European Medicines Agency

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OVERVIEW OF COMMENTS RECEIVED ON DRAFT GUIDELINE ON SAFETY AND EFFICACY FOLLOW-UP – RISK MANAGEMENT OF ADVANCED THERAPY MEDICINAL PRODUCTS

Table 1: Organisations that commented on the draft Guideline as released for consultation

	Name of Organisation or individual	Country
1	Arthro Kinetics Biotechnology GmbH	United Kingdom, EU
2	BioIndustry Association (BIA)	United Kingdom, EU
3	European Biopharmaceuticals Enterprises (EBE)	Belgium, EU
4	German Association of Research-Based Pharmaceutical Companies (VFA)	Germany, EU
5	German Pharmaceutical Industry Association (BPI)	Germany, EU
6	Johnson & Johnson Pharmaceutical Group	Global
7	North-East England Stem Cell Institute (NESCI)	United Kingdom, EU
8	Paul-Ehrlich Institute	Germany, EU
9	Pfizer Inc.	Global
10	TiGenix NV	Belgium, EU

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20)
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

Table 2: Discussion of comments

GENERAL COMMENTS – OVERVIEW AND RESPONSES	
1. EBE **<u>Overarching Guidance</u>** Overall we view this as a reasonable guidance and an appropriately cautious approach to the follow-up of advanced therapies after market approval, with some caveats as expressed below. This guidance presents a rational approach to addressing concerns specific to ATMPs. The list of risks to consider is particularly helpful and comprehensive. Patient protection is the key goal and we agree with the need to have a good post-authorization safety and efficacy follow-up system. We fully agree that the generation of long term data is not a substitute for the need for safety and efficacy data at the time of Marketing Authorization.	*Thank you*
Flexibility will be needed to make decisions on which areas are covered based on the product type (cell, gene or tissue therapy) and characteristics, with an emphasis on scientific basis for these decisions. With this in mind, we recommend that this be considered an overarching guideline and that the development of guidance specific to each product type (Cell, Gene or Tissue) be considered.	*This draft was prepared with the idea of overarching guideline in mind. It will be further emphasized in the introduction.*
EBE is proposing further therapy type specific guidance, and it is further suggested that immunotherapy, if it is to be included under the gene therapy umbrella, should be the subject of a specific guidance. The challenges faced by gene therapy whereby the gene is required to persist in order to deliver benefit are quite different to the transient expression of e.g. some GMO based vaccines. These differences should be reflected in the conduct of follow-up plans.	*It is expected that therapy area specific guidelines will continue to be produced. Follow-up plans as defined by this guideline are considered to be of sufficient flexibility to address the product specific issues.*
While it may be implied, it should be clear that this guideline is applicable to all sponsors (including non-corporate sponsors) of ATMP products.	*This guideline is primarily focused on post-authorisation issues. The term non-commercial sponsor is used in clinical trials setting; therefore it is not a relevant term for the scope of this guideline. Nevertheless, as a matter of principle the requirements for commercial and non-commercial sponsors in the area of pharmacovigilance are the same, and it was further emphasized in the text.*

Finally, in terms of process, we would like to draw attention to the following points: • what procedures will be used to monitor the safety and efficacy of ATMPs; • what sanctions will be in place, for individual, groups or companies who submit RMPs for ATMPs and then do not implement them; • it is likely that sponsors will need secondary PV databases just to meet the requirements with linkages to other vigilance systems. Who will be monitoring this aspect of implementation and how will that be done?	*A new chapter on Compliance Monitoring was added to the guideline.*
<u>Traceability/Privacy Issues</u> One of our major concerns relates to privacy issues. There is fundamental tension between the right to privacy and the need to mandate long-term follow-up of patients treated with new therapies in order to generate data to evaluate risk. Marketing Authorisation Holders are generally not allowed to have direct access to personal data or to keep records of these personal data. Marketing authorisation holders can be responsible for product traceability to some extent (i.e. to the same extent as medicinal products can be traced in accordance with the principles of GMP), but not necessarily for patient traceability. Given the need for long-term follow-up in the face of such issues, and the situation whereby industry cannot set up registries due to privacy concerns, EMEA should consider the establishment of a patient registry (or registries), which would be exempt of privacy requirements. Additional systems may need to be developed to ensure traceability for these situations. Informed consent for long-term follow up may become a precondition for acceptance into certain ATMP therapeutic programs, at least in their initial on market evaluation phases. Given the planned development of a guideline document specific to traceability, consideration should be given to making general references to this issue at lines 162, 228, 399, 406, 436, 438, 537, 583 (leaving specifics for discussion in the draft guideline).	*A new chapter on personal data protection issues was added to the guideline.*

Extension of the EU-RMP model This draft guidance relies strongly on the extension of the EU-RMP model to the field of ATMP. What evidence is there of its effectiveness? And what confidence is there that it is a useful model, even for standard pharmaceutical and biological products, much less for the new field of ATMP? Have EU-RMPs actually been implemented as written and have they really improved the benefit risk profile of recently approved medicinal products in the EU? Perhaps a critical review of the value of this tool should be undertaken before it is applied to this emerging field. This could be incorporated into the more general review of pharmacovigilance in Europe that is currently in progress.	*Review and Learning Project is looking at the usefulness of the EU-RMP concepts. When the guideline was drafted, the guiding principle was to use as many of the existing tools as possible to ensure smooth and cost-effective solutions. It is still too early to determine whether the EU-RMPs have improved benefit-risk profile of recently approved medicines. Both, the EU-RMP guideline and this guideline will be revised to take into account the Review and Learning project findings.* *The ongoing general review of the pharmacovigilance in Europe will lead to new legislation, which will need to be implemented in all affected guidelines. The EU-RMP model is, naturally, part of this review too.*
Prescribed RMPs should not limit freedom of exercising medical practice or result in unnecessary intrusion in a site selection process directed by MAH and/or member states.	*This limitation is a key part of a risk minimisation concept included in the EU legislation. Medical practice is already regulated by number of regulations and requirements of professional bodies and member states regarding qualifications and skills that a healthcare professional or a healthcare establishment needs to meet to be allowed to exercise certain medical procedures. Risk minimisation of advanced therapy follows the same principles, ensured by both MAHs and Member States.*

Issues Raised By Enhanced Post-Marketing Surveillance Requirements **Infrastructure** While these proposals generally seem sensible, compliance with these extensive guidelines may be a concern when new medicinal products in this category are launched. Some biotech companies may not have the infrastructure and capabilities to fulfil the special requirements (e.g., selection/training and certification of prescribers) and this may result in a limitation of access. In addition, for most companies, the infrastructure required to process the substantial amount of data required would be unsustainable.	*These systems will require some investments. As mentioned in the guideline, outsourcing will often be a good solution for SMEs, as it is already with other pharmacovigilance requirements. Sustainability over time, especially for an unsuccessful product, is an issue that needs to be addressed on case by case basis.*
Feasibility for Health Care Providers and Researchers Also, these proposed rules regarding enhanced post approval surveillance activities for such products may be unrealistic for researchers and health care providers (particularly those based in hospitals or in academia) to support and maintain, to the point that it could conceivably inhibit current ATMP development and curtail future ATMP development.	*The guideline is focused on post-authorisation requirements. At the time of marketing authorisation application, the product should get enough support by Marketing authorisation applicant/holder to meet the requirements. Therefore, these requirements should not limit development; they will rather slightly raise the threshold for marketing of the product.*
Feasibility for Donors It is currently standard clinical practice to follow living organ donors (for example, of kidney or liver) for their whole lives. It is by no means clear that this practice will extend to living donors of renewable cells or tissues. Some donors may not accept this approach.	*This was further clarified in the text. In terms of standard practice, follow-up of donors of cells or tissues will remain an obligation of tissue establishments.*
Risk Follow-up Theoretical risk events may be so infrequent as to elude a feasible follow-up plan for monitoring. Even if the theoretical long-term risk is severe, if it is very infrequent, how can it be feasibly and affordably monitored?	*Any need for or a form of a follow-up system to monitor particular medicinal product's theoretical risks will be agreed in the RMP. This will be done on case by case basis. The current text of the guideline is in line with this idea.*

