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COMMENTS AND PROPOSED CHANGES FROM THE SWEDISH MEDICAL PRODUCTS AGENCY ON THE EUROPEAN COMMISSION SANTE B5 PUBLIC CONSULTATION REF. TSC 01/2018 ON GCP FOR ATMPS

1.1. Introduction

1.1 Scope

- Add text after row 67: '**Investigational ATMPs should comply with the Guidelines on Good Manufacturing Practice for Advanced Therapy Medicinal Products and with other relevant Guidelines**'.

Rationale: In order to avoid conflicting information, we would recommend to remove topics that are included in the GMP guideline (https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-4/2017_11_22_guidelines_gmp_for_atmps.pdf) from this document OR add a reference to the GMP guideline where necessary and only discuss topics in general terms in the current document.

Depending on the publication date, the final document may also mention a new guideline under development by EMA, 'Guideline on quality, non-clinical and clinical requirements for investigational advanced therapy medicinal products in clinical trials'.

1.2 General Principles

- Change word row 82: replace ~~should~~ with '**must'**

Rationale: This is a legal obligation, not a guideline or a recommendation.

2. Clinical Trial Design

- Add word row 86: before 'subjects', add '**donors'**

Rationale: Potentially also risks for donors could be involved.

- Add text row 87: after 'others' add '**Since a clinical trial authorisation only involves assessment of risks to individual subjects, the sponsor should check whether additional authorisation is needed before the trial can start, e.g. assessing environmental risks by gene therapies that are GMOs (gene-modifying organisms).**

Rationale: The Clinical Trial Regulation, Article 6, is restricted to assessment of risks to the subjects.

- Move text row 91: Move first bullet to end of third bullet

Rationale: The text relates to future therapies (see below after row 102)

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0) 18 17 46 00 Fax: +46 (0) 18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se

- Add text row 96: after 'treatment' add '**or treatment of the mother bearing the child**'

Rationale: ATMPs could also involve treatment of the mother during pregnancy.

- Insert text after row 110 (originally in first bullet row 91, proposed to be moved to new third bullet or added to new second bullet, with minor changes, i.e. insert '**cell or**' and delete '~~of haematopoetic stem cells~~'): '**For populations that might ultimately be amenable to cell or organ transplantation** ~~of haematopoetic stem cells~~**, sponsors should consider whether exposure to the ATMP would cause sensitisation and potentially compromise future transplant success**'.

Rationale: This text relates to future therapies, why we recommend moving the text in the first bullet to the end of the last bullet of this section. Since transplantation may not be limited to haematopoetic stem cells but also include other cells, we recommend not restricting the text to one cell type only.

- Change text rows 111-114: replace (ii) ~~For some ATMPs an intra-subject control might be appropriate. For example, the investigational product could be injected into one eye and the untreated eye is used as a control. Comparison of local effects can be facilitated in this way by eliminating inter- subject variation.~~ with '**If an active comparator is not available or inadequate, the comparison to best standard of care or treatment with a placebo or sham procedure is acceptable as concurrent control for a confirmative clinical study. In some situations an intra-individual comparison can be considered when appropriately justified.**'

Rationale: We recommend the wording above in line with other ATMP guidelines, e.g. the Reflection paper on clinical aspects related to tissue engineered products EMA/CAT/573420/2009. There is scientific evidence that immune reactions occur both in the affected and non-affected eye (Cruz at et al., Invest. Ophthalmol. Vis. Sci. 2015;56:6612–6620), which introduces a bias analysing the effect and putative risks to the subject in the example given comparing the treated vs. non-treated eye.

- Add text row 117: after 'feasible.' add '**When the investigator is unblinded, outcome evaluation could be performed by a blinded observer.**'

Rationale: Difficulties in maintaining blinding when assessing the trial endpoints could be solved with appropriate trial design, e.g. blinded observers.

- Change first sentence row 118: replace ~~The use of placebo should be scientifically and ethically justified~~ with '**Although a randomised, double blinded placebo-controlled clinical trial is the preferred design, the use of placebo is not always ethically justified**'

Rationale: The methodological first choice for scientific studies is missing in the sentence.

- Change word row 120: replace '~~only'~~ with '**alone'**.
- Change text row 121: replace '~~if it presents~~' with '**with'**
- Change text rows 125-126: replace '~~control~~' with '**improve control of'**

Rationale: Changes introduced for linguistic and clarity reasons. Safety measures improve control of toxicity, rather than control toxicity.

