the product**."
3.1	After 200	Please consider the addition of a section on the need of retention of biological samples collected during the study (e.g. subject blood samples to follow ATMP safety).	
3	209	Suggestion to add underlined/italicized text	*risk evaluation when medical devices are used as example for gene therapy delivery or implant.*

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3	211	Suggestion to add underlined/italicized text	*Shedding studies should be considered. Provide risk of transmission to third parties with the environmental risk assessment, unless otherwise justified*
3.1	After 211	Addition of a section concerning the instructions to ensure blinding of the trial where needed as section 13-d (protocol) in the Detailed guidelines on GCP specific to ATMP (Brussels, 03/12/2009) would be welcome.	Proposal to add after line 211 «**(xi) Detailed instructions to ensure blinding of the trial where needed (e.g. where the person responsible for randomization of the subjects to treatment has to remain blind or where the person involved at the clinical site in the preparation of the ATMP cannot be blinded whilst the person responsible for the administration of the ATMP needs to be blinded »**.
3	216-217	Suggestion to add underlined/italicized text	Non-clinical studies should be *dependent on nature of ATMP and availability of relevant models, clinical use, targeted clinical population, intended route of administration, and treatment regimen*
3	233	Suggestion to add underlined/italicized text	as tumorigenicity, immunogenicity/immunosuppression, risks related to infection with vectors used in gene therapy medicinal products, *prior infection/vaccination with related viruses* etc
3	234	Updates to IB to include emerging scientific information should be encouraged to extend the knowledge of investigator sites.	
3	262-264	Suggestion to add underlined/italicized text	*Dosing used for biodistribution studies should mimic clinical use with appropriate margins, route of administration and treatment regimen should be representative for clinical use.* *When a classical dose finding is not possible, a minimal effective dose and a maximum tolerable dose may provide useful information on exposure and effect relationship.*
3	265-271	Suggestion to add underlined/italicized text	*In case of an anticipated risk including events with a late*

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			onset (e.g. tumourigenicity): implement measures to detect signal and to mitigate this risk
3.2	278-279	Traceability is addressed as stand alone section 6. In practice, detailed information on traceability (Chain of Identity/Custody) is normally provided in the Investigational Product Preparation Instructions (IPPI) and not the protocol.	Consider to consolidate guidance and/or cross-refer one section to the other. Also recommend the following modification: (viii) *Traceability*: In practice, detailed information should be provided on the measures that should be followed to ensure traceability of the cells/tissues contained in ATMPs. **If this information is provided in a separate document, the protocol should reference that document.**
4	283	Suggestion to add underlined/italicized text	The quality of ATMPs may be highly dependent on the *design, manufacture, characterization, testing,* storage, transport and handling conditions.
5	305-310; 359-360	We believe the role of the sponsor should be advisory and not involve the provision of patient care. Clarification is needed if in case of "*a posteriori* informing" of the subject on the Sponor's presence during the administration procedure the re-consent is required to be signed or not. Typo	Recommend modifying paragraph 3 of Section 5.0 as follows: The presence of the sponsor (or a representative thereof) during the administration of the ATMP to the clinical trial subject is only acceptable if it is duly justified. **The role of the sponsor should be advisory and not involve the provision of patient care**. If the presence of the ~~administration~~ **sponsor during** administration is envisaged before the start of the clinical trial, this should be explained in the informed consent. If, exceptionally, the presence of the sponsor (or a representative thereof) has not been foreseen from the outset of the clinical trial but it is justified for reasons related to the protection of the clinical trial subjects or to detect and prevent errors of administration, the clinical trial subject should be informed *a posteriori*.
6	311	Not clear how traceability from recipient of e.g. a stem	Clarification of traceability for stem cells.

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		cell derived therapy to the egg donor can work - please clarify as it seems not feasible	
6	314-315	In case of remaining product, include that it has to be returned/destroyed as well	Non-administered investigational products should be returned and/or destroyed, **according to procedures based on product handling and environmental risk**, and should be accounted for. **Remaining product after administration should follow same procedure.**
6	318-320	**Traceability** 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.	The traceability system should be bidirectional (from donor to subject and from subject to donor) and data should be kept for **a minimum of** 30 years **after clinical use [reference to** *Directive 2004/23/EC***]** ~~after the expiry date of the product~~, unless a longer time period is required in the clinical trial authorisation.
6	327	Addition of details on the conduct in the event that the clinical trial is suspended or prematurely ended or the product development discontinued as in section 24 of 7.1 "General requirements" of the Detailed guidelines on GCP specific to ATMP (Brussels, 03/12/2009) would be welcome.	"… as well as the location of the traceability records. **In the event that the clinical trial is suspended or prematurely ended or the product development discontinued, the sponsors retains their obligations to ensure that the traceability system is maintained. If the ownership of the ATMP is transferred to another legal entity, the new owner should take responsibilities for maintaining the traceability**. In the case when the sponsor ceases to exist, … »
6	After 333	Addition of an annex to detail traceability records as in the Detailed guidelines on GCP specific ATMP (Brussels, 03/12/2009) would be welcome.	
8.1	350	Section 8.1 outlines specific aspects that should be covered in informed consent forms for ATMP trials. In addition to those mentioned, it should also provide adequate information to patients about any risk associated with the administration procedure and any upstream interventions, as referred to earlier under section 3.1.	