Efficacy Follow-up Some of the recommendations, particularly regarding efficacy follow-up, need to be further defined. The concept of the efficacy of marketed products being reportable, to the same extent as risk, is novel and there needs to be clarification of the guideline's intent. If these new requirements stand after further review, then it should be clearly expressed that efficacy follow-up requirements should correlate with risk posed by lack of efficacy	*It was clarified that expedited reporting of positive efficacy is not required..*
Offer of a Solution To address these issues, consideration should be given to solutions to these potential problems. For instance, might a single ATMP data collection maintenance organization to be set up and supported by all ATMP sponsors and recognized by global regulatory authorities? Clearly, this would be a complex undertaking and would require further thought and details. This is an area where industry would be pleased to work with EMEA to further develop this concept. (EBE)	*Thank you for the offer of support. This option may be further discussed in future. EMEA does not consider this option to be feasible within the timeframe set out by legislation for this guideline.*
2. Johnson & Johnson In particular, we wish to draw your attention to one especially important issue, which is identified in the EBE comments. The draft guidance correctly recognizes the importance of long-term patient follow-up programs. We are concerned, however, that regulatory restrictions relating to patient privacy, established pursuant to the EC Data Protection Directive (Council Directive 95/46/EC) and other legal measures, will significantly impede the ability of manufacturers to carry out effective, long-term follow-up programs. For this reason, we believe it would be appropriate to consider establishing a system of registries under the authority of the EMEA or another appropriate European Union entity. If properly instituted, such registries may qualify for exemptions or derogations under the Data Protection Directive for data collection activities, which are required by law or are necessary for reasons of substantial public interest. We would be happy to discuss the specifics of this suggestion in more detail, or to work within EBE to achieve the suggested objective.	*Thank you for your support. Further discussion will be needed.*
3. BPI • There are general concerns about the collection of patient and donor data and data protection laws and handling of these data by different persons/ legal entities over long periods of time. Consent of donors and patients to conduct safety and efficacy studies over long period of time might be difficult to receive and to follow up.	*This is addressed in the new chapter on personal data protection issues.*

• The risk potential is varying between different kinds of ATMP. There is a lack of differentiation in the guideline especially between the requirements concerning allogenic and autologous ATMP. It is necessary to establish a risk based approach and to clearly define the requirements that are not relevant for autologous but only for allogenic ATMP.	*Risk based approach is already strongly present in the guideline (*"The content and extent of the EU-Risk Management Plan must be proportionate to the risks of the particular product.*"). Particular division between allogenic and autologous products is not emphasized, because it is considered to be just one of the important characteristics, not the ultimate characteriser of risks. The whole guideline is meant to be providing guidance for a risk-based approach targeted at individual products.*
• For the reason of clarity the "extended" EU-RMP containing efficacy follow-up that is proposed for ATMP in this guideline should have a specific name and should be distinguished from the "normal" EU-RMP that has to be provided for classical medicinal products. Otherwise there are implications feared on EU-RMP for classical medicinal products with the result that efficacy follow-up might be asked for, too. It is hence proposed to name the "extended" EU-RMP in the case of ATMP in accordance with the name of the guideline: "Safety and Efficacy Follow-Up Risk Management of Advanced Therapy Medicinal Products" to make a clear distinction in relation to the EU-RMP for classical medicinal products.	*The principles established for medicinal products should remain the same. ATMPs are understood as a special category of medicinal products. Therefore, only additional mechanisms and tools are introduced, not any replacements.*
• It is questionable if the EU-RMP is the best place to include information concerning efficacy follow-up. From BPI's perspective the PSUR would be a better place to provide these information as the PSUR contains already now a risk:benefit assessement of a medicinal product. To use the EU-RMP for this would lead to two documents running in parallel and containing quite similar information. Apart from that there is a provision in Article 14 (2) of Regulation (EC) 1394/2007 allowing that the "evaluation of the effectiveness of any risk management system and the results of any studies performed shall be included in the periodic safety update reports referred to in Article 24(3) of Regulation (EC) No 726/2004."	*The EU-RMP and PSURs have quite a different purpose. The PSUR is a reporting tool, EU-RMP is a management document. Generally, there is no need to report anything in the EU-RMP, there should be just a summary of information that supports the decisions made about the risk management, and information about its performance. Outcomes from the efficacy follow-up plans agreed in the EU-RMP will be reported and discussed in the PSUR. The text of the guideline is fully in line with the Article 14 (2) of* Regulation (EC) 1394/2007.

• It should be noted that apart from regular updates of the EU-RMP and the parallel provision of PSUR there will be annual reports resulting from the new Variations Regulations. The whole system will become very complex and hard to handle. As a lot of companies producing ATMP are SME the system should be kept simple and parallel reporting should be avoided.	*Annual reporting of certain minor variations foreseen in the new Variations Regulation is not a new burden; it is a simplification of the current status. It is absolutely independent from PSURs, which summarises new data, and EU-RMPs, that summarises management of safety issues. There should not be any parallel reporting, although a certain facts will be reflected in multiple reports from different perspectives.*
4. Pfizer Pfizer appreciates the opportunity to comment on the proposed guideline on Safety and Efficacy Follow-Up Risk Assessment of Advanced Therapy Medicinal Products, captioned above. The novelty, complexity, and technical intricacies of advanced therapy medicinal products (ATMPs) require a scientifically-based, harmonised approach to protect the safety of patients. While the safety of patients is paramount this must be balanced with a need to facilitate access to these novel therapies by the patients who may need them. In addition, the approach to patient safety and managing risks of ATMPs must be developed in a manner that complements existing relevant regulations and guidelines; the development of safety and efficacy follow-up guidelines for ATMPs in the EU should follow a considered approach that is harmonised with development of relevant regulation and guidance in other regulatory jurisdictions, i.e., the EU approach should be harmonised on a global level. Thus, to maximise patient protection, consensus guidelines should be developed in international forums such as CIOMS or ICH. The proposed guideline should provide an excellent starting point for discussion in such forums. Indeed, the proposed guideline provides an excellent framework for additional detailed guidance on certain aspects of pharmacovigilance, risk management planning, and safety and efficacy follow-up for ATMPs authorised in the EEA. We endorse the concepts implicit in the proposed guideline that stress consistency and clarity with which the science of pharmacovigilance is applied and, thus, protects the safety of patients. However, several sections of the proposal could be clarified further to provide enhanced patient safety protections. More detailed comments are provided below.	*Thank you. The need for global harmonisation will be further considered with growing experience.*

5. TiGenix NV TiGenix NV welcomes this guideline as it further clarifies the requirements in safety and efficacy follow-up and risk management of ATMPs. This pertains to the dossier requirements, to the particular points of attention regarding safety and efficacy follow-up for such innovative products, as well as to the reflections on the design of follow-up measures that can be taken. It is understood that the guideline does cover a very broad field of medicinal products, and that each product will necessitate a case by case evaluation with respect to meeting the requirements. The proposal to seek scientific advice for defining the product specific requirements is considered an efficient way to handle the complexity associated with the use of ATMPs. The recognition of the specific nature of ATMPs (influence of the administration procedures, dynamics of the clinical efficacy, sustainability of efficacy, and others) is important. The recognized utility and need of post marketing follow-up will allow both to ensure patient safety at long term as well as to accomplish clinical trials within a feasible design and timescale. Although not within the scope of the guideline, it needs to be recognized that many of these innovative ATMPs are developed by SME companies. It is of no doubt nor discussion that patient safety is of the first importance, but care should also be taken to manage the administrative and organizational burden in accomplishing these post marketing requirements.	*Thank you.*
6. BioIndustry Association (BIA) The BIA fully supports the Advanced Therapies Regulation which will enable patients to have access to ground-breaking new therapies and strengthen the bioindustry sector in Europe. Overall, we agree with the objective of the guideline and the need for designing a post-authorisation patients' follow-up system to further characterise risk factors relating to a given advanced therapy medicinal product so that an appropriate process can be developed to mitigate risks in a clinical setting.	*Thank you*