- Move text rows 127-133: see below move the entire sentence to a new point on early studies

Rationale: Texts relating to early studies should preferably come after issues relating to all studies (see below after row 136)

- Add text after row 136: insert modified text from rows 127-133 to a new point (viii), updated with reference to EMA's first-in-human/early trials guideline: delete ~~In early phase trials where it is not possible to re-administer the product (e.g. gene therapy) or when the re-administration involves the additional risk of a surgical procedure, the exploratory dose chosen should aim to be a therapeutic dose for the subject. (vi) Depending on the degree of safety concern, in early phase clinical trials staggered treatment of individual subjects within each new cohort and between cohorts should be considered as appropriate.~~ and insert '**In the EMA Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products (EMEA/CHMP/SWP/28367/07 Rev. 1 dated July 20 2017) should be applied also for ATMPs where appropriate. As examples, the starting dose for patients in section 7.3 and the recommended sentinel dosing in section 8.2.6 should be considered unless there is a risk-proportionate basis with a clear scientific rationale for not to use this strategy. The exploratory dose chosen should aim to be a therapeutic dose for the subject in trials in some situations as described under 7.3, e.g. where it is not possible to re-administer a gene therapy product or when the re-administration involves substantial additional risks, e.g. linked with surgical procedures. Early dose-finding studies should also aim at collecting proof-of-concept and pharmacodynamic data**'.

Rationale: The revised text of the EMA guideline on first-in-human and early clinical trials states under Scope:

> "The guideline applies to all new chemical and biological IMPs. *While advanced therapy medicinal products (ATMPs) (as defined in Article 2(1) of Regulation 1394/2007 tested or used in accordance with Article 2(d) of Directive 2001/20/EC) are not within this scope, some principles of this guideline are relevant on a case-by-case basis"*.

For this reason, it is helpful to give examples when the guideline should be considered also for ATMPs, e.g. sections on recommendations on the starting dose for patients under 7.3 and on sentinel dosing under 8.2.6.

3. Application dossier

- Change text row 140: replace ~~application~~ with '**cover letter, protocol, Investigator's Brochure (IB) or Investigational Medicinal Product Dossier (IMPD)**'
- Add text row 140: add '**For cells of animal origin only the second bullet applies**'.

Rationale: The clinical trial application is limited to certain documents following Annex I of the Clinical Trial Regulation. It will help the applicant to know the alternatives where this information should be provided and that the traceability system should also be needed for cells or tissue of animal origin.

- Add text row 147: after 'subjects' add '**including follow-up covering the regulated time period, possibly further extended based on the ATMP risk profile**'.

Rationale: The stipulated traceability is 30 years, but the outcome of the risk-based approach (Annex II, ATMP regulation) may require traceability for even longer time.

3.1 Specific considerations concerning the protocol

- Delete text rows 151-154: ~~(i) release specifications…transduction efficiency.~~

Rationale: This should not be in the protocol but in the Quality part of the IMPD. Delete this section, since it is mentioned in the GMP guideline. The risk is that conflicting information confuses the reader.

- Add text row 156: after pivotal trial add '-trial**s'. The starting dose should both be expected to have a pharmacological effect and to be safe to use. The overall goal is also to describe a correlation between exposure and effect in initial trials using a dose range, which is then verified as the finally recommended dose after further evaluation in expansion cohorts or in separate clinical trials. Dose finding of tissue engineered products also need to take into account the claimed regeneration/repair capacity (eg. size of tissue damage to be healed)'**.
- Change text rows 160-161: replace ~~'may contain inactive particles which assist in the mechanism of action of the ATMP, for example in transduction efficiency'~~ with '**The ATMP may involve use of conditions to improve the biological activity of the mode of action that is to be considered in defining the dose. For example, the efficacy of gene therapy medicinal products is expected to be related to the transduction of target cell populations by the chosen viral vector as gene-delivery vehicle.**'

Rationale: Important clarifications on dose selection and e.g. repair capacity. Note need to clarify confusing issue on transduction efficiency and inactive particles.

- Add text row 162: after 'products' add '**due to a subject's disease-related factors**'
- Add text row 164: after 'materials' add '**leading to defining a dose range'**.
- Add text row 166: after 'studies.' add '**Furthermore, a rationale for a dose definition based on published literature data requires thorough analysis of the comparability between products for example relating to starting material, manufacturing process or existing clinical experience in similar but not identical patient populations**'
- Add word row 169: before 'product' add '**final'**
- Add text row 169: after 'product' add '**All steps including required use of medical devices (eg. catheter size in apheresis) for collection of tissue biopsies/extracting cells should be described in detail. These processes may entail risks for the subject and may also have an impact on the quality and safety of the product. In addition, the formulation of the final product may occur at bed-side for which detailed information should be available with the product. The level of documentation should be adapted, so that more complex collection of starting material and administration of the final product may need preparation of educational material and collection of raw data during clinical trials to be presented in a future marketing authorisation application.**'
- Add text row 171: before 'biopsies' add '**tissue'**

Rationale: Important clarifications.