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8.1	355-358	**Informed consent** Where long-term follow up is applicable, the contact details of individuals involved in the conduct of the study may change over time. It is proposed therefore that a system for managing changes in contact details is maintained.	The need for long-term follow-up should be clearly communicated, where applicable, and subject commitment should be sought. **If long-term follow-up is applicable then a system for managing changes to the contact details of those involved in the study should be maintained.** In case the ATMP includes a bacterial or viral vector and thus a potential for "shedding", the risks and precautionary measures should be clearly communicated to the subject ***(*and close contacts of the subject, and/or caregiver)**.
8.2	361, 367-368	It would be helpful in the guidelines to emphasize the obligation of investigators to comply with the requirement of collecting the long-term data when they agree to the original protocol. As long-term data is in general more registry/administrative data collection (often in a separate protocol) our experience is that many sites decline and refuse to participate in the protocols designed to collect any long-term data as this diverts resources from the more "interventional" studies they want to focus on. Follow-up activities prior to and after the end of the trial should be defined in the core protocol. Protocol extension should be used for FU after end of trial.	It is recommended to emphasize the obligation of investigators to comply with the requirement of collecting the long term data when they agree to the original protocol. Studies designed to gather long term data should be appropriately resourced to minimize subjects being lost to follow-up.
8	374-377	Suggestion to add underlined/italicized text	*Clinically meaningful endpoint has to be investigated in long term follow up.*
8.2.2	374-383	Please clarify that arrangements for remote follow-up should only be anticipated prospectively in cross-border situations where a subject travels to another country for treatment and returns to their home country during the follow-up period. Compliance with the national laws of that country	Add: "**The clinical investigators should notify the study sponsor when a patient is moving to another country. This will allow the Sponsor to submit a CTA in the new country, if not already in place**."

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		should be required (generally for long-term follow up, a CTA is sent for information to the competent authorities, no approval is needed). In the case of ATMPs which require long-term follow-up tracking the movement of patients on an ongoing basis from one country to another during the follow-up period can present additional administrative challenges and may raise privacy concerns. The expectations for sponsors as well as investigators in the situation of remote follow-up should be clearly defined. Provisions should be made in Patient information and informed consent to encourage patients to contribute to remote follow-up, since it is in interest of public health.	
8.2.3	385-389	"If a subject stops participation in the trial or does not want to continue administration of the product (repeated dosing), the investigator should identify if the subject wants to withdraw completely from the trial and any follow-up, or if the subject accepts follow-up and the consent for this remains. The subject's decision and the follow-up activities should be appropriately documented." This will not be applicable to many treatments aiming at providing one curative administration. On the contrary if may be considered not to allow subjects to leave a trial after product administration until sufficient follow-up up has been obtained. A sensitive topic that may need further discussion.	Consider discussion on considerations on how to relate to subjects receiving "one time aiming at cure" treatment opting to leave the follow-up program.

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8.2.4	399-400	**Long-term follow-up -** *Patient alert cards* Where patient alert cards are needed, it is suggested that there is a regular review, update and redistribution of the cards (if the advice has changed), which would serve as a regular reminder to subjects and physicians on what to do in an emergency and to facilitate reporting of adverse events.	Alert cards should contain as minimum the name of the subject, an investigator contact number and information regarding the medical treatment received **and be reviewed, updated and redistributed (if the advice has changed) on a regular basis.**
8.3	402-403	Clarify that release specifications should be defined in the IMPD (please see comment on section 3.1)	Suggested rewording: "As explained in Section 3.1, the variability in the nature of the ATMPs should be taken into account when defining the release specification **in the investigational medicinal product dossier**."
8.3	404-413	Clarify that treatment of a patient with an out of specification product made available to a patient and accepted by the investigator in accordance with this guideline does not require prior notification or approval from the national competent authority. This is critical to ensure timely access to potentially life-saving investigational products in populations with an unmet need. Notification as a 'breach of predefined specifications' to be sent to the NCA within 14 days after infusion. Documentation required for notification should be harmonised and could include the investigator's request, the RBA and a CMC rationale supporting administration of the product. Making an out of specification product available to a patient on individual case-by-case basis does not fit the criteria for notification as an urgent safety measure. USMs should be reserved for scenarios where a safety	At the end of line 413 add: " **A patient can be treated with non-conforming product <u>without prior notification or approval</u> from the National Competent Authority of that country. In such cases notification by the sponsor to the relevant compentent authority may be made after administration as a breach of predefined specifications. Notification should include the investigator's request, the sponsor's risk assessment and a rationale supporting administration of the product."**

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		signal was detected and an action had to be taken for the safety of patients and physicians need to be informed accordingly. Specifically, we recommend harmonization with Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products, adopted by the European Commission on 22 November 2017 on this topic.	
9	414	Section 3.1 (x) discusses providing information on viral shedding and precautions when viral based therapies are used. The safety section does not cover any guidance on what data may or may need to be collected on non study subjects in certain cases and how to manage that given the challenges of the data privacy laws.	We recommend providing some guidance on the management and data-collection regarding non-study subjects given the challenges of data-privacy laws.
9	416	Please confirm that adverse event reporting should NOT be done as for combination products- cell based part and device part together. But to be treated separate since it is stated that causality should be done separately.	Clarification needed.
9	432	In large academic sites (e.g. hospitals) and in trials involving surgical procedures), non-trial personnel might have responsibility for patient care and need to be informed about AE/SAE reporting.	(this information might need to be extended to non-study personnel (e.g. in case of surgical procedures where hospital personnel might be in charge of the patient care)
9	433	*"The sponsor should provide information and training ..of adverse events".* It would be helpful if the guideline could further clarify, with some examples, kind of key adverse events to report, duration of reports…	
9	434	*"In cases where long-term follow up of trial subjects is foreseen, aspects related to the reporting of adverse events…".* It would be helpful if the guideline could further clarify, with some examples, kind of key adverse events to report, duration of reports…	

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10	441-446	Suggestion to add underlined/italicized text	*Early developing and validation of patient monitoring methods during clinical development needs to be considered.*
		Please add rows as necessary (with "copy and paste" empty rows)	