It should be recognised that the guideline concerns an area where the underlying science and technology is evolving. We believe that the recommendations provided in this guideline ought to incorporate some flexibility to reflect the fact that one deals with an array of products displaying a diversity of product characteristics. It is not in the best interest of the scientific community to have a set of rigid recommendations as they may potentially hamper innovation.	*Need for flexibility is recognised, and was further stressed in the guideline*.
It is important to emphasise that not all the points listed for consideration would be relevant to the three product types covered by the Advanced Therapies Regulation, namely gene therapy, somatic cell therapy and tissue engineered products, because 2 the risk factors are dependent upon the manufacturing process and the characteristics of the finished product. These may vary from product to product.	*The list is meant to be as comprehensive as possible. It is expected, that not all of the bullet points will be relevant to a particular product, but when it is relevant, it needs to be discussed. This was further clarified in the guideline.*
We would strongly favour a risk-based approach to determine the level of postauthorisation surveillance required for a specific product. Therefore, it is recommended that further consideration be given to the three product types and guidance be provided more specifically, as the risk and hence the level of follow-up activities and pharmacovigilance should be commensurate with the characteristics of the product in question and its mode of action.	*This idea is one of the guideline principles. The need for risk-based approach, tailored for a particular product was further emphasised in the guideline.*

SPECIFIC COMMENTS ON TEXT

EXECUTIVE SUMMARY

Line no.[1] + paragraph no.	Comment and Rationale	Outcome
Lines 32-40	Modified wording could clarify that the additional EU requirements of the safety specifications is also a subsection of the RMP. In Part I of the RMP, a new chapter for ATMPs is introduced within the section 8.1.1 Additional EU requirements of the safety specification. (EBE)	*Wording was amended accordingly.*

1. INTRODUCTION

Line no. + para no.	Comment and Rationale	*Outcome*
Lines 93-97	This paragraph properly refers to "…products that are either prepared industrially or manufactured by a method involving an industrial process." This may not adequately differentiate the intended products from "natural" products that have minimal, but some "industrial process" involved in their preparation for market. Propose slight modification of Lines 95-96 to read "…those ATMPs which are intended to by placed on the market in the European Economic Area under a Marketing Authorisation, and that are within the scope…" (Pfizer)	*The sentence put in the guideline reflects the legislative requirements. The proposed text would suggest that there are ways to get a medicinal product to the market without obtaining a marketing authorisation. The guideline should not promote such a notion.*

2. SCOPE OF THE GUIDELINE

Line no. + para no.	Comment and Rationale	Outcome
Lines 111-112	It is agreed that the generation of long-term data is not a substitute for data generated through clinical development.	*This will always be a matter of judgment in relation to the characteristics of the particular product and the data available at the time of the*

[1] Where applicable

	However, the requirement to generate long-term efficacy data is neither realistic nor appropriate for some products at pre-approval. Clarification is sought to ensure that additional requirements are not unnecessarily imposed. (BIA)	*marketing authorisation application. The guideline just builds on the newly emphasized legal possibility to generate long-term efficacy data after authorisation.*
Lines 122-123	In the Scope section, consider emphasizing the unique characteristics of the majority of these ATMPs with regard to manufacturing, handling and modes of application. Some adverse events may be related to these characteristics rather than to the active substance. (EBE)	*The general emphasis was added. The unique characteristics are further elaborated upon in the scientific rationale part of the guideline.*
Lines 122-123	The new regulation on risk management of ATMP should include provisions designed to address the special pharmacovigilance issues presented by similar or follow-on ATMP products, by analogy with the approach, which has been developed by the EMEA to the regulation of biosimilar therapeutic proteins. (EBE)	*Biosimilar approach in the area of Advanced Therapies is considered to be too early to develop. We need to accumulate experience with originators, and then we can work further on the biosimilar possibilities.*
Lines 122-126	We agree with the sentence "The Regulation defines ATMPs as gene therapy medicinal products, somatic cell therapy medicinal products and tissue engineered products." This is clear and should restrict application of the guideline to ATMPs, as defined in Regulation 1394/2007. Propose addition to Line 126 to read "…treated with such products. **Application of this guideline should be restricted to ATMPs, as defined.** The target audience includes…" (Pfizer)	*The text on restriction of the scope to ATMPs was added.*
Lines 128-130	As stated, since the follow-up of subjects in interventional clinical trials with ATMPs is not directly in the scope of this guideline and specific guidelines (including a recently issued gene therapy follow-up guideline) address this topic, the general reference in sentence 3 is appropriate. In paragraph 3, delete sentences 1 & 2 and begin sentence 3 with "When…" ~~"Follow-up of subjects in interventional clinical trials with ATMPs is not directly in the scope of this guideline. Nevertheless, it is appreciated that many subjects of such clinical trials will require very long or even life-long follow-up. Therefore,"~~ When designing a post-authorisation patients' follow-up system, it is always necessary to take into account any existing requirements and	*The original text is considered to be better expressing the intentions of regulators.*

	guidelines for follow-up of subjects in clinical trials, as well as the follow-up system that was, or still is, in place for subjects of clinical trials with the particular ATMP. (EBE)	
Lines 129-130	This statement is targeted at gene therapy products and other such high risk/long acting products. In certain instances, cell therapies and tissue engineered products do not pose the same level of risks requiring long-term follow-up. We believe that specific guidance needs to be provided for each product type. (BIA)	*The guideline text is meant to be a general fact statement. There is a clear need for Specific guidelines for various product types, they continue to be developed, and the text in the Introduction is emphasizing this fact.*
3. LEGAL BASIS		
Line no. + para no.	**Comment and Rationale**	**Outcome**
Lines 143-205	To decrease the amount of editing required as guidance continued to evolve, consider the creation of an Appendix to contain these references and/or replace specific legislation and guideline references with general website addresses where ATMP regulation/guidance can be located. Consider creation of Appendix and/or use of general links such as: ATMP Legislation http://ec.europa.eu/enterprise/pharmaceuticals/advtherapies/advanced_keydoc.htm ATMP Guidelines http://www.emea.europa.eu/htms/human/mes/advancedtherapies.htm (EBE)	*The Appendix 1 was created, that includes hyperlinks and list of relevant legislation and guidelines.*
Lines 171-175	Consider addition of reference to CHMP Guideline on Risk Management Systems (EMEA/CHMP/96268/2005) and Annex C template for EU-RMP (EMA/192632/2006) due to the distinct link between these guidelines. Pharmacovigilance Guidelines http://www.emea.europa.eu/htms/human/phv/phvwp.htm http://www.emea.europa.eu/pdfs/human/euleg/9626805en.pdf (EBE)	*The CHMP* Guideline on Risk Management Systems (EMEA/CHMP/96268/2005)*, including its annexes, has been integrated into the Volume 9A of the Rules Governing Medicinal Products in the EU. Nevertheless, a specific addition of this reference may be of use, and it was added.*

4. DEFINITIONS		
Line no. + para no.	**Comment and Rationale**	**Outcome**
Line 206	Classic definition for efficacy do not apply for TEP Efficacy for TEPs must be defined as the ability to repair, regenerate or replace the applicable tissue. (BPI)	*Regulators do not see a need for a separate definition of efficacy for TEP in this guideline. On the contrary, it would introduce some confusion and opportunity for double standards.*
Line 207	Ads – adds (BPI)	*Thank you.*
Line 238	"Active" and "passive" follow-up should be defined for ease of reference. (EBE)	*Reference was added to the guideline.*

5. COMMON RULES FOR POST-AUTHORISATION SURVEILLANCE OF MEDICINAL PRODUCTS		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	No comments.	