- Add text row 182: after 'risks.' add '**Risk profiling/analysis is preferably performed by implementing the risk-based approach analysing risks and risk factors associated with the product's quality aspects as well as potential and known elements related to non-clinical and clinical development (see Guideline on risk-based approach according to annex I, part IV of Directive 2001/83/EC applied to Advanced therapy medicinal products; EMA/CAT/CPWP/686637/2011)**'

- Delete text row 184: delete '~~for example~~'

Rationale: Important clarifications and reference to the guideline on risk-based approach.

- Change text rows 191-192: after 'follow-up activities' add the following text with changes (deletions and insertions) '~~will~~ **are intended to** be performed after the end of the trial (~~*e.g.* via an~~ **i.e. as a separate** interventional **clinical trial** ~~study,~~ **or as non-interventional clinical procedures in accordance with the terms of marketing authorisation**~~non-interventional study, registry~~'

Rationale: Since a prospective study on medicinal products from the legal point of view is either interventional (=clinical trial) or non-interventional, adding the technical tool 'registries' here leads to confusion. It is important that 'registry studies' are not understood as a separate category for clinical research. A registry is a tool used in research or in patient care, but not a term excluding the need for clinical trial authorisation.

- Add the following text after row 192: add an additional point '**(vii b) *Premature trial discontinuation:* Follow up of the subjects should be clearly described, both for situations when individual subjects discontinue the trial and when the entire trial ends prematurely. This includes situations where the product development is discontinued or the (former) sponsor ceases to exist, for instance, by providing appropriate information to the healthcare establishments involved in the clinical trial'.**

Rationale: The special need for long-term follow-up should also prepare for situations when the trial ends prematurely or subjects discontinue the trial.

- Add text after row 197: after 'trial' add '**in a separate interventional clinical trial. The follow-up can only be regarded as a non-interventional clinical study if the product has already been granted marketing authorisation and the follow-up is identical to what is specified in the SmPC. If the follow-up for a marketed product goes beyond such standard of care, the trial could be considered a low-intervention trial if additional diagnostic or monitoring procedures do not pose more than minimal additional risk or burden to the safety of the subject compared to normal clinical practice**'.
- Add text row 198: after 'expected' add '**, but this could be longer based on the outcome of the risk analysis. For such long-lasting trials, procedures could be simplified e.g. limiting follow-up to yearly or half-yearly visits and limiting clinical trial annual safety reporting to serious adverse events possibly related to the ATMP'**.

Rationale: See clear legal distinction between interventional clinical trials and non-interventional clinical studies (also below under 8.2 long-term follow-up).

- Delete text rows 199-200: delete '~~Follow up to subjects…clinical trials~~'.

Rationale: Premature end and early termination have both already been introduced as a new section (viib) above.

- Change text rows 204-205: replace '~~comply with the relevant general safety and performance requirements provided for under the~~' with '**is CE-marked in accordance with'**.

Rationale: The paragraph does not make sense unless it is clear that the first sentence refers to a CE-mark. The second sentence refers to non-CE-marked products, not to 'non-compliance with safety and performance requirements'.

- Add text row 208: replace 'component' with 'component**(s)'**
- Add text row 209: after 'protocol.' add '**The clinical investigation of the medical device component of the ATMP should preferably be integrated with the clinical trial to avoid exposing subjects to several studies.**'

Rationale: Important clarifications.

- Add text after row 211: Add the following three additional points
  '**(xi) '*future use of biological samples:* a detailed description of the collection, storage and future use of samples should be provided, also in the case of autologous ATMPs**'
  and
  '(xii): '*additional ethical consideration*': The protocol should also describe ethical considerations relating to the clinical trial if those have not been described elsewhere, e.g. affecting subject integrity. As an example, this could include the exceptional circumstance when a commercial sponsor is planned to be present during a surgical procedure when the investigator administers the ATMP to the subject.'
  and
  (xiii): 'auxiliary medicinal products': The risk analysis may resolve a safety concern that can be treated using prophylactic or symptom-based medical interventions. Such rescue medicinal products must be available at the unit where a patient is administrated with the ATMP and they should be described in the protocol, eg. anti-IL6 therapy in subjects receiving a CAR-T cell product.

Rationale: Although these points are valid for all clinical trials, their application on ATMPs benefits from being clarified, see Clinical trial Regulation Annex I D 17 (s) and (ag).