6. SCIENTIFIC RATIONALE FOR SPECIFIC RULES FOR POST-AUTHORISATION SURVEILLANCE OF ADVANCED THERAPY MEDICINAL PRODUCTS		
Line no. + para no.	**Comment and Rationale**	**Outcome**
Line 264	Although the list is very comprehensive and allows the MAH to consider every possible risk, it needs to be noted that some of these risks are not typical for ATMPs and would apply across all medicinal products (in particular also for biologics). This relates e.g. to the quality characteristics of the product (280) with the exception of the gene therapy vectors specifics, biologically active substances (295), administration errors (302), unwanted immunogenicity (or immunotoxicity) (306), re-administration risks (320), foetal and mammary transmission (328, 330). A note to this comprehensive list might be appropriate. (TiGenix NV)	*Clarification was added to the text introducing the list of risks. Indeed, not all of them are unique to the ATMPs, but still relevant.*

Lines 273-274	The statement that "The following features should always be part of such considerations:" is too broad since the features outlines in Section 6.1, 6.2 and 6.3 may apply to only one of the ATMP types (cell, gene or tissue therapy). Replace this sentence with, "If applicable to the ATMP, the following features should be part of such considerations. (EBE)	*The wording was changed so to make it clear that the list of points is intended to help stimulate the considerations, and not to serve as a prescriptive check-list.*
Line 274	There should be need to evaluate the risk of features that do not apply to a particular Advanced Therapy Product. When preparing a risk management plan for a particular advanced therapy medicinal product, comprehensive scientific consideration should be given to the important identified or potential risks, and to the important missing information. The following features should ~~always~~ be part of such considerations as applicable for the Advance Therapy Products. Due to the diversity of these products the applicant should indicate if the listed features below apply, on a case by case basis : "(BPI)	*The wording was changed so to make it clear that the list of points is intended to help stimulate the considerations, and not to serve as a prescriptive check-list.*
Line 274	There should be need to evaluate the risk of features that do not apply to a particular Advanced Therapy Product. When preparing a risk management plan for a particular advanced therapy medicinal product, comprehensive scientific consideration should be given to the important identified or potential risks, and to the important missing information. The following features should always be part of such considerations as applicable for the Advance Therapy Products. Due to the diversity of these products the applicant should indicate if the listed features below apply, on a case by case basis. (Arthro Kinetics Biotchnology GmbH)	*The wording was changed so to make it clear that the list of points is intended to help stimulate the considerations, and not to serve as a prescriptive check-list.*
Line 276	Please define what constitutes "conditioning" and in what context. (BIA)	*The definition was added to the guideline.*
Line 278	It should be noted that the donor will undergo the procedure whether the tissue is collected or not. (BIA)	*This note was added.*

Line 287	It appears necessary to extend the listing by the proposed text (in bold) "...composition, stability, ~~and,~~ biological activity, **and purity with reference to non-physiologic proteins and fragments thereof."** (VFA)	*The text was changed as suggested.*
Lines 281-282	Cells used during manufacturing may be primary human cells or established cell lines from diverse species (such as the viral vectors). Risk related to transmissible diseases is listed separately at line 299-289. Could the species of origin and testing performed (e.g. MCB/WCB) be added? Modify existing sentence as follows: Species of origin and characteristics of cells (and related body fluids, biomaterials, biomolecules) that are used during manufacturing, and the safety testing performed. (EBE)	*The text was changed as suggested.*
Line 297	Please define what constitutes "conditioning of the patient" and in what context. (BIA)	*The definition was added to the guideline.*
Lines 298-299	Clarification is required as to whether implantation covers topical products. (BIA)	*This point is just a list of examples. The words "or other application method" was added to the list to cover this comments (topical products are rather applied than implanted).*
Line 300	The aspect that any treatment (not only immunosuppression) can have an impact on the long-term performance of the ATMP (and vice versa) is missing (e.g. in theory an immunoglobulin treatment later in life could impact expression of a gene product by antibody interaction. This would not be "immunosuppression"). It is of course acknowledged that this can be a difficult task, but Companies should consider it. It is suggested to include an own additional bullet point, and to keep the bullet point "immunosuppression" as currently proposed, since it is an indeed important aspect. Add: "* Considerations on the potential impact of previous, concomitant, or future therapies typical for the diagnosis or treatment of the respective disease on the product, or of the product on those other therapies." (Paul Ehrlich Institut)	*Agreed. This point was added as this kind of consideration is more important for ATMPs than for other types of medicinal products.*

Lines 305 and 311	"Risks related to interaction with the patient" and "risks related to behaviour of the product in the patient" appear similar. While apparently "passive" issues like homing etc. and "active" issues are behind the wording, this might be made clearer. (Paul Ehrlich Institut)	*These two groups of risks were merged.*
Line 308	Clarification is required as to whether this is in relation to the intended mode of action of the product. It should be noted that this may not be relevant for all product types where genetic modification is not involved. (BIA)	*This should include both – result of an intended modification, as well as not intended one. The text was expanded.*
Line 312	The following additions are proposed Early and late consequences of homing/grafting, differentiation, **migration and proliferation.** (EBE)	*The text was expanded as suggested.*
Line 320	This may not be relevant for all product types. (BIA)	*Yes, the list is a general list for consideration, not a checklist. This was further emphasized.*
Line 323	"Close contacts" need to be defined. Provide definition for close contacts. (EBE)	*Definition was added.*
Line *328*	This may not be relevant for all product types. (BIA)	*Yes, see above.*
Line 332	There are not "concerns" with efficacy in its usual meaning. Replace with "issues" or "considerations". (Paul Ehrlich Institut)	*Although the word "concern" is not necessarily negative, in this context it is used appropriately as the efficacy follow-up will be needed only if there are real concerns regarding efficacy, such as unavailability of long-term data. The wording unchanged.*
Line 339-341	Long term follow-up of years and decades as proposed, will be difficult, as patients might not give their consent or might not be traceable anymore after decades. Medical practitioners and hospitals in Germany are e.g. only obliged to archive patient documents for a maximum of 10 years (§ 10 Berufsordnung für Ärzte). Long term follow up is restricted to a maximum of 10 years. (BPI)	*The guideline needs to address the situation in the whole EU. Art. 15.2 of the Regulation (EC) 1394/2007 require hospitals, institution or private practise where an ATMP is used to establish a system for patient and product traceability. Minimum time for archiving MAH's part of the traceability data is set for 30 years after expiry of the product (Art. 15.4). Although the similar requirement is not spelled out in the Regulation for healthcare establishments, per analogy it should be required for the similar period of time. Further details will be included in the traceability guideline. No limitation in time was included in the text.*
Line 342	"…and may not be fully documented": The word "documented" suggests rather a passive collection of data rather than a systematic evaluation of efficacy. It is suggested to change this to "evaluated" or	*The text was implemented as suggested.*

	"established". Further, it could at this point be stressed that loss of efficacy can be harmful to the patient (see recent case of granulomatosis therapy), and its impact might at the time of MAA not be fully known. The reference to living organisms lacks an important aspect, i.e. the impact of pre-existing immunity on the organism. (…), and **the consequences for the patient** may not be fully ~~documented~~ **evaluated/established** during the course of pre-authorisation clinical trials. **Likewise, the consequences of loss of efficacy of an ATMP on the disease course and future treatment options might not be fully established. Pre-existing immunity of the recipient to the vector and its change with potential repeat administrations at later stages (individual for each patient) can in itself alter the clinical course of efficacy and safety, and also add to heterogeneity in the patient group.** Therefore post-authorisation follow-up might be necessary. (Paul Ehrlich Institut)	
Line 344	„In such a situation proof of concept and a positive trend in clinical trials using acceptable surrogates (e.g. amount of newly formed cartilage tissue in a joint) might be sufficient for the unequivocal evidence of effect required for granting a marketing authorisation." This sentence is in its principle supported, but some wordings require refinement, since they are misleading: "a positive trend": This would suggest that also with a non-significant change a MAA is possible. This is a bit too "soft". The reference to "acceptable surrogates" will inevitably raise discussions. For some other guidelines, the term "surrogate" was avoided, since only a minority of endpoints are true "surrogates" where a clear correlation to clinical outcome is established and validated. This would thus restrict the possibilities for companies rather than open new ways.	*Implemented without the word "preliminary", as it would not appropriately reflect the fact that any assessment is based on a snapshot of the data in time.*

	The reference to "amount of newly formed cartilage tissue in a joint" is problematic, since it sets a precedent and might pre-empt any CHMP decision on MAA procedures. It should thus be deleted. The word "unequivocal" is too strong – it suggests that the level of evidence is high at the time of MAA, but the opposite is the concept of the guideline. Thus, the word should be changed to "preliminary" „In such a situation proof of concept and a positive clinical ~~trend~~ **outcome** in clinical trials using acceptable surrogates **methods for efficacy** ~~(e.g. amount of newly formed cartilage tissue in a joint)~~ might be sufficient for the ~~unequivocal~~ **preliminary** evidence of ~~effect~~ **efficacy** required for granting a marketing authorisation." (Paul Ehrlich Institut)	
Line 344	What is meant by "fully functional"? Provide a definition for fully functional. (EBE)	*The new text reads: "The time needed for the new tissue to be fully functional will depend upon the product and may be counted in years."*
Line 344-349	The example used (cartilage tissue) is inappropriate in this context given that there are already existing validated and widely used & accepted clinical endpoints (IKDC Score) for efficacy which could be used in the time frame for the re-growth of cartilage tissue (1-2 years). Therefore, there is clearly no need for surrogate endpoints in the evaluation of Advanced Therapy Products for the repair of tissues where clinical endpoints already exist, such as for cartilage tissue. The time needed for the new tissue to be fully functional may be counted in years. In such a situation and only where there is an absence of any documented or commonly used clinical endpoints defining efficacy, would proof of concept and a positive trend in clinical trials using acceptable validated surrogates (e.g. amount of newly formed cartilage tissue in a joint) might be sufficient as for the unequivocal evidence of effect required for granting a marketing authorisation. Nevertheless, the efficacy profile, including clinical endpoints (e.g. prevention of osteoarthritis), might would need to be confirmed in post-authorisation phase. (Arthro Kinetics Biotchnology GmbH)	*Agreed – the example in brackets will be deleted as per the PEI comments above.*

Line 344-349	The example used (cartilage tissue) is inappropriate in this context given that there are already existing validated and widely used & accepted clinical endpoints (IKDC Score) for efficacy which could be used in the time frame for the re-growth of cartilage tissue (1-2 years). Therefore, there is clearly no need for surrogate endpoints in the evaluation of Advanced Therapy Products for the repair of tissue where clinical endpoints already exist, such as for cartilage tissue. The time needed for the new tissue to be fully functional may be counted in years. In such a situation and especially where there is an absence of documented or commonly used clinical endpoints defining efficacy, would proof of concept and a positive trend in clinical trials using ~~acceptable~~ validated surrogates ~~(e.g. amount of newly formed cartilage tissue in a joint)~~ ~~might~~ be sufficient as ~~for the~~ ~~unequivocal~~ evidence of effect required for granting a marketing authorisation. Nevertheless, the efficacy profile, including clinical endpoints (e.g. prevention of osteoarthritis), might need to be confirmed in post-authorisation phase. (BPI)	*See above.*
Lines 347-349	The clinical trial process is such that specific endpoints must be met with statistical significance in an appropriate sample size of the treatment population. It would be unreasonable to make mandatory further efficacy studies for all advanced therapy products after clinical trial endpoints have been met. Many products will not require efficacy follow-up post authorisation. Furthermore, this may not be technically feasible. Many products will be treating chronic diseases in which the patient deteriorates with time. Long term follow-up of these individuals may give skewed data as the condition worsens. (BIA)	*This is one of the reasons why the efficacy follow-up plans are considered to be exceptional. The need for such a plan for a particular product will be evaluated (see chapter 8.4 of the guideline), and only when a clear need for it is identified, the plan is included as Annex 9 of the RMP.*
Lines 350-351	The statement is more appropriate for gene therapy products where the transgene is stably integrated into the genome of the host cells. Clear guidance needs to be given to i) define what is meant by long term efficacy follow-up and ii) define when long term follow-up is applicable. Otherwise, this might be extremely burdensome to industry and unnecessary in many cases. (BIA)	*The wording was further clarified. The guideline defines what the efficacy follow-up is. How long it will be and when it will be applicable is outside of the scope of this guideline – this is or will be addressed by specific guidelines for particular product types, and further determined on case by case basis.*
Line 357 ff	Additional consideration should be laid on ATMP that have to be applied multiple times (consist of cells with a limited life-time,	*The text addressing repeat use was added.*

	therefore, depending on efficacy endpoints of previous clinical trial, special consideration of shorter efficacy follow-up periods) (BPI)	
Lines 368-373	It should be recognized that the theoretical risk events might be so infrequent as to elude a feasible follow-up plan to monitoring Perhaps the last sentence in this section should come after the first sentence and the rest of the information in this section should be considered items to consider. (EBE)	*Any need for or a form of a follow-up system to monitor particular medicinal product's theoretical risks will be agreed in the RMP. This will be done on case by case basis. The current text of the guideline is in line with this idea.*
Lines 373-374	"When a subset of exposed patients is used, scientific justification should be provided. A subset will not be acceptable for orphan drugs." We propose that in any case the choice of sample size should be based on a scientific rationale. Scientific justification should be provided for the chosen sample size, including exposure to orphan drugs. (EBE)	*See the variation of the text as proposed below.*
Line 374	"A subset will not be acceptable for orphan drugs" is a strong wording that reduces flexibility that might be required for certain circumstances. It is suggested to soften the wording. A subset ~~will~~ **might** not be acceptable for orphan drugs. Or: A subset ~~will not be~~ **is normally not** acceptable for orphan drugs. (Paul Ehrlich Institut)	*Implemented text: "A subset is normally not acceptable for orphan drugs."*
Lines 375-376	It is agreed that many individuals will be lost and could not be used for long term follow-up. However, to base sample size calculations on this high level of drop-outs is not reasonable. This would be economically unviable for many sponsor companies and may be restrictive to product development. (BIA)	*The new text: "Sample size calculations should consider the high potential for drop-outs…"*
Lines 381-383	"Tailoring" laboratory investigations seems unrealistic given the current health care cost environment. The design of studies that require specific timing of procedures (line 382) and the use of "normal practice" (line 390, Section 6.3.3) may not be compatible and will add to cost. A clear distinction must be made between the costs of diagnostic tests required for ongoing patient care, which would be funded by the health care provider, and the cost of tests undertaken solely for the purposes of	*The risk management plan is a condition of marketing authorisation and is obligatory for everyone, including healthcare professionals. Therefore, there should not be any difference between the way the product is used and the way it should be used as required by its risk management plan. To make this clear, the new text reads:"…take into account such dynamics, and* ***good medical practice*** *that may require specific timing of procedures, treatment …"*