3.2 Specific considerations regarding the Investigator's Brochure (IB)

- Delete text rows 220-222. '~~In some cases…In contrast~~'
- Change text row 225: replace 'assessed' with '**justified by the developer**'
- Add text to row 229: after *etc.* add '**However, biodistribution studies are of key importance. The ATMP developers are encouraged to put effort in developing analytical tools to study the biodistribution of the ATMP in humans.**'
- Add text rows 242-243: after 'product' add '**that can be performed during early phase of clinical development**'
- Change text in rows 247, 250, 256, 258: replace '~~protocol'~~ with '**IB'**

- Change text row 255: replace 'handing' with '**handling'**
- Change text row 268: replace '~~risk-minimisation~~' with '**the chosen risk-based approach**'
- Change text row 279: replace '~~should~~' with '**must'**

Rationale: Clarifications on the IB (note that these rows now wrongly refer to a different document of the application dossier, the protocol, although they all appear under the heading IB). As an alternative, the parts on reconstitution and administration could be moved to the previous section on 'Specific considerations regarding the protocol'.

4. Quality of the investigational ATMPs

- Add text row 280: before 'Quality' add '**Specific considerations regarding the**', after 'ATMPs' add '**in the Investigational Medicinal Product Dossier (IMPD)**' and consider changing format to subtopic 3.3 as part of the application dossier above.
- Add text row 282: after '..Products.' add '**Typically all quality-related aspects of the trial, including reconstitution and administration of the ATMP, should be described in detail in the Quality part of the IMPD'.**
- Change test row 284: after 'conditions' add **'from the collection of the starting material to the handling of the final product'**
- Add text row 287: after 'explained.' add '**Note that such risks to the environment and individuals that are not participating as trial subjects need additional authorisation not included in the decision on the clinical trial, e.g. following legislation on environmental effects of GMOs. In some Member States this procedure is integrated and parallel with the decision on the clinical trial'**.

Rationale: Consider including the name IMPD in the heading, since this is the preferred section for all quality issues. Please note that most of the points mentioned in this section, are already mentioned in the GMP guideline.

5. Administration procedures

- Add text after row 298: after 'procedure' add '**The sponsor should consider the need to collect raw data during clinical trials on specific ATMP administration-related details, especially if surgery or other high-risk interventions are required. This is often missed and it is burdensome for the sponsor to reconstruct information on required data for the marketing authorisation application**'

Rationale: Sufficient details on the administration procedure is often missed and difficult to reconstruct when data are required during the MAA assessment.

- Add text row 304: after 'during' add '**procedures described above including**'
- Add text row 306: after 'justified' add '**in the protocol as additional ethical considerations involving subject integrity**'
- Change text rows 306-308: after 'If' change text to '~~the~~ **such** presence ~~of the administration~~ is envisaged before the start of the clinical trial, this should be **part of the written information to subjects provided before** ~~explained in~~**'**

- Add text row 310: after 'a posteriori' add '**and the sponsor should consider if this represents a serious breach defined in the Clinical Trial Regulation (EC) No 536/2014**'

Rationale: Correct terminology for clinical trials should be used (serious breach), additional ethical considerations on subject integrity, written information to subjects before informed consent etc.

6. Traceability

- Change text rows 319-320: after 'product' add '**see also archiving rules in the section on clinical trial master file**' and delete '~~unless a longer time period is required in the clinical trial authorisation~~'

Rationale: Avoid repetition by referring to archiving rules in the suggested new section on clinical trial master file.

8. Protection of clinical trial subjects

8.1 Informed consent

- **Add text to row 360**: after 'Section' add 'Sections **3.1 and**'

Rationale: The presence of a commercial sponsor during administration affects the integrity of the subject and is proposed to be part of the protocol.

8.2 Long-term follow-up

- Change text rows 363-364: after 'follow up' delete '~~(e.g. interventional study, non-interventional study, registry)~~', after 'should be described' add '**and justified**'.

Rationale: Since a prospective study on medicinal products from the legal point of view is either interventional (=clinical trial) or non-interventional, adding the technical tool 'registry' here leads to confusion. It is important that registries are not understood as a separate category for clinical research. A registry is a tool used in research or in patient care, but not a term excluding the need for clinical trial authorisation.
The protocol should not only describe the follow-up but also justify the chosen approach.

- Change text rows 367-368: delete '~~prior to and~~'
- Add word row 368: before 'clinical trial' add '**initial'**

Rationale: Not clear what is meant by 'follow up activities *prior to*' a clinical trial. Suggested adding 'initial' to distinguish between the clinical trial where the IMP is administered and the trial with the follow-up activities.