	gathering risk management information, which would probably be borne by the MAH as part of the overall cost of the RMP, and would therefore need to be factored into the pricing of the therapy. *Modify the last sentence in this section as follows: Design of studies need to take into account such dynamics.* ~~*and may require specific timing of procedures, treatment adjustments and laboratory investigations to be tailored for individuals patients.*~~ (EBE)	
Line 384	"Comments" is not considered the appropriate heading. Suggest to replace by "considerations" on clinical follow-up. (Paul Ehrlich Institut)	*Implemented.*
Line 390	Suggest more clear language. "Studies used…should use the "*normal practice*" of clinical follow-up procedures…" "Safety and efficacy studies should use usual clinical practice for follow-up whenever possible to limit additional procedures and interventions." (EBE)	*Implemented.*
Line 394	The described risk does not apply for autologous donation. Comments on safety follow-up of living allogenic donors (Arthro Kinetics Biotchnology GmbH)	*Clarification to the definition of "living donors" was added.*
Line 394	As for 384. Suggest to replace by "considerations" on "safety follow-up of living donors (Paul Ehrlich Institut)	*Implemented.*
Line 394	The described risk does not apply for autologous donation Comments on safety follow-up of living <u>allogenic</u> donors. (BPI)	*Clarification to the definition of "living donors" was added.*
Line 394	There is no doubt that donor safety is part of the safety assessment and follow-up, but the complexity of the legal framework in the European Community needs to be recognized. Whereas the PhV activities of the centrally authorized medicinal product fall under the community law on medicinal products 2001/83/EC and Regulation (EC) No 726/2004, the safety and traceability for the donor falls under the scope of the Tissue Directives (2004/23/EC and implementing directives). Reporting requirements to be considered are therefore multiple: central (for the MP) and at national level (donor), as well as across different legal frameworks for the donor (the current guideline and the Tissue	*This complexity is recognised. A new paragraph to further clarify the requirements was added. The EMEA will continue to work with all established authorities and law makers to streamline this system.*

	Directives). It is highly recommended that the European Authorities take this complexity into account and that an unnecessary burden and complexity of the reporting systems is avoided through streamlining and harmonizing the requirements and administrative procedures across the member states and systems. (TiGenix NV)	
Line 395-402	The MAH can address traceability from procurement through manufacturing; however, there are major confidentiality issues with requiring patient traceability data. **"**Traceability from procurement throughout the manufacturing process is required." (EBE)	*This will be further addressed in the separate traceability guideline. Further clarification was added.*
Line 395-411	The Marketing Authorization Holder (MAH) usually does not have information/ personal data about the donor of the material, if the material is taken from the donor in hospitals the data have to be anonymised before transfer to MAH 409: Safety follow-up of "close contact" and offspring is not feasible. Definition of "close contact" not given, who is a "close contact"? Data from "close contacts" and offspring might be difficult to transfer to MAH, as informed consent is required 410: Study designs for generation sufficient information about "close contact" and "offspring" will not be feasible. It should be tried for ATMPs with documented pre-clinical events of germ-line modification. 409: No safety follow-up of "close contact" and offspring, as not feasible. (BPI)	*The dedicated new paragraph on data privacy issues was added. Close contacts were defined. The difficulties with feasibility were reflected in the guideline text, and scientific advice on case by case basis is recommended in this respect.*
Lines 396-399	There should be consideration given to the difficulty in follow-up of living donors in some circumstances. Depending on where the tissue is procured from, this may become burdensome to the MAH. For example, if blood is procured from a blood bank, the blood bank may not keep information long-term, and may be unable to share this information with the sponsor. In addition, the donor follow-up requirements may severely limit potential donors. Addition of a sentence such as: "It is understood that long-term follow-up of living donors may not be feasible in every case. This should be considered on a case-by-case basis." (EBE)	*This is recognised and the text of the second paragraph in this chapter reflects this concern.*

Line 409	Given the difficulties of follow-up on patients themselves, the notion of follow-up of close contacts and offspring is quite challenging. The cost of this approach would need to be clearly justified by the likely benefits in risk management. This requirement would surely be infrequent. (EBE)	*Yes, it is expected to be infrequent.*
Line 409	This seems to be directed at gene therapy products. Clarification is sought regarding the products requiring such follow-up. (BIA)	*This is expected to be infrequent, and determined by the product characteristics.*
7. ADDITIONAL REQUIREMENTS FOR THE PHARMACOVIGILANCE SYSTEM OF MARKETING AUTHORISATION HOLDERS		
Line no. + para no.	**Comment and Rationale**	**Outcome**
Line 430	See also comment on Line 394. Data exchange between the different vigilance systems is indeed necessary to establish a comprehensive safety tracking system. Given the current complexity, support from the European Authorities is highly advisable to ensure the MAH can indeed establish efficient data exchange procedures. (TiGenix NV)	*We appreciate the need for the electronic data exchange. EMEA will continue to support international standardisation in the area of electronic data exchange of medicinal product safety information (in the ICH process, as well as ISO standardisation). In future, these activities may be expanded to cover wider area than pharmacovigilance.*
Line 432-435	It should be emphasized in this paragraph that the exchange of information between different systems should be performed electronically (in bold). "Procedures for data exchange with other vigilance systems as applicable based on the nature of the products of the marketing authorization holder/ applicant (for example tissues and cells vigilance, haemovigilance, and vigilance of medical devices – see the legislation references above). **This needs to include the requirement to exchange information between these systems electronically, whenever possible. "** (VFA)	*The sentence* "Whenever possible, the data exchange should be performed electronically." was added.
Lines 432-435 or 436-437	For the exchange of information between different systems a general platform with defined format (similar to M2) should be established. This appears necessary in order to avoid the constant necessity for adjustments/modifications of interfaces. (VFA)	*The need is clearly there. Please, see the answer to Line 430 above.*
Lines 432-440	"In addition, the pharmacovigilance system of ATMP marketing authorisation holders should include, where applicable: …. The	*A clarification was added that this data linkage is meant to happen between databases of the same MAH. As such, data privacy issue should*

	marketing authorisation Ensuring full traceability is essential for follow-up of safety of ATMPs. However, it is questionable whether the requirements (e.g. record linkage between pharmacovigilance and traceability and/or other record systems) are feasible for MAHs according to legal provisions in MS (e.g. data protection). (Paul Ehrlich Institut)	*not be an obstacle.*
Line 438, Table 1	Record Linkage between pharmacovigilance and traceability databases and/ or record systems (e.g. medical records) It is not clear, how this can be achieved and patient and donor data are protected at the same time. Marketing Authorization Holders do not have access to medical records of patients or donors. Patients and donors cannot be obliged to transfer their data to Marketing Authorization Holders or other third parties. Hospitals/ medical practitioners may not transfer any patient data to a third party as this is a criminal offense in some Member States. This would only be possible, if all data were anonymised. If all data were anonymised, it is not quite clear, how the system would work efficiently. Pharmacoviligance data might be obtained from different sources: the patient, the hospital, one or more medical practitioners at various time over long periods of time. How should the Marketing Authorization Holder know, that the data are from the same patient, if he received already anonymised data from patients (e.g. from the patient and later from the medical practitioner of the patient or hospital? How should the Marketing Authorization Holder know that the patient data coming directly from the patient and the data received from the medical practitioner are data from the same patient, if these data were anonymised beforehand?) If the Marketing Authorization Holder receives several sets of data from one patient without having the possibility to find out that these are the same data, these might significantly increase the number of adverse events and might render the medicinal product unsafe (in the worst case scenario). Discussions with European Data Protectors to find a solution: safety concerns versus personal data protection. (BPI)	*This is a daily challenge of pharmacovigilance professional today. It is recognised, that there is a need to work with anonymised data. Nevertheless, the anonymisation should be done in such a way that allows duplicate detection. A new chapter on data privacy issues was added.*

8. ADDITIONAL REQUIREMENTS FOR THE RISK MANAGEMENT SYSTEM OF ADVANCED THERAPY MEDICINAL PRODUCTS		
Line no. + para no.	**Comment and Rationale**	**Outcome**
Lines 467-468	Delete the statement concerning cross-referencing the MAA in the EU-RMP. Since the EU-RMP is a stand-alone document, it remains questionable as to whether cross-reference to the MAA should be included when presenting safety specifications. Specification should be presented in a summary fashion ~~(if necessary, with appropriate cross referencing to other parts of the dossier)~~ with the aim of providing sufficient information within the EU-RMP to enable a decision on whether additional risk minimisation activities are needed, and whether the routine ones are appropriate. (EBE)	*It is agreed that this wording may be confusing for less experienced users of this guideline. Revised as suggested.*
Line 472	There are many Advanced Therapy Products currently available on the European Market which have been used widely and over many years and which now fall under the Transition period described in Article 29 of 1394/2007. In the case of some Advanced Therapy Products manufacturers and/or physician have generated data, including; investigator trials, case series and/or observational studies which are available to substantiate the safety and efficacy of the Product but which may not controlled. Such studies should be allowed to support registration. Additional controlled trails or further observational studies in post-authorisation phase could also be considered on case by case basis. New paragraph: For Advanced Therapy Products which are already legally on the market under Article 29 of 1394/2007 and for which there is data from their use in the market (for example; observational studies, case series and/or investigator studies) that is strongly indicative of the efficacy and safety of the Product, then in such cases this data should be considered sufficient evidence for granting of a marketing authorisation. (Arthro Kinetics Biotchnology GmbH)	*The proposed statement is outside of the scope of this guideline. Nevertheless, wording regarding this particular group of product was added to make it clear that these data on post-authorisation use are to be included in safety specification.*
Line 472	There are many Advanced Therapy Products currently available on the European Market which have been used widely and over many years	*As above.*

	and which now fall under the Transition period described in Article 29 of 1394/2007. In the case of some Advanced Therapy Products manufacturers and/or physician have generated data, including; investigator trials, case series and/or observational studies which are available to substantiate the safety and efficacy of the Product but which may not be controlled. One reason is that the products are used for several years and it was not clear that the product will what frame would be applicable (medicinal law, medical product law, special law tailored to these products) Such studies should be allowed to support registration. Additional controlled trails or further observational studies in post-authorisation phase could also be considered on case by case basis. New paragraph: For Advanced Therapy Products which are already legally on the market in accordance with Article 29 of Regulation (EC) 1394/2007 and for which there is data from their use in the market (for example; observational studies, case series and/or investigator studies) indicating the efficacy and safety of the Product, then in such cases this data should be considered sufficient evidence for granting of a marketing authorisation. (BPI)	
Line 473	Although it is understood that same reporting systems are advantageous, it does not seem appropriate to use exactly the same systems for efficacy as for safety. For example, reporting individual efficacy reports in an expedited manner does not look to be of necessity. Moreover, efficacy follow-up reporting frequency can also be determined in the MA commitments and could not follow the established periodicities of the regular safety reports. It is proposed that clarification is brought on the most relevant and efficient way to update the efficacy reports. (TiGenix NV)	*Further clarification was added. Spontaneous or expedited reports on good efficacy are not required.*
Lines 473-474	This suggests that all efficacy follow-up should be reported to the competent authorities as expedited reports. This would require new plans for most companies, as currently only “lack of efficacy” or “decreased therapeutic response” are likely to be captured. These are usually not expedited reports (unless the condition is life-threatening as a rule). Would we need to capture “good” efficacy outcomes and report	*Further clarification was added. Spontaneous or expedited reports on good efficacy are not required.*

	them as expedited cases? Suggest further clarification on what constitutes reportable efficacy data and how to report it, also suggest changing line 474 to " i.e. expedited reports for lack of efficacy in life-threatening diseases and periodic reports for non-life threatening situations." The concept of the efficacy of marketed products being reportable as well as the risks is novel, and not restricted to the field of ATMP. While the idea is worth exploring as part of a general review of pharmacovigilance practice, it is not appropriate to tie it solely to the ATMP arena. (EBE)	
Lines 473-475	"For practical reasons, efficacy follow-up should also use the same reporting systems to competent authorities, i.e. expedited and periodic reports." Clarification is needed. (Paul Ehrlich Institut)	*Agreed (see above).*
Lines 502 and 504	How do these risks differ? Please combine or leave 504 502: Risks related to interaction of the product with the patients 504: delete line (BPI)	*These lines were combined as suggested.*
Line 510	The summary of safety specification only lists the important identified and potential risks according to Volume 9a. For clarity, the following addition is therefore proposed For many ATMPs, the following examples are likely to represent important potential or identified risks. (EBE)	*The words "potential or identified risks" are changed to "important safety concerns", as per the Volume 9A.*
Lines 510-518	It should be ensured that the collection of (S)AEs associated with ATMPs are identifiable by specific product (manufacturing process) rather than at generic level. Add bullet point: Where appropriate, ensure the collection of (S)AE s associated with ATMPs is identifiable and retrievable by specific product (manufacturing process) rather than by active compound. There are implications in this guidance for the development of a unique naming system for ATMP products, similar to the INN system for medicines. There is an opportunity to learn from the confusion that has been created by applying identical INNs to biosimilar therapeutic proteins that may differ in their risk benefit profile.	*This issue is already addressed by the latest update of Volume9A, where the requirement of the product name and batch number is specifically added for biologics and biosimilar products. The need for the collection of data per specific product (including batch number), was added to chapter 7 of the guideline – Additional Requirements for the Pharmacovigilance System of Marketing Authorisation Holders.*

	The WHO INN committee should be asked to consider this question in the context of risk management for ATMPs. (EBE)	
Line 515	Impossibility of discontinuing the product: Does it mean "removal"/"extraction" Impossibility of discontinuing or removal of the ATMP (BPI)	*Yes, clarification was added.*
Line 537	The proposed guideline is silent on data privacy issues, particularly regarding safety follow-up. For example, the statement, "Use of traceability data for surveillance purposes….. and its record linkages…" suggests that personally identifiable data may be freely available and freely exchanged. Propose addition to Line 539, "…database of reports received from hat centre.) **Note, however, that strict adherence to data privacy laws is both expected and required.**" (Pfizer)	*The issue of data privacy is addressed in a new chapter of the guideline.*
Line 544	It is not clear what is intended by "…existing systems for safety follow-up should be used…" Clarify the meaning of the term "existing systems" (EBE)	*Changed to "...the system that is or will be established..."*
Lines 547-548	Potential lack of efficacy seems to be overly emphasised. The intended uses of ATMPs include restoring, correcting or modifying physiological functions, or for diagnosis of disease or other medical conditions. The concern arises if the therapy works initially, but the therapeutic effect(s) is not appreciated for the intended duration of treatment, i.e., the therapeutic benefit is not permanent or does not persist as desired. This effect can be experienced for manyoncology drugs, for example, or in serious infections when resistance develops due to an antigen shift in the causative pathogen after treatment with an otherwise potent antiinfective agent. Lines 547-548 state: "It should be highlighted [in the RMP] that 'loss of efficacy' or 'less than expected efficacy' of a medicinal product used in lifethreatening diseases is considered to be a safety issue (see Volume 9A)." The potential benefit afforded by the ATMP should be considered in this section, but the proposed guideline is silent on the benefit-risk balance. If, after a time-course of treatment, an ATMP is considered to have less than expected efficacy (or efficacy erodes or becomes not	*The benefit-risk discussion is not in the scope of this guideline. The decision about any regulatory action is based on complex considerations, including the information provided from the safety and efficacy follow-up systems, and risk management systems. This clarification was added to chapter 2 (Scope of the Guideline).*