- Add text after row 368: add '**In most cases, long-term safety and efficacy monitoring of subjects should be done in the framework of a separate follow-up clinical trial. Since the ATMP was administered in an interventional clinical trial, any systematic follow-up beyond normal clinical practice should always be defined as an intervention, i.e. require a new clinical trial application submission for which the protocol describes the nature and frequency of planned follow-up**

based on a risk-based approach. Simplification of safety reporting for such trials without any IMP administration is generally acceptable.'

Rationale: Follow-up of an investigational medicinal product administered in a clinical trial must be done within a clinical trial framework. For products without marketing authorisation such follow-up can't be regarded as normal clinical practice. For authorised medicinal products a Risk Management Plan (RMP) will be the usual measure for post marketing safety follow-up and agreed on during the assessment of the marketing authorisation application. Post marketing long-term efficacy and safety studies, where the follow-up is more extensive than normal clinical practice, should as a general rule be performed as clinical trials. While a CHMP scientific and protocol advice is a suitable forum to agree on detailed objectives and on the extent of such follow-up, it is always within the remit of Member States, not the European Medicines Agency, to decide whether a clinical study is regarded as a clinical trial or not - see Article 6.1 (i) second indent of the clinical trial regulation.

- Add text row 372: after 'product' add '**As a general principle, if the follow-up is described in the SmPC for an ATMP with marketing authorisation, the procedure should be considered as normal clinical practice, i.e. no additional clinical trial application is needed. However, additional diagnostic or monitoring procedures compared to such normal clinical practice require a clinical trial application also after marketing authorisation has been granted**'.

Rationale: Post-authorisation study commitments cannot overrule the clinical trial regulation. Thus if a study is a clinical trial or not is independent on the mentioning of 'registry follow-up in the decision on marketing authorisation' – see Article 6.1 (i) second indent of the clinical trial regulation.

8.2.3 Premature end or termination

- Change word row 388: replace '~~should'~~ with 'must'
- Change word row 389: after 'documented' add '**and the procedures should be described in the protocol'.**
- Change text row 390: replace '~~there is~~' with '**the protocol provides**'

Rationale: These topics should also be part of the protocol, see above under 3.1 vii b.

8.2.4 Patient alert cards

- Change row 394: replace 'Patient' with '**Subject'**

Rationale: Consistent terminology using 'subject' instead of 'patient' is preferred.

8.3 Administration of out of specification products

- Add text row 408: after 'justified.' add '**A procedure for administration of out of specification products as well as related roles and responsibilities should be described in the study protocol or in a separate document, when applicable.**'
- Insert text row 413: before 'breach' add **'serious**'

Rationale: Correct terminology for clinical trials should be used.

9. Safety Reporting

- Change rows 422 and 425: replace '~~application'~~ with '**administration'**
- Add row 434: after 'foreseen' add '**as a separate clinical trial**'
- Add row 435: after 'events' add '**and adverse reactions**'
- Change rows 435-436: ~~as part of the long term follow-up arrangements~~ '**and justified, e.g. limiting safety reporting from the investigator to the sponsor to serious adverse events at least possibly related to the ATMP or to its related procedures**'

Rationale: Proposed consistent terminology replacing 'application' with 'administration'. Safety reporting can be simplified in a long-term follow-up trial without ATMP administration. However, the legal framework for such follow-up activities requires a clinical trial application, and they could not be performed as a non-interventional clinical study or registry records.

10. Monitoring

- Delete text rows 447-448: ~~Where applicable, compliance with the arrangements for long-term follow-up to subjects (as described in the protocol) should also be verified~~

Rationale: Monitoring is restricted to a particular trial and cannot include processes after the trial has ended. Long-term follow-up should preferably be performed in a separate clinical trial.

11. Clinical Trial Master File

- Add text after row 448: add an additional chapter with the title '**11. Clinical trial Master File**':
  'In addition to the standard requirements that are needed for the reconstruction of the trial and verification of trial conduct, the Clinical Trial Master File (CTMS) for ATMPs should also contain documents related to documentation on the confirmation of the traceability systems, the traceability responsibility matrix and the location of the traceability records. In cases where the administration procedure may have an impact on the safety or efficacy outcome, this procedure must be appropriately documented. Importantly, the sponsor should note that the legal requirement for keeping traceability documents is longer for ATMPs compared to documents relating to other investigational medicinal products (30 years instead of 25 years).'

Rationale: This section should preferably be discussed with the GCP-Inspectors' Working Group. It is important that sponsors are informed in this document about e.g. the longer archiving requirements compared to other investigational medicinal products.