	clinically meaningful), does this mean that the ATMP fails on the basis of benefit-risk? Certain oncology agents are expected to gradually lose effectiveness over time, but patients experience a very meaningful initial response that both extends life and improves their quality of life. Benefit-risk should be discussed, stating explicitly that a loss of efficacy or less than expected efficacy over time does not necessarily constitute a reason for removing an ATMP from use in the population. This would deprive other people of the benefits of the ATMP. Such wording should probably go in the EU-RMP. Propose modification of Line 548-549 to read "…used in lifethreatening diseases is considered to be a safety issue **concern** (see Volume 9A**) that may merit follow-up**. Therefore, for this kind of concern, safety follow-up alone might be appropriate**, although known benefit information must be considered when interpretingnew information on 'loss of efficacy' or 'less than expected efficacy.'** The efficacy follow-up …" Propose addition to Line 551 to read "…safety follow-up alone for this purpose**. A loss of efficacy or less than expected efficacy over time does not necessarily constitute a reason for removing an ATMP from use in the population. This would deprive other people of the benefits of the ATMP. Wording to this effect should be included in the EU-RMP**." (Pfizer)	
Lines 547-552	Discussions about the need to evaluate efficacy and loss of efficacy as a safety issue is complex and needs further specification of the guideline's intent. While long-term efficacy may need to be followed up as a post-marketing commitment, this often cannot be evaluated as a safety concern for an individual subject. For example, many outcomes are a continuum and may be a reduction of disease progression or deterioration in the treated group relative to controls (eg, multiple sclerosis). For any one patient, it would be difficult to determine at a later date that they had a "loss of efficacy" that would constitute a safety issue. Tracking efficacy as a safety issue will have to ***(should)*** be individualized to the product and disease and not automatically required across all "advanced therapy" products.	*It is agreed that the follow-up systems should be individualized to the product and disease. For this reason, the guideline does not require one particular system to be applied across all "advanced therapy" products. Clarification in this respect was added. The suggested text "identified by MAH" cannot be added, as the EU-RMP constitutes an agreement between MAH and a regulator, and is a part of the product licence.*

	For clarity the following additions are proposed The efficacy follow-up should only be considered, ***on a case by case basis,*** in situations which require further study of the product's efficacy profile in the post-authorization phase, and when it is inappropriate to use safety follow-up alone for this purpose. Suggest change to line 552 "When a need for efficacy follow-up is identified by MAH, …" (See comments on lines 473-474) (EBE)	
Lines 557-558	The limitation of use including certification of prescribers is not very practical and infringes on the freedom of exercising medical practice by physicians. Recommend deleting the accreditation Limitation to Hospital use (in countries where this restriction exists) Recommendations for use developed in association with the appropriate Scientific Medical Societies. (EBE)	*This is an example of a measure already used in the past. The list of examples in the guideline is based on what is legally possible. Scientific Medical Societies are usually involved in drafting of a particular EU-RMP, but have no formal authority to enforce it.*
Lines 557-560	According to German Law, it is not possible to limit doctors in such a way. Doctors may use any product that is adequate to treat the patient. Delete lines 557-560 (BPI)	*This is an example of a measure already used in the past. The list of examples in the guideline is based on what is legally possible.*
Lines 561-565	It is not clear, how the patients could be alerted by the Marketing Authorization Holder, if only anonymised data may be transferred to the Marketing Authorization Holder (see above, comments to 438, Table 1) See above, 438, Table 1 (BPI)	*These lines talk about use of communication documents designed for patients. Use of them does not require any contact data for patients. The MAH simply provides the documents to Healthcare Professionals who then use them for education of patients. Some of the communication tools are even part of the labelling or package insert.*
Lines 566-567	According to German Law, only the medical practitioner/ hospital has access to patient data See above, 438, Table 1 (BPI)	*That is right; the barriers to errors need to be introduced by hospitals, and may be part of the accreditation required by the risk management plan. Further clarification was added.*
Lines 568-570	A potential method of risk minimization provided is to limit use to trained sites. The question is - who identifies these particular sites? The document states "selected by MAH and/or member states". This is an unnecessary intrusion in a selection process that should be directed by the MAH. Delete "member states" and substitute "and appropriate medical organisation". (EBE)	*Member states cannot be deleted as they are legally obliged to enforce risk minimisation plans. Medical organisations co-operate in the selection, and some member states delegate the role in accreditation to them. Cooperation with an appropriate medical organisation has been added.*
Lines 571-573	Education of support personnel, family etc. should not occur at the costs of the Marketing Authorization Holder	*When a need for a particular risk minimisation activity in a form of education is identified, the cost needs to be met by MAH. Please note,*

	Education of support personnel, family … is desirable, but not compulsory (BPI)	*that this is an additional risk minimisation activity, so far used in very exceptional cases. Additional risk minimisation activities are compulsory only when included in the RMP.*
Lines 598-615 (specifically 611-613)	It is not clear whether this section refers to interventional or observational studies or both. Lines 611-613 appear, through the use of the term observational in parens, to be specific to observational studies, yet the second and third lines would appear to be related to interventional not observational studies, such as a registry where one would expect to include a cohort of patients reflecting clinical practice. Please revise this section to clarify the applicability of the statements made to interventional versus observational studies. (EBE)	*This section refers to both, interventional and observational studies. Further clarification was added.*
Line 606	It is recognized that broad use of endpoints can lead to a better understanding of efficacy and its parameters. On the other hand, following "limitations" in observational studies need also to be considered: - These studies take place in routine practice, and it is likely that "normal practice" of clinical follow-up will be used (this is also concurrent with the suggestion in the present guideline (line 390)). - Endpoint measurements for ATMP might often not belong to the "normal practice" and therefore not be well-established and harmonized. This can potentially impact on their value in assessing the clinical outcomes. - As the products will be used in routine practice, the burden of additional interventions and reporting to the treating physician needs to be considered. This impacts both the possibility and the willingness to participate in the follow studies. Using endpoint measures outside the "normal practice", which would benefit the efficacy assessment of the ATMP, might be considered as interventional. National legislation on the rules on interventional vs observational studies might need to be considered. (TiGenix NV)	*This bullet point refers to both, interventional and observational studies. The clarification was added to the text. The notion of wider spectrum of endpoints reflecting the real life effectiveness should make it easier to use non-interventional designs.*
Line 611	"Long-term efficacy (observational) studies should normally be of comparative design." This is overly prescriptive and may be difficult to accrue when the ATMP has been shown to be superior.	*The wording is not perceived as too prescriptive, but very flexible. First of all, this is an exceptional situation, secondly, the word "normally" reflects what the usual design of efficacy studies is, and thirdly, the*

	Say instead: "The appropriate design of the long-term efficacy studies will be discussed at the time of approval." (EBE)	*sentence on choice of comparators leaves all the opportunities opened for discussion.*
Line 611	Although the ideal situation, it should be recognized that it might be very difficult to run comparative observational studies. Lack of randomization, difficulties in controlling the patient populations, changes in standard of care, and other factors can have a major impact on the final datasets that needs to be compared. Clear guidance from the authorities in the design of the trial is therefore recommended. (TiGenix NV)	*The particular design will be discussed at the time of approval, and will take into account all the factors mentioned, as well as other characteristics of the product, treated population and healthcare system. The text of the guideline is sufficient.*

9. USE OF REGULATORY TOOLS IN POST-AUTHORISATION SURVEILLANCE OF THE ADVANCED THERAPY MEDICINAL PRODUCTS		
Line no. + para no.	**Comment and Rationale**	**Outcome**
Line 616	Authorisastion – Authorisation (BPI)	*Thank you*.

10. ELECTRONIC EXCHANGE OF PHARMACOVIGILANCE INFORMATION		
Line no. + para no.	**Comment and Rationale**	**Outcome**
Lines 635 to 640	Business rules and validation procedures of the authorities need to ensure that ICSRs of ATMPs can clearly be separated/distinguished from ICSRs of "normal" products. Otherwise all already existing ICSRs would have to undergo adjustments concerning E2B mapping again. Furthermore requirements for expanded data entry into further E2B fields would be necessary for <u>all</u> ICSRs (including non-ATMPs). (VFA)	*Further clarification will be added.*